



Coccidioidomycosis

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Abstract 1: Soil Isolation of *Coccidiodes immitis*

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Coccidiodes immitis, the causative agent of Valley Fever, has been isolated from the environment on several occasions (Egeberg, 1956; Omieczynski, 1967; Kemp, 1974; Lacy, 1974) but never without the utilization of a mammalian host. A protocol for the isolation and identification of *C. immitis* based on DNA sequence has been developed. It is being used to obtain environmental samples for population genetic analysis, mating experiments and virulence studies.

535 soil samples from throughout the San Joaquin Valley were obtained in the spring of 1997. Samples were plated using Swatek's double pour method (Omieczynski, 1967) and incubated under biocontainment. Cultures were heat killed in lysis buffer and DNA extracted using a modified fungal DNA extraction protocol (Lee and Taylor, 1990).

Cocci specific primers were designed based on the noncoding ITS sequence of rDNA and were tested with 40 clinical cocci isolates and 20 various other fungi to ensure specificity and sensitivity. From the 535 soil samples over 1000 fungal isolates were obtained. 27 isolates were identified as *Coccidiodes* using the ITS primers. They were further checked by sequencing 2 satellite regions and the ITS 1, 5.8S and ITS 2 region of DNA. 16 of the 27 isolates were successfully subcultured and are being prepared for virulence testing. Four of the isolates are being used in mating experiments.

Coccidiodes is not an obligate pathogen. As a saprobe, it is free living in the environment and does not require a host as part of its life cycle. The isolation of environmental samples that have not infected a host, and thus have not caused disease, makes possible a wide range of population genetic studies to estimate its genetic diversity, to ascertain if different strains are infecting different hosts, to determine rates of recombination in nature and to further elucidate the ecology of the organism.

Abstract 2: Molecular epidemiology of the Bakersfield coccidioidomycosis epidemic: genetic diversity within a recombining population.

M.C. Fisher, D. Carter, G. L. Koenig, T.J. White and J. W. Taylor

Between September 1991 and January 1994 the San Joaquin Valley experienced an epidemic of coccidiomycosis characterized by increases of up to 10X the expected case rate. Clinical samples collected over this time period provide the raw material for a population genetic analysis of patterns of infection and the ecology of *Coccidioides immitis*. Here, we used 11 polymorphic loci to genotype 40 isolated of *C. immitis* collected, during the epidemic, by the Kern medical center. Polymorphisms in nine loci consisted of single base substitutions or small insertions/deletions, and were scored by digestion with restriction endonucleases. Two loci were highly polymorphic repeat sequences (microsatellite 621.2 and minisatellite B34) and were scored as length polymorphisms. Analysis of the data set shows high levels of genetic variation with a total of 36/40 unique genotypes recovered. Although meiotic structures have yet to be observed in *C. immitis*, linkage between loci was not found suggesting that these isolates are sampled from a sexually reproducing population. From these data, it appears that the epidemic was largely composed of a random sample of *C. immitis*, and that no single clone predominates. However, identical duplicated genotypes were observed and further investigation will show whether these isolates originated for the same, or different foci of infection.

Abstract 3: The Characterization of a Tc1 -Like Transposase in *Coccidioides immitis*.

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During the analysis of the Proline Rich Antigen (PRA) gene, a region with homology to a Tc1 transposable element was discovered upstream of the PRA open reading frame. This area of homology has been cloned from a lambda library of the Silveira strain of *Coccidioides immitis*. We have named this sequence Tcim1 for transposon *C. immitis* 1.

The transposon is approximately 1.8 kb in size, and contains a single open reading frame with homology to the Tc1 class of transposases. Inverted terminal repeats of 29 bp flank this transposon, which is characteristic of this class of elements. The element has been sequenced and two introns have been identified. DNA hybridization analyses have shown variation in the copy number among strains of *C. immitis*, ranging in copy number from no copies to eight copies. Different intensities of hybridization are seen in California-type isolates in comparison to Arizona-type isolates and could represent differences in their sequence as a result of genetic divergence. Further analysis of sequence differences among strains of *C. immitis* will allow for improved classification. Once other copies of the element have been cloned and analyzed for differences in sequence, further analysis of these clones may lead to the identification of an active copy of the element that could be used for insertional mutagenesis. Such a transposable element could be a valuable tool for the study of the biology of the organism.

Abstract 4: Coccidioidomycosis (cocci) in Tulare County Calif.

