



Coccidioidomycosis

STUDY GROUP

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Abstract 1: Neuroimaging in Coccidioidal Meningitis

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The neuroimaging studies Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) of 60 patients with coccidioidal meningitis from the clinic for coccidioidomycosis at Kern Medical Center were reviewed. Patients ranged in age from 17 to 78 years with a mean of 34. Two patients were known to be HIV positive, 41 were negative and 20 were unknown. Forty eight were male and 15 female. Forty one of these individuals are alive, 14 have expired and eight are lost to follow up. Forty-nine of the 63 patients had magnetic resonance imaging, the remainder computerized tomography only.

The most common abnormal finding was hydrocephalus which was found in 27 of 60. The majority of these required a ventriculo peritoneal shunt. Presenting symptomatology was most often ataxia and confusion. The cerebrospinal protein was substantially higher in those with hydrocephalus. The mortality in the hydrocephalus group was approximately 50%.

Twenty-one patients were identified as having basilar meningitis. Thirteen by MRI, six by MRI and CT and two with CT only. Thirteen of 21 individuals with basilar meningitis had coexistent hydrocephalus. Of the 21 individuals with basilar meningitis, 17 are alive, two expired and two are lost to follow up.

Twenty individuals were identified to have cerebral vasculitis or infarct secondary to coccidioidal meningitis. This finding was documented in nine patients by MRI, five patients by CT and six patients by CT and MRI. One brain abscess was identified, nine individuals with vasculitis or infarct are currently alive and on treatment, nine have expired and two are unknown.

Neuroimaging is a crucial part of the diagnosis and evaluation of individuals with known or suspected coccidioidal meningitis. Particularly the finding of basilar meningitis and the complications of hydrocephalus, vasculitis and cerebral infarction associated with coccidioidal meningitis can best be appreciated by neuroimaging. The MRI would appear to be the more sensitive tool for the evaluation of basilar meningitis vasculitis and infarct.

Abstract 2: Forme Fruste Coccidioidal Meningitis

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Patients with documented evidence of coccidioidomycosis and equivocal findings of meningitis have been noted for many years. Presented here are ten patients seen since 1987 with apparent forme fruste meningitis with and analysis of epidemiology, clinical presentation, laboratory findings and outcomes.

Patients ranged in age from 17 to 54 years with a mean of 28. One was Caucasian, five Latino, three African-American, and one other racial group. None of the cases were HIV positive. Half the patients were male and half were female. Ninety percent of patients had respiratory symptoms and abnormal chest films, disseminated skin disease was present in three, pregnancy in two, and a positive skin test at the time of study in six out of nine. The serum CF titer at the time of presentation ranged from 1:2 to 1:32. Two individuals had a titer of 1:2, two a titer of 1:4, one a titer of 1:16, and four a titer of 1:32. Central nervous symptoms in the ten patients at the time of presentation included headache in seven, neck pain in three, dizziness in five, and visual disturbance in three. CSF pleocytosis was noted in all subjects. Two had between five and 10 cells, two had 11 to 20 cells, four had 21 to 30 cells, and one had an initial CSF with greater than 200 cells, which rapidly declined to lower numbers. Treatment rendered to this group included fluconazole 400 to 1000 mg in seven and intrathecal amphotericin B and fluconazole in two individuals. One patient was untreated. The most recent CSF examination in these individuals revealed zero to 10 white cells in seven patients, greater than 30 cells in two patients, and one patient was not re-evaluated. The outcomes in these individuals show three persons on therapy with no evidence of active disease, one is not treated and asymptomatic, three that are off therapy for greater than four months and asymptomatic with normal CSF, two patients are on therapy without symptoms but continue to have an abnormal CSF, and one individual that has been off therapy for approximately six months and lost to follow-up.

Conclusion: Forme fruste meningitis is fairly common in a large population of patients with other manifestations of coccidioidomycosis. Those with other sites of disseminated disease may be more likely to develop severe meningitis. No single or combination of clinical or laboratory parameters unequivocally yields a firm diagnosis or prognosis in patients with modest pleocytosis.

