

## Research Article

# Relapse and Its Relationship with Treatment in Patients with Coccidioidomycosis in Tijuana

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## Abstract

**Background:** In Mexico, the proportion of patients with coccidioidomycosis who respond favorably to antifungal treatment is unknown, according to the American Society for Infectious Diseases, there is no consensus on the duration of treatment.

**Aim:** To determine the relationship between relapse of coccidioidomycosis and its treatment at Hospital General Regional #20 (HGR 20) of Tijuana, Mexico.

**Design and Setting:** Analytic cross-sectional study.

**Methods:** Analytical cross-sectional study. A census of 49 patients with diagnosis of coccidioidomycosis in the HGR 20 in Tijuana was carried out, during January 2017 to December 2018. Descriptive and inferential statistics were used; in the association of variables a logistic regression analysis with a confidence interval of 95% was made ( $p < 0.05$ ).

**Results:** 49 patients with coccidioidomycosis were included, 65% ( $n=32$ ) women and 35% ( $n=17$ ) men, 34.7% ( $n=17$ ) had relapse of the disease. Relapse association was observed with the following variables: treatment with fluconazole ( $p=0.001$ ), treatment less than 12 months ( $p=0.017$ ) and use of steroids ( $p=0.004$ ).

**Conclusion:** The positive association between relapses and the type of antifungal, as well as the duration of treatment was verified.

**Keywords:** Coccidioidomycosis; Relapse; Fluconazole

## Introduction

Coccidioidomycosis is a severe systemic mycosis caused by two dimorphic fungi species *Coccidioides immitis* and *Coccidioides Posadasii*. Both species of *Coccidioides* grow as mycelia in the soil and produce air-borne arthroconidia that can be inhaled by susceptible hosts, the fungus undergoes a morphological change to spherules that produce and release endospores that can be eliminated, inactivated or progress to a pulmonary or disseminated mycosis [1]. After arthroconidia are inhaled, the incubation time before symptoms is 7 to 28 days [2]. Risk factors for disseminated coccidioidomycosis include exogenous immunosuppression (steroids and biologics drugs), pregnancy, race, and genetic defects [3].

It is estimated that 60% of infected people are asymptomatic or develop mild symptoms, the remaining 40% have various symptoms and conditions that can include weeks or months of fatigue, dyspnea, cough, fever, night diaphoresis, loss of appetite and weight, chest pain, headache, skin rash and pneumonia. Less than 5% of patients develop disseminated disease [4]. The diagnosis of coccidioidomycosis is made through epidemiological and mycological studies, complemented by histopathological, immune and molecular studies [5]. Current guidelines recommend the treatment of patients with immunosuppression, significant comorbidities, those with prolonged infection and with complement fixation that exceed 1:32. Other

factors include weight loss of more than 10%, nocturnal diaphoresis for more than 3 weeks, infiltrates of more than one-half of one lung or portions of both lungs and prominent or persistent hilar adenopathy [6].

In treatment, fluconazole has excellent bioavailability, few drug interactions, and is well tolerated even at high doses. It has been shown to be effective for the treatment of coccidioidomycosis and is the preferred agent for pulmonary and central nervous system disease [6]. The efficacy of itraconazole for extrapulmonary disease and chronic infection is well established and it is the preferred therapy for skeletal disease. The role of the newer azoles, voriconazole, posaconazole and isavuconazole in the care of coccidioidomycosis has not yet been defined due to cost concerns when these drugs are used as primary therapy. The duration of therapy varies according to the site and severity of the disease [6-7].

Relapses occur 6 to 12 weeks later after stopping treatment, with elevation of complement fixation. In chronic pulmonary coccidioidomycosis, it occurs in 30% of cases, regardless of the duration of treatment or the agent used; for this reason, the patient must be strictly monitored to identify the time to restart treatment. In Mexico, the proportion of patients who have responded favorably to treatments is unknown [8], therefore, the main objective of the research was to determine the relationship between relapse of

coccidioidomycosis and its treatment in the HGR 20 of Tijuana.

## Material and Methods

### Study design and population

An analytical cross-sectional study was conducted with patients diagnosed with coccidioidomycosis at the HGR 20 of the Instituto Mexicano del Seguro Social (IMSS) in Tijuana, Mexico, during January 2017 and December 2018. Patients older than 18 years, HGR 20 users diagnosed with coccidioidomycosis according to the International Classification of Diseases (ICD-10) were included; the exclusion criteria were pregnancy and abandonment of treatment, patients with incomplete information or death were eliminated.

### Variables

The study variables were classified as sociodemographic and clinical; the sociodemographic variables were place of birth, time living in Tijuana, nationality, marital status, occupation, school grade; the clinical variables were age, sex, comorbidities, site of infection, clinical and radiological follow-up and type of treatment; this last variable identified the type of azole administered, dose, duration of treatment, relapses, and treatment after relapse. Since there is no definition of relapse in these patients, relapse was defined as the presence of signs and symptoms of the disease, 6 weeks after completing treatment indicated by the treating physician [8].

### Statistical analysis

Descriptive statistics with measures of central tendency and dispersion for quantitative variables were used, frequencies and percentages for qualitative variables. Chi square analysis and multivariate logistic regression were used for inferential statistics with the statistical program SPSS version 21 in Spanish.

### Ethics

The study was approved by the local committee of ethics and health research number 204; with registration number R-2019-204-025. The research was conducted under the general health law on health research, the Helsinki declaration and bioethical principles.

