Received: 6 November 2019 | Revised: 5 March 2020 | Accepted: 10 March 2020

DOI: 10.1111/myc.13074

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases | WILEY

ORIGINAL ARTICLE

Risk factors and outcomes of culture-proven acute *Coccidioides* spp. infection in San Diego, California, United States

Jeffrey D. Jenks[1,2] | **Sharon L. Reed**[2,3,4] | **Martin Hoenigl**[2,4]

[1]Department of Medicine, University of California San Diego, La Jolla, California

[2]Clinical and Translational Fungal – Working Group, University of California San Diego, La Jolla, California

[3]Department of Pathology, University of California San Diego, La Jolla, California

[4]Division of Infectious Diseases and Global Health, University of California San Diego, La Jolla, California

Correspondence
Jeffrey D. Jenks MD, MPH, Department of Medicine, University of California San Diego, San Diego, CA 92103, USA.
Email: jjenks@ucsd.edu

Summary

Background: *Coccidioides* spp. are dimorphic fungi endemic to parts of the United States, Mexico, Central and South America. Infection can cause a range of disease from self-limited acute pneumonia to severe disseminated disease.

Methods: We performed a retrospective chart review of medical records of cases of culture-proven acute coccidioidomycosis at the University of California San Diego between 1 April 2015 and 31 December 2019 and described the demographics, risk factors and outcomes of these cases.

Results: Over the study period, fifteen evaluable cases of culture-proven acute coccidioidomycosis were identified. Of these, 87% (13/15) had traditional risk factors for coccidioidomycosis infection while two lacked known risk factors, including one patient with cirrhosis and one with chronic hepatitis C infection. Seven of fifteen (47%) had primary coccidioidomycosis of the lungs without dissemination and 7/15 (47%) disseminated disease. Of those with disseminated disease, 6/7 (86%) had either high-risk ethnicity or blood type as their only risk factor. At 90 days, 11/15 (73%) were alive, 3/15 (20%) deceased and 1/15 (7%) lost to follow-up. Of those not alive at 90 days, 1/3 (33%) had disseminated disease and 2/3 (67%) primary coccidioidomycosis, both on immunosuppressive therapy.

Discussion: *Coccidioides* spp. infection occurs in a variety of hosts with varying underlying risk factors, with the majority in our cohort overall and 86% with disseminated disease lacking traditional risk factors for invasive fungal infection other than ethnicity and/or blood phenotype. Clinicians should be aware of these non-traditional risk factors in patients with coccidioidomycosis infection.

KEYWORDS

Coccidioides immitis, *Coccidioides posadasii*, coccidioidomycosis, dissemination, epidemiology, risk factors, Valley Fever

1 | BACKGROUND

Coccidioidomycosis is an infection caused by dimorphic fungi of the genus *Coccidioides* (*C immitis* and *C posadasii*). *C immitis* is endemic to the south-western United States (US), primarily the state of California, with the highest incidence in California's Central Valley; *C immitis* is also found in Nevada, New Mexico, Utah, increasingly in previously non-endemic parts of the United States such as

Results of this manuscript were presented, in part, at the 9th Trends in Medical Mycology (TIMM) conference in Nice, France 2019 (Poster number 238).

Washington State,[1,2] as well as parts of Baja California, Mexico.[3] *C posadasii* is endemic in parts of the United States including southern California,[4] Nevada, Arizona, New Mexico and Texas,[3] as well as parts of Mexico, Central and South America.[1,5]

The changing climate is likely to expand the region of endemicity for *Coccidioides* spp. and increase the incidence of coccidioidomycosis in endemic areas. Incidence rates have been shown to be positively associated with warmer air temperature and drier soils.[6] It is hypothesised that increases in soil moisture are necessary for the fungal spores to germinate, but drier periods are necessary to loosen the soil and facilitate distribution of fungal spores in the wind. In addition, dry, hot temperatures are suspected to sterilise the topsoil and reduce competition against the *Coccidioides* spp. spores. The spread of fungal spores may be further exacerbated by the increasing incidence of droughts and wildfires in endemic areas such as California and the south-western United States.[7]

Infection can cause a range of disease from self-limited acute pneumonia to severe disseminated disease.[8] Of 150 000 cases of acute coccidioidomycosis infection that occur annually in the United States, about 1% results in disseminated disease and one third of these disseminated cases are fatal.[9] Risk factors for severe and disseminated disease include pregnancy,[10]

TABLE 1 Demographics, treatment and outcomes of culture-proven acute *Coccidioides* spp. infection