Abstract 3: Coccidioidal Cutaneous Lesions Predictive of Meningitis

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The clinical association of coccidioidal face lesions with meningitis has never been studied due to a low incidence of cases. The recent epidemic of coccidioidomycosis in Kern County, California, provided an opportunity to study this relationship.

A retrospective study identified 26 cases of cutaneous dissemination. These were divided into three categories; lesions above the mandible only, lesions below the mandible only, or both. To be included: histopathologic or micro biologic confirmation of the lesion were required. The study group consisted of 18 males and eight females of which 50% were African-American, 38% Latino and 11% Caucasian or Asian. In comparing the group with meningitis (n=9) to those without meningitis (n= 17) face only lesions were found in 44% vs. 6% lesions on the face and body and 22% vs. 35% and body only lesions in 33% vs. 58% respectively. Serum CF titers were unrevealing. Skin tests were negative in 16 patients, unknown in seven and positive in three. These three had lesions only below the mandible and never developed meningitis. Meningitis occurred in four of the five patients with facial only lesions (80%). In those with both lesions (n=13), only four (25%) developed meningitis. Those with body only lesions (n=8) had a similar rate (23%). There was a statistically significant association with face lesions compared with patients in the other two categories. (Odds ratio 12.8, p=0.03).

CONCLUSION: Eighty percent of patients with lesions occurring only on the face experienced meningitis. This is significantly different from the 25% rate in those with lesions above and below the mandible and the 23% rate when lesions were only on the body.

Abstract 4: Efficacy of Two Novel Morpholines UR-9746 and UR-9751 against Systemic Murine Coccidioidomycosis

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UR-9746 and UR-9751, novel azole derivatives containing a morpholine ring (Uriach), were examined for in vitro and in vivo activity against *Coccidioides immitis*. In vitro, UR-9746 and UR-9751 were active against *C. immitis*, Silveira, with MICs of 25 and 3.1 ug/ml, respectively. However, the MFCs for both drugs were >100 ug/ml. Systemic disease was established in 6-week old female CD-1 mice by iv injection of 232 arthroconidia of *C. immitis*. Therapy with doses of UR-9746, UR-9751, fluconazole (F), carboxymethyl cellulose diluent or no Rx were given QD, PO on days 4-24 postinfection. Eighty to 100% of mice given >10 mg/kg of UR-9746 or UR-9751 or 100 mg/kg of F survived through day 49, whereas 0 to 10% given 1 mg/kg of UR-9746 or UR-9751, 10 mg/kg of F, diluent or no Rx survived. Ten or 100 mg/kg of UR-9746, UR-9751 and 100 mg/kg of F were equivalent and superior to all other regimens (P<.05-.001). Determination of residual burdens in the spleen, liver and lungs showed that UR-9746 and UR-9751 dose-responsively reduced infection. However, no treated mice were free of infection in any organ other than the spleen; UR-9746 at 100 mg/kg (1/10) and UR-9751 at 100 mg/kg (3/10). UR-9746 at 10 or 100 mg/kg were superior to 100 mg/kg of F in the reduction of burden in all organs (P<.05-.001). UR-9751 at 10 mg/kg was better than 100 mg/kg of F in the spleen or liver (P < .05-001) and 100 mg/kg of UR-9751 better in all organs (P<.001). In summary, both UR preparations lacked observable toxicity and were >10-fold superior to F in prolonging survival and clearing *C. immitis*. These results indicate that UR-9746 and/or UR-9751 should be further tested in other models of fungal infection, and considered for clinical trials in coccidioidomycosis.

Abstract 5: the Pharmacoeconomics of Early Azoles in primary Coccidioidomycosis

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Medical records from over 600 patients with coccidioidomycosis was analyzed retrospectively for medical costs, utilization of medical services and treatment and outcome. Early azole treatment in a previous evaluation was associated with a 68% reduction in serious illness. To evaluate whether early treatment (within 30 days of symptoms) for all patients would save money, a cost-benefit pharmacoeconomic model was developed comparing ketoconazole to fluconazole and itraconazole each at 400mg/day in a population of 358 patients with mild to moderate symptoms who were untreated in the first month of illness.