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Tulare County is the location for significant numbers of cases of (coccy). The first case reported from this county was a 26 y/o Mexican woman from Dinuba who developed coccy in 1925 and died of the disease 2.5 years later. By 1931, Tulare County was the site of numerous cases in humans and non-human animals. In a study of Valley Fever in Kern and Tulare Counties in 1937-1939, Smith noted that almost 20% of the cases were from Tulare County, and the disease had a higher incidence in the south central part of the County (which includes the town of Porterville) than in more northerly areas.

Our own serologic surveillance (1987-1997) detected significantly more cases than were being reported to the Calif. Dept. of Health Services (CSDHS), ours ranging from 67 cases in 1988 to 565 in 1992. The ratio of cases detected by us to those reported the CSDHS ranged from 204/32 in 1991 to 169/143 in 1995, the improved reporting in the mid- 1990's due to efforts of the Tulare County Health Dept. During our surveillance in 1991, the south central portion of the county (area around Porterville) had an attack rate of 110/100,000 compared with 65/100,000 population in more northerly areas for 1991 (Durry et al, 1997, J.Med.Vet.Mycol.). The town of Porterville, representing only 10% of the population of the County, contributed from 31 to 51% of the total for the County. Some factors which may influence the relatively large contribution from Porterville: proximity to the foot of the mountains (Sierra Nevada) a barrier which may lead to accumulation of airborne particles from the Valley, abundant water for growth of *C. immitis* (runoff from mountains, and Tule River), nature of the soil (e.g. granitic) near the base of the mountains, and continued 3% annual new population growth.

***(We thank Stanley Bissell, CSDHS, for assistance with the cases reported to CSDHS.)**

Abstract 5: What's the actual incidence of cocci?

Thomas R. Larwood, M.D.

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These broad figures, with data to support them, were generally accepted by the group:

- ~12.5% of people **infected** (have a positive skin test) become **cases** that "are sick enough to go to the Dr."

(about 1/8 of those infected)

- ~4-5% of the **cases** **DISSEMINATE**
~1/160-1/200 of those infected

Based on Kern County's figures that 4.7% of cases disseminate and about 1/4 of those who disseminate die,

- ~1/667 (**~0.15%**) of those infected die of cocci
- Galgiani finds that ~5% of **cases** disseminate and ~1/10 - 15 of those who disseminate die of cocci (0.03 - .05% of those infected).
- There are about as many more cocci deaths from non-disseminated cocci as from disseminated disease, suggesting that ~0.06 - 0.1% of those infected die of coccidioidomycosis.

Proposed working estimate: *~0.1% or ~1/1000 of those infected DIE of cocci*

Applying these figures to the reported number of cocci deaths (the most reliable index, itself far from perfect), ~14% of presumed actual cases are reported in CA (skewed upward by 83% in Kern Co, where awareness has always been high) and ~9% in AZ. Much lower in NV & TX, with less interest in reporting.

Cocci is greatly under reported. Skin test surveys give the most accurate estimate of cocci incidence. Putting all that's known together we conclude that:

- **about 70,000 new cocci infections yield**
- **about 8,500 cases annually in the U.S.**

The total number in all of the Americas may well be double that.

**Abstract 6: A Rabbit Model of Meningeal Endarteritis Obliterans(MEO)
Associated with Coccidioidal Meningitis (CM)**

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We report the first animal model of an infection-induced MEO. Stroke complications associated with coccidioidal meningitis in humans are thought to occur in 40% of patients. Histopathologically, in humans, these stroke events have been attributed to small and medium vessel MFO. An animal model of MEO associated with CM would have obvious potential benefits in improving our understanding of pathogenesis and evaluating preventive and therapeutic strategies. We were able to induce an animal model of MEO by introducing 2×10^4 - 5×10^4 arthroconidia (A) of *Coccidioides immitis* into the cisterna magna of 13 immunosuppressed, anesthetized NZW male rabbits (R) using a blind cisternal approach. The MFO was characterized by mononuclear infiltration of vessel adventitia with fibrous deposition within the intima and media leading to impingement of the lumen. Thrombosis was seen along with disruption of the internal elastic lamina meeting the classic histopathologic criteria for MEO. All R demonstrated MFO and severe coccidioidal meningitis. Although all R demonstrated neurological abnormalities (ataxia, posturing, head canting) beginning 7 to 35 days after inoculation, spinal cord and/or brain infarction was identified in only 6.2 demonstrated convulsions and 12 demonstrated paresis. Duration of illness prior to death/euthanasia ranged from 8 to 47 days. In contrast, 4 R given 4×10^3 A and 8 R given 1.5×10^5 - 1.0×10^6 A failed to demonstrate consistent MEO presumably due to inadequate inflammatory response in the former group and inadequate duration of inflammation prior to death/euthanasia in the later group (6-8)). We conclude that an inoculum of 2.0×10^4 to 5.0×10^4 A produces a universal MEO in conjunction with a severe CM and is associated with both systemic and neurological abnormalities simulating those identified in human disease. This model should allow the study of the patho genesis of such vasculitic complications. Infarction does not appear to be essential for the development of neurological manifestations implying other factors responsible for neuronal injury (e.g., cytokines, nitrous oxide, etc.).

