PROCEEDINGS OF THE ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

Meeting Number 48
April 3, 2004
Rosarito Beach, Mexico

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FORTY EIGHTH ANNUAL

COCCIDIOIDOMYCOSIS STUDY

GROUP MEETING

ABSTRACTS

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April 3, 2004

University of Arizona

Tucson, Arizona

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Chair

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Program for the 48th Coccidioidomycosis Study Group
Rosarito Beach, Mexico
April 3, 2004

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Chairperson: Karl Clemons

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Panelists: Ampel N, Blair J, Catanzaro A, Johnson RH, Stevens D and Williams P

Business Meeting
Chairperson: Hillel Levine

ABSTRACTS

1. Climate, Airborne Dust and Valley Fever

Andrew C. Comrie and Brenda Bonanno
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We examined the hypothesized roles of climate in coccidioidomycosis al disease in two parts. First, we examined the correlation between airborne dust concentrations and Valley Fever to determine relationships to dispersion conditions. Second, we examined the role of antecedent precipitation, in particular as it related to potential fungal growth and spore development. A limited number of previous studies have provided strong evidence of climate controls on Valley Fever, but these relationships are quite complex because of inhomogeneities and noise in the disease data from reporting problems (especially prior to the early 1990s), demographic changes, changes in diagnostic tests, and imprecise estimation of disease onset dates. We used 1992-2002 Valley Fever human incidence data for Pima County, Arizona, along with Tucson precipitation data from the National Climatic Data Center and dust data (particulate matter < 10 μm, or PM_{10}) from the Orange Grove site in Tucson. Using data aggregated to the seasonal level, we separately evaluated the roles of fungal growth versus spore dispersion ("grow or blow") via correlation analyses. In estimating date of exposure, we found the best signals using the estimated onset of symptoms date lagged by 14 days, rather than lagged diagnosis dates. Using dust as a proxy for dispersion, we found strongly positive significant correlations with Valley Fever during winter, the arid foresummer and the monsoon. Examining the effect of precipitation after the dust effect was removed (i.e., fungal growth and spore formation) we found significant correlations (all positive unless noted) for winter Valley Fever concurrently and in the previous monsoon (negative), between monsoon Valley Fever and the prior foresummer and monsoon, and for fall Valley Fever concurrently and in the previous foresummer. The implications are that the dispersion effect is dominant ("blow more than grow") in all seasons but the fall and that the growth and formation effect, while less significant, was present to a lesser degree in current and antecedent moisture conditions for most seasons.

2. Role of Macrophage Mannose Receptor Inhibition on T-Cell Reactivity to a Coccidioidal Antigen

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The mannose receptor (MR) is a surface receptor on human peripheral blood macrophages and other antigen presenting cells. It binds terminal mannoses that exist on a variety of pathogens, including fungi, and internalizes these glycosylated moieties for antigen processing. We assessed the effect of blocking the MR on the in vitro cellular immune response of human peripheral blood mononuclear cells (PBMC) incubated for 3 days with the coccidioidal antigen preparation T27K, a generous gift from Dr. D. Pappagianis. MR was expressed on human PBMC incubated for 3 days whether or not the cells were co-cultured with T27K. There was no difference in the expression of MR in cells from coccidioidal immune and non-immune donors. Incubation with either 3 mg/ml mannan or 20 μg/ml of the monoclonal antibody anti-CD206, which is directed against MR, resulted in significant loss of MR expression on cultured PBMC. Concomitantly, there was a significant reduction in IL-2 release and a marked reduction in the release of interferon-gamma in PBMC from immune donors cultured with either mannan or anti-CD206 in combination with T27K compared to T27K alone. However, mannan resulted in significant increases of IL-10 in all samples, including controls. The attachment of T27K to PBMC was measured after labeling with FITC. Anti-CD206 but not mannan blocked the attachment of T27K. These results suggest that MR mediates coccidioidal cellular immunity in vitro. Mannan, which has been used in the past to measure MR activity, appears to have non-specific effects.

3. Protection of Mice with Coccidioidal GFI Vaccine: A Comparison of Adjuvants and Immunization Routes

Johnson S, Simons K, Lunetta J, Pappagianis D.
University of California, Davis California
Kern Medical Center, Bakersfield California

Two separate studies were undertaken to evaluate the effect of different adjuvants and immunization routes on survival following respiratory challenge with Coccidioides immitis arthroconidia using the mouse model. The coccidioidal antigen GFI, prepared from mature endosporulating spherules, previously shown to protect mice against lethal respiratory challenge when given with alum, was used.