Patients were grouped into low (n=247), medium (n=75) and high (n =36) risk groups based on age and complement fixation titer. The rate of serious illness occurring over one year was 2.0%, 9.3% and 19.4% respectively. Drug treatment duration was projected from duration of symptoms to range from 2-5 months. A reduction in serious illness was estimated at 50%, thus benefitting 1/100 (low risk), 4/100 (medium risk) and 10/100 (high risk) of those treated.

Cost benefit analysis revealed cost savings in the medium and high risk groups. Ketoconazole was projected to save \$57,000 (medium risk) to \$368,000 (high risk) over 2 years in medical costs. Itraconazole or Fluconazole was projected to save \$113,000, but only in the high risk group.

Conclusion: Ketoconazole appears cost beneficial in patients over 40 years of age with primary coccidioidomycosis who in standard practice would not receive early treatment.

Abstract 6: The Association of Age and Mortality in Coccidioidomycosis

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Objective: To evaluate the association of age and other factors with survival in patients with coccidioidomycosis.

Design: Retrospective chart review of 536 patients with a diagnosis of coccidioidomycosis

Setting: Kern County California.

Patients: 536 patients of a population of 913 diagnosed with coccidioidomycosis between September 1, 1991, and December 31, 1991.

Results: Seventeen of 536 patients (three percent) diagnosed with coccidioidomycosis expired during the observation. Eleven of the patients who died were over the age of 65. This represents 26.8% of the patients over the age of 65 in the epidemic, and it is a significantly higher mortality rate when compared with 1.2% (6/495) of patients under the age of 65 who expired ($p < 0.001$). The mean age of patients who expired overall was 63.1 years compared with 36 years on those who survived ($p < 0.001$). *Diabetes mellitus* and chronic illness were more common in patients over the age of 65 who expired.

Conclusions: In symptomatic coccidoidomycosis occurring in a community population, a mortality of rate of three percent was observed. Of the characteristics reviewed in this study, age was significantly associated with mortality (26.8% mortality with age of 65 or greater vs. 1.2% for those less than 65). Physicians should be aware of the increased risk in this population and manage cases aggressively.

Abstract 7: Coccidioidomycosis and Pregnancy: The Kern County Experience

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There has long been an association between pregnancy(P) and the prognosis of coccidioidomycosis(C). It has been noted that individuals who acquire primary coccidioidal disease in the third trimester or postpartum experience increased severity of illness, dissemination and death. Because of this, an analysis of (P) patients taken from the recent coccidioidal epidemic in Kern County was initiated. Birth records were compared with new discrete positive serologic results as reported from the laboratory of the Kern County Health Department. Medical records of these cases were entered and evaluated on Epi Info Version 5.0.

Forty-nine individuals with (P) and (C) were identified from the 1993 data set. Total pregnancies for 1993 in Kern County were 12,529. The epidemiology of the (P) population with and without (C) will be presented. The attack rate for (P) and non(P) female individuals between the ages of 15 and 45 were not statistically different. Sixty-eight symptomatic collected from 1987 through 1994 were identified. Disease occurred most frequently in the third trimester (40%), followed by the second trimester (21%), then by the first trimester (16%). There was no difference in complement fixation titers between (P) and non(P) females. Fifty-seven percent of symptomatic cases did well without treatment. Of the 29 treated cases, there was a trend toward decreased dissemination and chronic treatment when therapy was given during (P) as compared to post-partum. Dissemination occurred in 16% of symptomatic cases. Meningeal dissemination was a more frequent dissemination site in (P) than in non(P) females from the clinic. Individuals with an initial negative skin test had a substantially greater risk of dissemination and the need for chronic treatment than did individuals with positive skin tests. Patients with CF titers greater than or equal to 1:64 also had a greater risk of dissemination and the need for chronic treatment. The risk for dissemination and chronic treatment was not different between those acquiring disease between the third trimester and earlier in (P).