Abstract 7: Comparison of Fluconazole and Itraconazole in the Treatment of Coccidioidal Meningitis in a Rabbit Model

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Coccidioidal meningitis is a devastating disease that requires long-term therapy with little hope of cure. A rabbit model of coccidioidal meningitis was used to compare the therapeutic efficacies of fluconazole (FCZ) and itraconazole (ITZ). Immune suppressed male NZW rabbits were infected intracisternally with 5×10^4 , *Coccidioides immitis* arthroconidia. Oral treatment with polyethylene glycol (PEG) 200 (n=9), FCZ (n=8; 80 mg/kg/day) or ITZ (n=8; 80 mg/kg/day) began 5 days after infection and continued for 28 consecutive days. Clinical evaluation showed both compounds were effective at reducing some neurological and systemic signs. FCZ was more effective at reducing head/body shakes, posture changes, and incontinence; and ITZ was more effective at reducing continuous fever. Both treatments resulted in lower CSF protein concentrations and WBC counts, and faster clearing of CSF fungal cultures when compared with PEG-treated controls. Neither drug affected CSF glucose levels. Mean serum and CSF drug levels were determined by bioassay from samples collected between 17 and 26 hr post-dose. Mean drug levels were 28.1 to 40.0 and 22.4 to 29.9 ug/ml for FCZ, and 0.77 to 2.51 and 0 ~g/ml for ITZ, and serum and CSF, respectively. Both compounds reduced *C. immitis* CFU in the spinal cord and brain ($p \leq 0.003$) when compared with PEG-treated animals, but were not different from each other. Histopathologic severity (semi-quantitative scoring system by an observer blinded to treatment) was equally reduced in both FCZ and ITZ treatment groups as compared with controls ($p \leq 0.0004$). In conclusion, both FCZ and ITZ showed similar efficacies against rabbit coccidioidal meningitis despite lower serum and CSF levels of ITZ.

Abstract 8: Treatment of Coccidioidomycosis in Mice with Lufenuron

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The cell wall of *Coccidioides immitis* contains chitin, a linear polymer of N-acetylglucosamine. The absence of chitin in mammalian cells has provided potential target for antifungal treatment. Recently, a new chitin synthase inhibitor, lufenuron, a benzoylphenylurea derivative, has been introduced for control of fleas in cats and dogs. In this study, the ability of lufenuron to increase the survival of mice infected with *C. immitis* was evaluated.

Four groups of 7 mice were infected with 500 or 2,500 arthroconidia via the respiratory route. Twenty-four hours following infection, the mice were treated orally with lufenuron (20 mg/kg) or placebo with subsequent therapy given every other day. A fifth group was not infected but received lufenuron therapy. The experiment was terminated at Day 22 and surviving mice were sacrificed and lungs, liver, and spleens cultured.

All of the mice that were not infected but given the lufenuron therapy survived and showed no observable toxic effects. The survival curves for the infected mice given lufenuron or placebo therapy were similar. One mouse in each of these groups survived. The lungs, liver, and spleen were culture positive for *C. immitis*. There was no significant difference in survival between these groups.

Our results appear to show that with the dosage and treatment regime used that lufenuron did not increase the survival of the mice with respect to the placebo untreated controls.