In the first study, GFI (100 μg per dose, 3 doses) was given with alum, Montanide ISA 720, or alum and Montanide ISA 720. Control mice were immunized with formalin-killed spherules (FKS) or adjuvant only. Of the mice that were challenged with 500 arthroconidia, 100 % (7/7) vaccinated with either FKS or GFI + alum survived through 80 days while only 29% (2/7) and 71% (5/7) vaccinated with GFI + Montanide and GFI + alum + Montanide respectively survived though the same period. Of the mice challenged with 1,500 arthroconidia, 100 % of mice immunized with FKS, 57% (4/7) immunized with GFI + alum, 14 % (1/7) immunized with GF I+ Montanide, and 29 % (2/7) immunized with GFI + alum + Montanide survived through 80 days. Surviving mice were held through 150 days following challenge to evaluate the long-term protective ability. In all groups except GFI + alum, low challenge, deaths were observed after 80 days. These results appear to indicated that the GFI + Montanide formulation made the vaccine less protective than GFI + alum. Secondly, the GFI + alum + Montanide protection was intermediate to GFI with alum and Montanide alone.

In the second study, GFI vaccine was given subcutaneous (SC), intradermal (ID), or intranasal (IN). Vaccines were formulated with alum for SC and ID and with L-α-phosphatidylcholine dipalmitoyl for IN. Mice were challenged by the respiratory route with either 500 or 1,500 arthroconidia. One hundred percent (7/7) of mice that were vaccinated either SC or ID survived through 55 days at both challenge levels. In contrast there were no survivors that were vaccinated IN at the high challenge level and only 50% (3/6) survived at the lower challenge level. Antibodies in pooled serum collected prior to challenge were detectable by ELISA for each immunization route group. These results indicate that there is no difference between SC and ID immunization. However, these animals are being followed through 160 days monitor long-term protection.

4. Protection of Mice Against Intranasal Infections with *Coccidioides spp.* by a single chimeric expression product composed of both Ag2/PRA$_{1-106}$ and CSA.

Galgiani JN, Shubitz L, Peng T, Perrill R, Simons J, Cloud G, Orsborn KI, Kirkland TN, Cole GT. Valley Fever Center for Excellence, University of Arizona; University of Alabama at Birmingham, Birmingham, AL; University of California at San Diego, LaJolla CA; and Medical College of Ohio, Toledo OH.

As a continuation of the Valley Fever Vaccine Project, two recombinant antigens (rAg2/PRA$_{1-106}$ and Coccidioides-Specific Antigen or rCSA) have demonstrated significant protection individually and a mixture of the two has demonstrated significantly greater protection than either alone. As a practical approach to formulating a multi-component vaccine, expressing the two antigens as a single chimeric recombinant protein would be less expensive and therefore advantageous if there was no loss of protective effect. To analyze this possibility a chimeric fusion protein consisting of Flag-Glu-Phe-Ag2/PRA$_{1-106}$-Gly-Ser-CSA was expressed in Saccharomyces cerevisiae (strain BJ3505) using the YEpFlag-1 vector. rAg2/PRA$_{1-106}$ and rCSA were similarly expressed in yeast. C57BL/6 mice were vaccinated and boosted two weeks later with 1 μg subcutaneously with adjuvant (MPL+CpG) of either rAg2/PRA$_{1-106}$, rCSA, the two antigens mixed together, the chimeric antigen, or adjuvant alone. One month after boosting, all animals were infected intranasally with a very stringent challenge: 251 (first experiment) or 218 (second experiment) arthroconidia. Composite analysis demonstrated median survival to be 14 days for rCSA and adjuvant alone, 17 days for rAg2/PRA$_{1-106,}$ 54 days for the chimeric antigen, and 57 days for the mixed antigens. By Kaplan-Meier analysis, utilizing the Gehan's Wilcoxon test at the 0.05 level, survival with either the mixed antigens or the chimeric antigen was significantly greater than either alone. In other studies using 40 to 70 arthroconidia intranasally, the chimeric antigen vaccine has produced >95% survival as had previously been found with the rAg2/PRA$_{1-106}$-rCSA mixtures. These studies support the use of the chimeric antigen in a vaccine candidate for human clinical trials.