Abstract 8: Cerebral Spinal Fluid Complement Fixing Antibodies Without Meningitis

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Many prior investigators enunciated that complemented fixing (CF) antibodies in the cerebral spinal fluid (CSF) unequivocally diagnose meningeal dissemination of coccidioidomycosis. The Bakersfield group has noted exceptions to this for many years. Ten recent cases are offered. These patients range in age from 19 to 59 years with a mean of 35. Two are Caucasian, five are Latino, and two African-American. One patient was noted to be HIV positive, seven were negative and the results in two were unknown. MI patients had an abnormal chest x-ray and 50% experienced respiratory symptoms. Disseminated disease was present in 80%, and headache was noted in 50%. Central nervous system symptoms were absent in the remainder. All patients had negative initial skin tests. The serum CF titer at the time of presentation ranged from a low of 1:32 to a high of 1:512. Eight of the 10 patients had titers of 1:128 or higher.

Cerebral Spinal Fluid CF antibody titers ranged from 1:1 to 1:8. There was no correlation between the height of the serum titer and the CSF titer. Five patients had titers of 1:1, one had a 1:2, 1:4 was present in two, and two had a 1:8. CSF pleocytosis was absent by definition in all patients.

Nine of the 10 patients remain free of meningitis. One patient, who is HIV positive, developed meningitis subsequent to the initial evaluation.

Conclusion: Small to moderate amounts of complement fixation antibody in the CSF in the absence of other indicators of meningitis are not necessarily diagnostic of meningeal disease.

Abstract 9: Detecting Antibodies Against a 33kDa Antigen in Serum and CSF of Patients with Primary Infections or Meningitis

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In patients (pts) undergoing evaluation for coccidioidomycosis, at least one serum was obtained from 138 pts with an illness suggestive of recent infection. In this group, conventional tests were positive in 25, and 49 additional pts had 1 or more reactive test results obtained from Premier® EIA or anti-33 kDa ELISA. At least 11 of these 49 pts had coccidioidomycosis as determined by culture or subsequent conventional serologic conversion. Pts identified only by EIA or ELISA had fewer or milder clinical abnormalities than did pts detected by conventional tests. EIA IgM and IgG results qualitatively mimicked TP and CF results, resp., but quantitative correlations were poor.

In other studies, anti-33 kDa antibodies were detected by ELISA in pts' cerebrospinal fluid (CSF). Anti-33 kDa antibodies were detected at dilutions >1:80 in only 1 of 73 (1.4%) pts without coccidioidal meningitis, but in 74 of 103 (71.8%) with meningitis. Anti-33 kDa antibodies were detected in 53 of 58 pts (91.4%) whose anticoccidioidal complement fixing (CF) antibodies were detectable, and in 21 of 45 (46.7%) pts whose CSF was negative by CF (positive predictive value = 99%; negative predictive value = 71 %; sensitivity = 72%; specificity =99%). Anti-33 kDa antibodies, among which IgG-1 was the dominant immunoglobulin subclass, increased when infections worsened, and decreased when pts improved. Antibody concentration appeared to be independent of most baseline findings although only 1 of 5 pts co-infected with the human immunodeficiency virus had initially detectable antibodies. Detecting anti-33 kDa antibodies is a sensitive indicator of coccidioidal meningitis and of its clinical course.

Abstract 10: Canine Coccidioidomycosis: Correlation between Initial Complement Fixation Titer level and Extent of Disease at the Time of Diagnosis

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A survey of canine cocci positive CF titers submitted to Southwest Veterinary Diagnostics by Arizona veterinarians was performed from 1-15-94 to 6-15-94. A total of 386 cases were followed. Of these there were 154 (42%) with respiratory disease; 126 with suspected primary pulmonary and 28 with disseminated pulmonary infections. Of the 123 (32%) cases with bone disease, 96 had single lesions and 27 had multiple bone lesions. There were 24 (6%) cases with known dissemination; respiratory disease and at least one other area of infection (eye, skin, testicle, bone or neurological). The remaining 84 (22%) cases were unclassified as to infection type.