Abstract 9: Fluconazole (FLU) versus Itraconazole (ITRA) for Nonmeningeal Progressive Coccidioidomycosis: A Randomized, Multicenter, Double-Blinded Trial

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To assess the relative efficacy of fluconazole and itraconazole as therapy for chronic pulmonary or extrapulmonary nonmeningeal coccidioidomycosis, we randomized 198 patients with *C. immitis* recovered from lung infections of > 3 months duration or from soft tissue or skeletal sites to receive for one year either FLU (400 mg/d) or ITRA (200 mg b.i.d.) and the placebo for the other treatment (double placebo design). Outcome was assessed every 4 months by a predefined scoring strategy. Excluded were 7 patients (*C. immitis* not isolated, disease not evaluable, or HMO permission not obtained). Baseline characteristics were evenly balanced for median age (38), male (73%), race (40% white, 33% hispanic, 17% black), and HIV infected (4%). Tabulated are number of patients responding (defined as > 50% improvement within 8 months) per number of patients treated:

Category	N	FLU	ITRA	p value
Total	191	47/94 (50%)	61/97 (63%)	0.07
Pulmonary	70	19/35 (54%)	20/35 (57%)	0.81
Soft Tissue	71	21/32 (66%)	29/39 (74%)	0.42
Bone/Joint	50	7/27 (26%)	12/23 (52%)	0.06

Both drugs were well tolerated. Overall, efficacy of FLU and ITRA are within the hypothesized 20% difference; although underpowered, there is a trend (26% higher efficacy) for ITRA to be superior in skeletal disease.

Abstract 10: Protection by and Characterization of the *C. immitis* 27K Vaccine

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We conducted a protection experiment to compare 27K vaccine combined with alum to 27K vaccine mixed with the Ribi MPL adjuvant. Groups of seven outbred Swiss Webster mice were vaccinated with 27K vaccine with alum or Ribi MPL 3 times at weekly intervals then rested for 4 weeks before infective challenge. Alum- and Ribi-only and whole spherule groups served as our negative and positive controls, respectively. Following infective challenge with 1,500 arthroconidia, the mice were monitored for 2 months for mortality or survival. After the end of the two month period, the surviving mice were killed, and their lungs, livers, and spleen homogenized, and quantitatively plated. The results showed that, although one or two mice receiving only the alum or Ribi adjuvant survived, all of the mice vaccinated with the 27K vaccine combined with either the alum or the Ribi adjuvant survived. Since there was no difference between the two adjuvants when mixed with the 27K vaccine in regard to overall survival of the mice, we determined if there was some difference in the viable *C. immitis* organ load of the surviving mice. However, the counts from the whole spherule and 27K adjuvant mixtures were found to be similar. The results show that there may be both antibody and cell-mediated immune responses working in concert to resolve a *C. immitis* infection and implies that there may be a number of antigens involved in eliciting an immune response. To isolate these antigens we have been trying different methods to fractionate the 27K vaccine. One of the methods used was isoelectric focusing (IEF) in acrylamide gels followed by immunoblotting. We were able to visualize a number of differently migrating bands that may represent different 27K vaccine antigens.

Abstract 11: Proline-Rich Antigen from Spherules of *Coccidioides immitis* as a Vaccine against Experimental Murine Coccidioidomycosis

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We have expressed the proline-rich antigen (PRA) from *Coccidioides immitis* in *Escherichia coli* and evaluated its potential as a vaccine candidate. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis of the recombinant protein (rPRA) revealed two bands, which exhibited virtually identical primary amino acid sequences. T cells from rPRA-immunized BALB/c mice showed a significant in vitro proliferative response to rPRA. A small but statistically significant proliferative response was also induced by rPRA in T cells from mice immunized with whole-cell coccidioidal vaccines. BALB/c mice immunized with rPRA and challenged intraperitoneally with virulent *C. immitis* had a greatly reduced fungal burden in their lungs and spleens compared to unvaccinated mice. The number of organisms in the lungs was reduced 500-fold, and similar reductions were observed in the spleens of immunized mice. These studies support the continued development of rPRA as a candidate vaccine for prevention of coccidioidomycosis.