5. Status of the Valley Fever Vaccine Project

Hector RF and the Valley Fever Vaccine Project Investigators

The Valley Fever Vaccine Project is in the 5th year of a 5-year effort to identify, evaluate and develop a suitable vaccine for the prevention or amelioration of coccidioidomycosis. Through the efforts of the five academic-based laboratories, a candidate antigen has been identified and selected for pharmaceutical development and human testing. Recombinant Ag2/PRA106+Csa is a chimeric fusion protein that is produced in a yeast host. Using murine models, the vaccine has demonstrated the ability to protect mice against an otherwise lethal challenge, as demonstrated by increased survival and reduced fungal burdens. The vaccine is presently being evaluated in a cynomolgus model that was designed to assess its safety, immunogenicity and efficacy. Plans have been put in place for the manufacture, formulation, and toxicology testing as a prelude to submission of an IND and Phase 1 testing in humans in 2005.

The Project has also completed a Phase 1 study of the skin test antigen coccidioidin in human volunteers as a prelude to anticipated incidence/prevalence studies in target populations in California and Arizona.

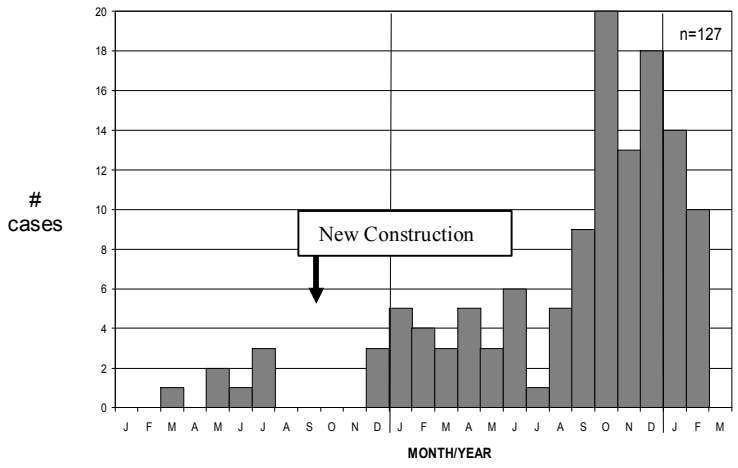
6. Outbreak of Coccidioidomycosis in California Prisons 2003-2004

Pappagianis D[1], Sacks HD[2]
University of California[1], Davis, California
California Department of Corrections[2]

In a prior Coccidioidomycosis Study Group (year 2000), we described occurrence of coccidioidomycosis (cocci) among inmates of prisons in California, several of which are located in areas to which cocci is endemic. That study was prompted particularly by an epidemic among 23 inmates from one prison.

We have tabulated the new cases of cocci for the period 3/2003 through 2/2004 from a number of institutions including impressive incidence among inmates of Pleasant Valley State Prison (PVSP) – Coalinga. The latter prison was established in 1994 but our serologic surveillance began in 2002. In 24 months we detected 207 new cases from various prisons which, based on an estimated $8,000.\underline{00}$ per case (Caldwell, et al., 1996), cost the State of California 1.7×10^6. Most cases (127) were from PVSP where the inmate population was 5,000. In 2002, the incidence rate was $^{200}/_{100,000}$, in 2003 it was $^{1,840}/_{100,000}$ population, more than triple the incidence rate ($^{572}/_{100,000}$) for Kern County in the epidemic year 1992 (Pappagianis, 1994). Aside from customary seasonal influences, the high incidence at PVSP in 2003-2004 was anthropogenic, associated with construction of a new mental health facility beginning in the Fall 2002 adjacent to PVSP.

Outbreak of Coccidioidomycosis in California Prisons 2003-2004



7. Coccidioidomycosis in Diabetes Mellitus

Santelli AC, Blair JE, Roust L
Mayo Clinic, Scottsdale, Arizona

Background: Coccidioidomycosis is a fungal infection endemic to the southwestern United States. Though this is typically a self-limited respiratory infection, some persons, such as those with impaired immunity, have increased risk of severe or disseminated infection. Scan old literature suggests that persons with diabetes mellitus (DM) may have more cavitary lung infection than nondiabetics, and more recent literature suggested that diabetics have more clinically severe infections requiring hospitalization. We reviewed our own experience to further characterize the clinical manifestations of coccidioidomycosis in this population.