	Risk Factor (Comorbidity)	Blood Type	Immunosuppression	Sex	Ethnicity	Age	Pregnant (Yes/No)
1	Ethnicity (None)	A POS	No	M	Black	41	No
2	Lung cancer	O POS	Yes: Prednisone (>80 mg daily)	F	White	74	No
3	Lung Transplant in 2006 (DM II)	Unknown	Yes: Mycophenolate 250 mg thrice daily, tacrolimus 1 mg twice daily, prednisone 5 mg daily	M	White	64	No
4	Chronic HCV c/b liver cirrhosis and HCC	O POS	No	M	White	66	No
5	None	A POS	No	M	White	30	No
6	AIDS (CD4+ T-cell count 293 cells/uL)	O POS	No	M	Black	27	No
7	Ethnicity (Poorly controlled DM II)	Unknown	No	M	Hispanic	41	No
8	Ethnicity (None)	Unknown	No	M	Asia (Laotian)	34	No
9	DM II	O POS	No	F	White	41	No
10	Cystic Fibrosis (DM II)	Unknown	No	M	White	21	No
11	None (Chronic HCV)	Unknown	No	M	White	56	No
12	Ethnicity (None)	A	No	F	Hispanic	36	No
13	Ethnicity (None)	O POS	No	M	Black	32	No
14	Ethnicity (None)	Unknown	No	F	Hispanic	21	Yes
15	Ethnicity (DM II)	Unknown	No	M	Hispanic	62	No

Abbreviations: AIDS, acquired immune deficiency syndrome; BALF, bronchoalveolar lavage fluid; BID, twice daily; CNS, central nervous system; DM II, type II diabetes mellitus; FLU, fluconazole; HCC, hepatocellular carcinoma; HCV, hepatitis C infection; LAmB, liposomal amphotericin B; PSC, posaconazole; VRC, voriconazole.

immunocompromised status[11] including HIV infection[12] and transplant status,[13-15] belonging to a high-risk ethnic group such as African American/Black, Filipino, American Indians/Alaskan Natives, and Hispanic groups,[11,16-18] underlying genetic factors,[17] blood group A or B phenotype,[17] diabetes mellitus[19] and being elderly.[20] Lipid-based formulations of Amphotericin B are currently the preferred treatment for severe diseases, with high-dose fluconazole and itraconazole alternatives, particularly for moderate disease.[21-23]

The objective of this study was to describe the demographics, treatment and outcome of patients with culture-proven acute *Coccidioides* spp. infections in San Diego, California, United States, an area endemic to *C immitis*.

2 | METHODS

Adult patients age > 18 years with *Coccidioides* spp. isolated in any sample/material from the Center for Advanced Laboratory Medicine (CALM) at the University of California San Diego between 1 April 2015 and 31 December 2019 were included in this study.

Specimen Source (Histology)	Primary Site of Disease Disseminated (Yes or No)	Treatment	Surgery	Survival at 90 Days
Peritoneum (Not done)	Lung (Yes)	FLU (initial); VRC 200 mg BID + LAmB 375 mg daily (s); FLU 800 mg daily (final)	No	Yes
Lung (Not done)	Lung (No)	FLU 800 mg daily	No	No
Lung (Spherules noted on BALF)	Lung (No)	LAmB 284 mg daily + VRC 310 mg IV daily	No	No
Lung (BALF negative for spherules)	Lung (No)	FLU 400 mg BID	No	Yes
Lung CNS (Spherules on brain biopsy and BALF)	Lung (Yes - to CNS)	None (diagnoses made postmortem	Craniectomy	No
Lung (Spherules on BALF)	Lung (Yes – to lymph nodes)	LAmB 250 mg daily (initial); FLU 1200 mg daily (s); PSC 300 mg daily + LAmB 230 mg daily (third); PSC 300 mg BID (current)	No	Yes
Lung (BALF negative for spherules)	Lung (No)	None (diagnosis made postdischarge from hospital, lost to follow-up	No	Unknown
Peritoneum (Yes – fungal forms on peritoneal biopsy)	Lung (Yes)	FLU 800 mg daily	Laparoscopy	Yes
Lung (Not done)	Lung (No)	FLU 800 mg daily	No	Yes
Lung (Spherules on BALF)	Lung (No)	FLU 400 mg daily	No	Yes
Lung (Spherules on BALF)	Lung (No)	FLU 400 mg daily	No	Yes
Skin (left ear) (Spherules on skin biopsy)	Cutaneous (No)	FLU 400 mg BID	No	Yes
Skin (back) (Capsules and endospores on skin biopsy)	Lung (Yes—skin and CNS)	FLU 400 mg twice daily (initial); LAmB 320 mg daily (s); VRC 400 mg daily (third); PSC 900 mg BID (current)	Yes – VP shunt placement	Yes
Skin (right flank) (Spherules on skin biopsy)	Lung (Yes—skin and CNS)	FLU 800 mg daily	No	Yes
Lung and Lymph node (Spherules on lymph node biopsy and BALF)	Lung (Yes—lymph nodes)	FLU 800 mg daily	No	Yes