## Results

The baseline characteristics of the population are shown in Table 1. Of the 49 patients, 65% (n=32) were women and 35% (n=17) were men, the age range was 18-86 years with a median 54 years old. Pulmonary presentation was the most frequent with 93.9% (n=46), followed by cutaneous with 4.1% (n=2) and one patient with bone disease. In the treatment received, 55.1% (n=27) of the patients received fluconazole and 44.9% (n=22) itraconazole. In the antifungal dose, 73.5% (n=36) received 400-600 mg per day, 16.3% (n=8) received 200-400 mg per day, 6.1% (n=3) a dose greater than 600 mg per day and only 4.1% (n=2) a dose less than 200 mg per day. The duration of treatment with the antifungal was a median of 12 months, with a minimum of 3 months and a maximum of 300 months (patient with a diagnosis of bone coccidioidomycosis). Of the 49 patients, 34.7% (n=17) presented relapse of the disease.

In the associated comorbidities (graphic 1) it was observed that 42.9% (n=21) of the patients had a comorbidity independent of the diagnosis of coccidioidomycosis, 28.6% (n=14) two comorbidities, 14.3% (n=7) had more than 3 comorbidities and 14.3% (n=7) had no

**Table 1:** Basal characteristics of patients.

Variables	n	%
Sex		
Male	32	65
Female	17	35
Birth place		
Tijuana	25	51
Another state	10	20
No data	14	29
Cohabitation		
Nuclear Family	1	2
Procreative family	42	86
No family	1	2
No data	5	10
Occupation		
Employee	20	41
Housewife	12	25
Retired	5	10
Another jobs	12	24
Schooling		
No education	1	2
Primary	18	37
Secondary	6	12
High school	7	14
University	2	4
No data	15	31

n=frequency, %=percentage

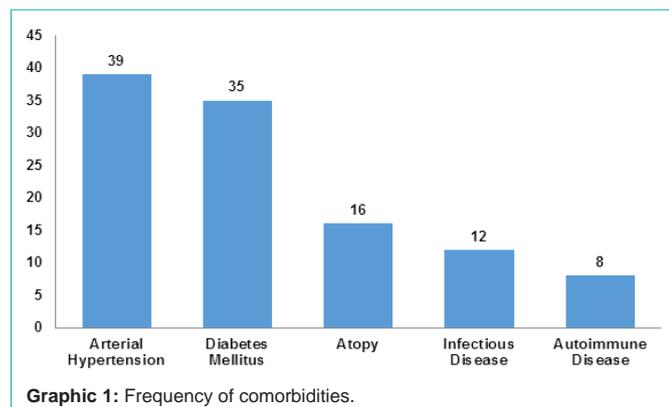
**Table 2:** Associated variables to relapse of coccidioidomycosis.

Variables	β	p	Exp (β)	95% CI
Fluconazole	3.2	0.005	26.9	2.7-266.4
Treatment <12 months	1.8	0.01	6.5	1.3-31.0
Steroid use	2.9	0.009	18.8	2.0-173.5
Diabetes Mellitus	2.3	0.003	10	2.1-45.6

p= logistic regression, Exp (β)= Odds ratio, CI= Confidence Interval

associated comorbidities. When analyzing our categorical variables through Chi-square test, the association between relapses and the type of antifungal prescribed at the beginning of the diagnosis was studied, finding statistical significance for treatment with fluconazole (p=0.001). We also found statistical significance when it was associated with a duration of treatment less than 12 months (p=0.017) and finally relapses were associated with the use of steroids (p=0.004).

Multivariate analysis was performed through logistic regression to evaluate the probability of relapse with the independent variables studied (Table 2). Statistical significance was found between relapse and fluconazole treatment (p=0.005), steroid use (p=0.009), treatment time less than 12 months (p=0.018) and comorbidity with diabetes mellitus (p=0.003). Of all the variables studied, the one with the greatest strength to explain relapses in our patients was the use of fluconazole.



## Discussion and Conclusion

According to Santelli et al., patients with diabetes mellitus had a higher probability of relapse (RR 3.39,  $p < 0.003$ ) compared to patients without this disease [9], a result similar to our study where it was established the relationship between relapses and the diagnosis of diabetes mellitus. The American Association for Infectious Diseases in their guideline about treatment of coccidioidomycosis mentions that the use of steroids at high doses is associated with an increase in severe and extra pulmonary coccidioidomycosis [7], in agreement with our study, the relationship between relapses and the use of steroids was found.

In the study by Oldfield et al., a relapse rate of 25-35% was demonstrated after the apparent success of treatment with azoles [10], compared with our study the relapse rate was 34.7%. In the same study, a higher percentage of relapses was observed for fluconazole (37%) versus Itraconazole (16-25%), this was also demonstrated in the study by Galgiani et al., where the percentage of relapses for fluconazole was higher than itraconazole; 28% and 18% respectively [11], a result similar to our study. Galgiani et al., found that the duration of antifungal treatment has not yet been established, 3 to 6 months of treatment or more is recommended according to clinical situation of the patient; although there is no standardization in the treatment time [7], in our study statistical significance was found between relapses with treatment less than 12 months.

It was possible to demonstrate a positive association between relapses of coccidioidomycosis and its treatment based on the type of azole and duration, the main objective of the research. In conclusion, an association was found between relapses, the use of steroids and having diabetes mellitus. Therefore, during the medical evaluation we should consider using itraconazole over fluconazole (if there are no contraindications) and a longer duration of treatment in patients diagnosed with coccidioidomycosis who have risk factors for relapse.

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