Initial titer levels at the time of diagnosis were 1:16 or greater in 59% of suspected primary respiratory cases, 92% of suspected disseminated respiratory cases, 65% of bone cases, 57% of disseminated cases, and 84% of unclassified cases. Acceptable clinical cures were achieved with single or combined imidazole therapy in 30% of respiratory cases, 14% of bone cases, 16% of disseminated, and 23% of unclassified cases. The mean treatment duration to cure was 11.2 months in respiratory cases and 19.4 months in bone cases; and 17.5 months for the unclassified cases. No difference in efficacy was noted between imidazole types. The majority of cases were treated with ketoconazole.

Abstract 11: Coexisting Pulmonary Coccidioidomycosis and Tuberculosis

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Pulmonary tuberculosis is always in the differential diagnosis of a patient presenting with a cavitary lesion. In an endemic area for valley fever, infection with *Coccidioides immitis* must also be considered. Previous papers have stressed the coexistence of both diseases when a cavitary lesion is the presentation.

We conducted a retrospective review of medical records at Kern Medical Center from 1992 to 1994. Cases were selected from the pulmonary, Tuberculosis and Valley Fever clinics if they had proven tuberculosis (bacteriologic) and valley fever (serologic or culture proven). These were further divided into those that had concurrent infections. A total of 28 patients were identified that fit the criteria and of these eight had concurrent infections. The findings on these eight patients is as follows: seven males, one female, all were of Hispanic origin. The ages ranged from 24 years to 47 years. The diagnosis of concurrent illness was made within a month of the index diagnosis for five of the patients, the remainder were diagnosed after four months. The skin test was positive for PPD in six and for Coccidioidin in five. The CF titer at presentation ranged from 1:2 to 1:64. There were two peaks: at 1:4 and 1:32. The chest x-ray findings at presentation included: lobar infiltrate (2), cavity (1), patchy infiltrate (1), fibro-cavitary changes (2), lung mass (1), mediastinal mass (1). The x-ray location was biapical (4), left upper lobe (1), L apex (1), bilateral (1).

CONCLUSION: Tuberculosis and valley fever can exist in the same patient at remote instances. Twenty-eight patients in a two year period meeting those criteria were treated at Kern Medical Center. However a concurrent infection is frequent (28% of the patients) and can be diagnosed within one month of the index case. The x-ray presentation was varied with the majority presenting as a cavity or fibro-cavitary changes, but infiltrates, masses and mediastinal masses were also seen. Careful evaluation for both diseases should be routine in areas where valley fever is endemic and a patient presents with tuberculosis regardless of immune status

Abstract 12: Musculoskeletal Coccidioidomycosis

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Coccidioidomycosis is a fungal infection endemic to the southwestern United States. Reports of musculoskeletal involvement are rare with no specific recommendations established for treatment, especially in the pediatric population. The purpose of this study was to review a series of patients with musculoskeletal coccidioidomycosis, to assess their outcomes and to determine logical protocols for treatment. The medical records, laboratory data and radiographs of 23 patients were reviewed. Demographic factors, mode of presentation and scope of treatment were noted. Among the 23 patients there were 34 lesions, including seven in the spine, three each in the knees and feet, with the remainder distributed throughout the body. Sixteen had a delay in diagnosis of at least one month. All patients underwent biopsy and culture with 22/23 undergoing formal irrigation and debridement. Amphotericin B was the primary pharmacologic agent utilized, typically a dose of one gram over a period of six months to a year. The average follow up was three years four months, ranging from seven months to 10 years. Eighteen of the 23 patients were free of infection at final follow up, but six patients had recurrent lesions that required further surgical intervention. In this series there were three fulminant, fatal cases. Because coccidioidomycosis involving the skeleton is so rare, it is often overlooked. Fortunately, successful treatment of this condition is possible, even after a delay in diagnosis. We found that an evaluation with CT and MRI was helpful in planning the initial debridement and that complement fixation titers were useful in determining the efficacy of therapy. Amphotericin B toxicity was a commonly encountered complication. Therefore, treatment should be individualized and carefully monitored. Patients need to be followed over a prolonged period of time as recurrences were frequent.