A retrospective chart review of medical records of these cases was performed to confirm that these culture-positive isolates represented acute coccidioidomycosis infection. Acute coccidioidomycosis was defined as the presence of new signs or symptoms of coccidioidomycosis infection with compatible radiologic findings plus positive *Coccidioides* spp. culture from the site of infection. For cases of acute coccidioidomycosis, the health records of these patients were than analysed further and demographics, risk factors and infection outcomes assessed. Disseminated disease was defined as culture-proven *Coccidioides* spp. from more than one non-contiguous anatomic site.

Descriptive statistical analyses were performed using SPSS 26 (SPSS Inc). The Human Research Protections Program at the University of California San Diego approved the study protocol and all study-related procedures.

3 | RESULTS

There were 15 individuals with *Coccidioides* spp. isolated from culture at our institution that were identified and evaluable over the study period. Of these, 14/15 (93%) had confirmed infection from *C immitis* based on DNA testing of the isolate; for one patient, no DNA testing was done so speciation was unknown. In all, 87% (13/15) had traditional risk factors for coccidioidomycosis infection including belonging to a high-risk ethnic group (7/13), chronic immunosuppression (2/13), lung transplant recipient status (1/13), diabetes mellitus (DM) (5/13) and blood group A phenotype (3/13). Six patients had multiple risk factors including transplant status and DM (1/6), AIDS and black ethnicity (1/6), belonging to a high-risk ethnic group and DM (2/6) and belonging to a high-risk ethnic group and blood group A phenotype (2/6). Two patients lacked traditional risk factors for coccidioidomycosis infection, including one patient with cirrhosis and one patient with chronic hepatitis C infection (Table 1).

Seven of fifteen (47%) patients had primary coccidioidomycosis of the lungs without dissemination, one of fifteen (7%) cutaneous coccidioidomycosis without dissemination and seven of fifteen (47%) disseminated disease with lungs thought to be the primary site of infection. Three patients had dissemination with central nervous system (CNS) involvement; of those, all had elevated white blood cell (WBC) counts on cerebral spinal fluid (CSF) analysis with lymphocytic predominance ranging from 36% to 68% and eosinophilia ranging from 2% to 10%; and CSF studies were not available for one patient. Of those with disseminated disease, 6/7 (86%) had either high-risk ethnicity or blood type as their only risk factor, including black ethnicity (3/7), Asian (Laotian) ethnicity (1/7), Hispanic ethnicity (2/7), and one patient had no known risk factors except blood group A phenotype (1/7). One patient with black ethnicity and disseminated disease also had AIDS. Of those who received antifungal therapy, 4/13 (31%) received combination therapy including an azole plus liposomal amphotericin B and 9/13 (69%) received monotherapy with fluconazole. At 90 days, 11/15 (73%) were alive, 3/15 (20%) deceased and 1/15 (7%) lost to follow-up. Of those who were not alive at 90 days, 1/3 (33%) had disseminated disease but no risk factor for infection and 2/3 (67%) primary coccidioidomycosis, both who were on immunosuppressive therapy.

4 | CONCLUSIONS

Coccidioidomycosis infection occurs in a variety of hosts, and infection can cause a range of disease from self-limited acute pneumonia to severe disseminated disease.