Abstract 12: Treatment of *Coccidioides immitis* Spinal Infection

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Twenty-three patients with spinal infection from *Coccidioides immitis* were treated during a five year period. There were 22 males and one female with an average age of 39 years (range 20-76 years). There were 17 blacks, 5 whites, and one native American. The lesion location was cervical in six, thoracic in 11, lumbar in eight, sacroiliac joint in one, and disseminated spinal in three. Five patients had significant lesions in both the cervical and thoracic spine and one patient had lesions in the thoracic and lumbar spine. The duration of disease at the time of first encounter with the authors averaged 15 months (range 3 to 48 months). Four patients had associated medical disease, diabetes in three, Addison disease in one, and renal failure in one diabetic patient. The neurologic status was intact in 17 patients. Two patients had incomplete quadriplegia, three patients incomplete paraplegia, and a sixth patient a lumbar root lesion. Treatment was medical alone in five patients and combined medical and surgical in 19 patients (including one patient who failed medical surgery). The surgical procedures were anterior decompression and fusion in 16 patients with anterior plate instrumentation in three and use of a vertebral cage replacement in one, posterior spinal fusion with instrumentation in eight patients, sacroiliac joint debridement and fusion in one patient, and lesional excision in four patients. Two patients were treated surgically for separate cervical and thoracic disease sites and one patient was treated for disease extending from the lower cervical spine to the upper thoracic spine. Nineteen patients underwent a total of 29 operations, including two patients with separate cervical and thoracic surgeries totaling five procedures, and eight patients who underwent anterior spinal surgery and posterior spinal surgery at the same time.

All patients received amphotericin B intravenously. The outcome in five patients treated medically alone was one death, one remission, one patient with disease progression requiring surgery, and two lost to follow-up. The outcome in the combined medical and surgical group was 12 fusions, two pseudoarthroses, three lesional excisions with remissions, and four lost to follow-up. Recommended treatment for spinal coccidioidal infection includes aggressive debridement of the infection accompanied by anterior spinal fusion for anterior lesions, and anterior spinal canal decompression if necessary for neurologic compression secondary to anterior disease. Anterior instrumentation or posterior fusion and instrumentation is recommended in patients with three column disease and/or spinal instability. All patients should receive amphotericin B preoperatively and postoperatively to the maximal dosage allowable. Fluconazole given orally is recommended on a long term basis. The successful outcome of this disease is to be considered as disease arrest, as opposed to "cure".

Abstract 13: Disseminated Cutaneous Coccidioidomycosis: Portrait of an Epidemic

David Elbaum, M.D.

A presentation of nine cases and a review of the epidemiologic data.

Background: Recent changes in population and climatic conditions have greatly increased the number of cases of coccidioidomycosis. During the early 1990's an epidemic occurred in Kern County, California. Physicians practicing in the southwestern United States and other endemic areas should keenly be aware of this disease and its consequences. Furthermore, because of frequent travel to endemic areas, all physicians should be aware of this disease.

Objective: My objective was to study findings of patients with disseminated cutaneous coccidioidomycosis and relate this data to that observed by previous studies and that by the Kern County Health Department.

Methods: Nine consecutive patients diagnosed by myself as having disseminated cutaneous coccidioidomycosis based upon identification of organisms in skin tissue and/or by changes in titer were admitted to this study.

Results: There was a 3.5:1 male predominance in this study. Seven of the nine cases occurred on the head and neck. The two female patients in this study were either pregnant or on estrogen and progesterone. There was a high predominance of non-whites with this disease.

Conclusion: Granulomatous plaques occurring on the head and/or neck in non-whites in areas endemic for coccidioidomycosis should alert the physician to possible disseminated cutaneous coccidioidomycosis.

Abstract 14: Miliary Coccidioidomycosis

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Coccidioidomycosis, a disease caused by the fungus *Coccidioides immitis*, is endemic in the southwestern and western United States as well as in parts of Mexico and South America. Its clinical manifestations range from symptomatic to fulminant disseminated disease involving multiple organs including the lungs, central nervous system, skin and bones. Miliary cocci is a rare manifestation which is considered a severe form of dissemination. It is associated with fungemia and high fatalities. The purpose of this study was to delineate the patient characteristics, establish risk factors and x-ray findings. Diagnosis of *C. immitis* infections was determined by a positive sputum, bronchial specimen, positive tissue sample cytology, culture or positive serology. Various factors predicting the survival of patients with miliary cocci were analyzed. Age, race, gender, skin test results, complement fixation titers at time of diagnosis of cocci and time of miliary diagnosis, treatments, other sites of dissemination, associated conditions, and symptoms at the time of x-ray findings were analyzed. Our study showed no significant demographic difference between the survivors and non survivors. All patients with miliary disease had a negative skin test regardless of the outcome. All non survivors had a complement fixation titer of 1/16 at the time of diagnosis of cocci. They also had a CF titer of 1/16 or greater at the time of diagnosis of miliary cocci. There was no difference in presenting symptoms. Associated conditions in non survivors were IDU, HIV, SLE, and disseminated TB. Associated conditions in survivors: IUP. Non survivors presented more often with micronodular or reticulonodular interstitial chest x-ray pattern.