Risk factors for severe or disseminated coccidioidomycosis infection are similar to risk factors for other invasive mould infections, such as immunocompromised status, although otherwise healthy individuals from certain ethnic groups such as African American/Black, Filipino, Native Americans/Alaskan Natives, and Hispanic groups are at particular risk for severe and disseminated disease. This is thought to be related to certain genetic factors, as A and B blood phenotype increases the risk for severe disseminated disease in Hispanics and HLA class II DRB1*1301 allele is associated with severe disseminated disease in African Americans, Hispanics and Caucasian individuals. Conversely, milder disease is associated with HLA class II DRB1*0301-DQB1*0201 allele in Caucasian and Hispanic individuals and DRB1*1501-DQB1*0602 allele in African Americans.[17]

In our patient cohort, in 3/15 patients the only known risk factor for coccidioidomycosis infection was belonging to a high-risk ethnic group, and in 2/15 patients, the only known risk factors were belonging to a high-risk ethnic group and a group A blood phenotype, with one patient identifying as black and the other Hispanic. In one patient, his only risk factor was group A blood phenotype although he self-identified as White and not Hispanic, and to our knowledge, there is no known association between group A blood phenotype and Caucasian ethnicity. One patient lacked any traditional risk factors for infection but had chronic hepatitis C infection without cirrhosis. Another patient had cirrhotic liver disease, a risk factor not typically associated with coccidioidomycosis infection, although there are some data suggesting that end-stage liver disease may be a risk factor for coccidioidomycosis,[24] including coccidioidomycosis infection of the gastrointestinal tract.[25] Further research is needed to determine whether underlying liver disease may be a risk factor for coccidioidomycosis.

Disseminated coccidioidomycosis infection occurred in 47% of patients in our cohort. Of these, all belonged to high-risk ethnic group (5/7), had a high-risk blood phenotype (1/7) or both (1/7), and one belonged to a high-risk ethnic group and also had AIDS. Unlike other invasive mould infections, severe or disseminated infection may occur in otherwise healthy individuals belonging to a high-risk ethnic group or with a high-risk blood phenotype, so evaluation for disseminated disease should be considered in all individuals belonging to one of these a high-risk ethnic groups.

In total, 73% of patients were alive at 90 days. In those who received antifungal therapy (diagnosis was made in one patient postmortem, and one patient was lost to follow-up), four received combination antifungal therapy (including three with disseminated disease) and nine received monotherapy with fluconazole (including three with

disseminated disease). Our cohort was too small to evaluate treatment outcomes by antifungal strategy, and there is no consensus regarding combination antifungal treatment for severe disseminated disease. There is evidence supporting combination therapy for disseminated disease from case reports,[26,27] and in one case, expert opinion recommends combination antifungal therapy with amphotericin B plus a triazole in certain situations, including disseminated disease or in severely immunocompromised individuals.[28] Consensus guidelines are needed to determine clinical situations where combination therapy is warranted and what regimens are recommended.

Limitations of our study include its single-centre design, small sample size, and lack of genetic or HLA data available on these patients. Still, this case series describes clinical characteristics of fifteen cases of acute coccidioidomycosis infection and emphasises that traditional risk factors for invasive fungal infections such as immunosuppression may be insufficient to predict disease or outcome as belonging to a high-risk ethnic group or having a high-risk blood phenotype is associated with disseminated or severe coccidioidomycosis infection. Improved education for clinicians regarding signs and symptoms of coccidioidomycosis, diagnosis, reporting and surveillance will be increasingly important in tracking the spread of coccidioidomycosis,[7] particularly in areas that are not yet endemic to coccidioidomycosis.

CONFLICT OF INTEREST

MH received grant funding from Gilead. Other authors: No conflicts.

AUTHOR CONTRIBUTIONS

Jenks JD and Hoenigl M conceived the idea for this study. Reed SL compiled the data for analysis. Hoenigl M and Jenks JD analysed the data. All authors contributed to the writing, revision and finalisation of this manuscript.

ORCID

Jeffrey D. Jenks https://orcid.org/0000-0001-6632-9587

REFERENCES

1. McCotter OZ, Benedict K, Engelthaler DM, et al. Update on the Epidemiology of coccidioidomycosis in the United States. *Med Mycol*. 2019;57(Supplement_1):S30-S40.
2. Benedict K, McCotter OZ, Brady S, et al. Surveillance for Coccidioidomycosis - United States, 2011–2017. *MMWR Surveill Summ*. 2019;68(7):1-15.
3. Kirkland TN, Fierer J. Coccidioides immitis and posadasii; A review of their biology, genomics, pathogenesis, and host immunity. *Virulence*. 2018;9(1):1426-1435.
4. Teixeira MM, Barker BM. Use of population genetics to assess the ecology, evolution, and population structure of coccidioides. *Emerg Infect Dis*. 2016;22(6):1022-1030.
5. Laniado-Laborin R, Arathoon EG, Canteros C, Muniz-Salazar R, Rendon A. Coccidioidomycosis in Latin America. *Med Mycol*. 2019;57(Supplement_1):S46-S55.
6. Gorris MECL, Zender CX, Treseder KK, Randerson JT.Coccidioidomycosis Dynamics in Relation to Climate in the Southwestern United States GeoHealth.
7. Matlock M, Hopfer S, Ogunseitan OA. Communicating risk for a climate-sensitive disease: a case study of valley fever in central California. *Int J Environ Res Public Health*. 2019;16(18):3254.
8. Thompson GR 3rd. Pulmonary coccidioidomycosis. *Semin Respir Crit Care Med*. 2011;32(6):754-763.
9. Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. *Emerg Infect Dis*. 2017;23(2).
10. Bercovitch RS, Catanzaro A, Schwartz BS, Pappagianis D, Watts DH, Ampel NM. Coccidioidomycosis during pregnancy: a review and recommendations for management. *Clin Infect Dis*. 2011;53(4):363-368.
11. Brown J, Benedict K, Park BJ, Thompson GR 3rd. Coccidioidomycosis: epidemiology. *Clin Epidemiol*. 2013;5:185-197.
12. Ampel NM. Delayed-type hypersensitivity, in vitro T-cell responsiveness and risk of active coccidioidomycosis among HIV-infected patients living in the coccidioidal endemic area. *Med Mycol*. 1999;37(4):245-250.
13. Hall KA, Sethi GK, Rosado LJ, Martinez JD, Huston CL, Copeland JG. Coccidioidomycosis and heart transplantation. *J Heart Lung Transplant*. 1993;12(3):525-526.
14. Cohen IM, Galgiani JN, Potter D, Ogden DA. Coccidioidomycosis in renal replacement therapy. *Arch Intern Med*. 1982;142(3):489-494.
15. Holt CD, Winston DJ, Kubak B, et al. Coccidioidomycosis in liver transplant patients. *Clin Infect Dis*. 1997;24(2):216-221.
16. Ruddy BE, Mayer AP, Ko MG, et al. Coccidioidomycosis in African Americans. *Mayo Clin Proc*. 2011;86(1):63-69.
17. Louie L, Ng S, Hajjeh R, et al. Influence of host genetics on the severity of coccidioidomycosis. *Emerg Infect Dis*. 1999;5(5):672-680.
18. McCotter O, Kennedy J, McCollum J, et al. Coccidioidomycosis Among American Indians and Alaska Natives, 2001–2014. Open Forum. *Infect Dis*. 2019;6(3):2001-2014.
19. Santelli AC, Blair JE, Roust LR. Coccidioidomycosis in patients with diabetes mellitus. *Am J Med*. 2006;119(11):964-969.
20. Blair JE, Mayer AP, Currier J, Files JA, Wu Q. Coccidioidomycosis in elderly persons. *Clin Infect Dis*. 2008;47(12):1513-1518.
21. Galgiani JN, Blair JE, Ampel NM, Thompson GR. Treatment for early, uncomplicated coccidioidomycosis: what is success? *Clin Infect Dis*. 2019.
22. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63(6):e112-46.
23. Hoenigl M, Gangneux J-P, Segal E, et al. Global guidelines and initiatives from the European Confederation of Medical Mycology to improve patient care and research worldwide: New leadership is about working together. *Mycoses*. 2018;61(11):885-894.
24. Blair JE, Balan V, Douglas DD, Hentz JG. Incidence and prevalence of coccidioidomycosis in patients with end-stage liver disease. *Liver Transpl*. 2003;9(8):843-850.
25. Weatherhead JE, Barrows BD, Stager CE, Finch CJ, El Sahly HM. Gastrointestinal coccidioidomycosis. *J Clin Gastroenterol*. 2015;49(7):628-629.
26. Antony SJ, Jurczyk P, Brumble L. Successful use of combination antifungal therapy in the treatment of coccidioides meningitis. *J Natl Med Assoc*. 2006;98(6):940-942.
27. Park DW, Sohn JW, Cheong HJ, et al. Combination therapy of disseminated coccidioidomycosis with caspofungin and fluconazole. *BMC Infect Dis*. 2006;6:26.
28. Ampel NM. The treatment of coccidioidomycosis. *Rev Inst Med Trop Sao Paulo*. 2015;57(Suppl 19):51-56.

How to cite this article: Jenks JD, Reed SL, Hoenigl M. Risk factors and outcomes of culture-proven acute *Coccidioides* spp. infection in San Diego, California, United States. *Mycoses*. 2020;63:553–557. https://doi.org/10.1111/myc.13074