Abstract 15: Disseminated Coccidioidomycosis in Diabetes Mellitus

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Introduction: Coccidioidomycosis is endemic to the southwestern United States; the fungus present in the soil is *Coccidioides immitis*. Since the 1991-1993 epidemic in the San Joaquin valley, the clinic at Kern Medical Center, Bakersfield, CA, cares for patients in a dedicated Coccidioidomycosis clinic. Clinicians who care for this disease have perceived that diabetes was a risk factor for poor outcome.

Objective: To evaluate outcome of disseminated coccidioidomycosis in diabetic patients compared to non-diabetics

Design: Retrospective case control study.

Methods: Two hundred twenty-five adult patients with disseminated coccidioidomycosis were screened. Thirty-two patients with diabetes were identified and blindly case matched for age, sex, race and dissemination site. Twenty-four matches were found. HIV patients were excluded. Outcomes were evaluated at six months and last visit for patient status, culture positive sites, CF titers, skin test reactivity, relapse rate, and disease score as described by the Mycoses Study Group (MSG). Results: Seventy-five percent of the cultures were positive in diabetics, compared to 42% in non-diabetics. Relapse rates were 71% for diabetics and 25% for non-diabetics. Death rate was 73% for diabetics with CNS disease and 0% for non-diabetics with CNS disease. Thirty-eight percent of non-diabetics with non-meningeal disease completely recovered, compared to only 15% of diabetics. Disease scoring showed only 25% of diabetics had significant improvement in their disease, as compared to 63% of non-diabetics.

Conclusion: Diabetic patients with disseminated coccidioidomycosis did worse than non-diabetics. The death rate for diabetics with coccidioidal meningitis was exceedingly high.

Abstract 16: Fluconazole Shoulder Syndrome: The Rheumatologic Complications of Fluconazole Therapy in Coccidioidomycosis

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Rheumatologic complaints have been noted in a significant minority of patients treated with fluconazole in the Coccidioidomycosis Clinic at Kern Medical Center in Bakersfield, California. We present data on 3 ½ years of fluconazole use in patients with disseminated coccidioidomycosis. Sixteen patients evidenced unilateral or bilateral shoulder pain with or without change in range of motion. All but one of these patients had onset of symptoms within six months of initiation of fluconazole. Epidemiology of these patients is presented. Clinical evaluation with bone scan and/or radiographs were used to rule out disseminated disease. Two were excluded based on bone scan results. Therapy was discontinued or altered where possible with resolution of symptoms in seven of the fourteen. One was lost to follow-up. Two continued fluconazole due to active disease with no documented change in symptoms, and four had no further clinical data available at the time of writing this paper. A proposed mechanism of rheumatologic symptoms including the shoulder syndrome involves inhibition of trans retinoic acid by fluconazole.

Abstract 17: Clinical Association of *Coccidioides immitis* Culture and Sensitivity in Disseminated Coccidioidomycosis

R. Johnson, J. Caldwell

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Sensitivity of *Coccidioides immitis* to four antifungal agents (fluconazole, itraconazole, ketoconazole and amphotericin B) have been performed on positive cultures in disseminated coccidioidomycosis in 18 consecutive patients from June 1996 to present by the Fungus Testing Laboratory, University of Texas Health Science Center, San Antonio, Texas. Twenty-four and forty-eight hour sensitivities were obtained for each agent. The purpose of this evaluation was to assess the clinical correlation with minimum inhibitory concentrations to better define the utility of these results in patient management.

Patients were evaluated for length of disease, site of involvement, prior treatment, coexisting disease, previous culture, drug levels and response as defined by the Mycoses Study Group scoring system. The group included nine patients with meningitis and nine with non-meningeal dissemination. The median MIC's at 48 hours in mcg/ml were: fluconazole 16, itraconazole 0.5, ketoconazole 0.5, and amphotericin B 0.25. There were no associations noted in length of disease, months of treatment, site of disease, dose or drug level to MIC's of any agent. The response rate of all cases was 61%. There was a trend for those with lower MIC's to respond better to treatment. In cases with a 48 hour fluconazole MIC of 16 or less the response rate was 71% (10 of 14), while in those with MIC's of 32 or greater the response was 25% (1 of 4) $p=0.09$. Non responding cases were also more likely to have had a previous positive culture at some time in their history (57% versus 27%).

Conclusion: A 48 hour fluconazole MIC of 32 mcg/ml or higher appears to predict a relatively poor response to treatment in disseminated coccidioidomycosis.