Methods: A retrospective chart review of all persons with coccidioidomycosis at our institution from 1/1/99 through 10/31/03. Persons with immunosuppressive diseases or medications were excluded. Persons without DM served as controls. Comparisons between the persons without DM and with any DM, DM with serum glucose levels ≥220 milligrams per deciliter (mg/dl) and DM with serum glucose <200 mg/dl were all performed using Fishers Exact test.

Results: 329 non immunosuppressed persons with coccidioidomycosis were identified in this study, including 44 patients with DM and 285 without DM. Diabetics were more likely than non diabetics to have cavitary lung disease (p=0.001), to receive antifungal treatment (p=0.005), and to experience unresolved (p=0.01) or relapsed infection (p=0.003). The combined group of 21 patients with glucose <220, or unknown glucose (n=3) were more likely to experience relapse when compared with the non DM group, but were not more likely to have cavitary or disseminated infection, require treatment, or experience less resolution of infection. In contrast, the 20 patients with DM and glucose ≥220 mg/dl had more cavitary lung disease (p=0.002), required treatment (p= 0.01), and experience less resolution (p=0.005) and more relapsed infection (p=0.03). This latter group of diabetics also had more disseminated infections, though not statistically significant (p=0.09).

Conclusions: Compared with nondiabetic patients, diabetics with coccidioidomycosis have more cavitary lung disease, are more likely to require treatment, have more difficulty resolving their infection, and are more likely to experience relapsed infection. These findings are seen primarily among those with serum glucose levels ≥220 mg/dl.

8. Respiratory Failure in Pulmonary Cocci: Is There a Role for Steroids?

Sajid S, Spinello IS, Munoz AM, Mehtani P, Talakkottur C, Johnson R
Kern Medical Center, Bakersfield California

Respiratory failure in pulmonary coccidioidomycosis is associated with high mortality. In these patients, there have been anecdotal reports of improvement in hypoxia with steroids, but only one such case is reported in literature. Accordingly, we proposed to identify the role that steroids play in this setting by doing a retrospective study. 174 admissions between 12/1993 and 12/2003 with a diagnosis of pulmonary coccidioidomycosis were identified at KMC. The patients who received steroids along with antifungal treatment were then identified using their pharmacy profiles. Patients who were already on high dose steroids for preexisting conditions were excluded. Finally 16 cases of pulmonary coccidioidomycosis with respiratory failure who received steroids were included in the study. The majority of the patients were male (n =13), caucasian (n=11) and their age ranged between 31-50 (n=11). Their coexistent conditions included DM (n=6), renal insufficiency (n=4), hepatitis C (n=3), and adrenal insufficiency (n=1). Substance abuse was seen with alcohol (n=3), tobacco (n=3) and IDU (n=1). Shortness of breath, fatigue, cough and sputum production were the major symptoms at presentation. Acute Lung Injury Scores using PEEP, compliance, chest x-rays and PaO2/FiO2 ratio was calculated for each of the patients and it was found that the majority (n=10) had severe disease and the rest (n=6) had mild to moderate lung injury. For antifungal therapy these patients received amphotericin (N=7) liposomal amphotericin (n=4) or lipid complex amphotericin(n=5). For steroid therapy they got hydrocortisone (n=3), methyprednisone (n=3) or prednisone (n=10). The majority got PCP dosing of methylprednisone and prednisone, for a mean duration of 22 days. Of the 16 patients, 10 patients required ventilation, and of those 6 survived and 4 died. The median number of days on the ventilator for survivors was 8 versus 16 for the non-survivors. The PaO2/FiO2

ratio was calculated at admission (T1), prior to steroid therapy (T2), 24 hours post steroid therapy (T3), 1 week after steroid therapy (T4) and finally at the time of discharge or death (T5) for each of the cases as well as an average for the entire group. There was an improvement of 50 in the PaO2/FiO2 ratio between the time that steroids were started and one week later for all the patients. A comparison of these cases was done with our own historical controls that did not receive any steroid therapy (Arsura et al Chest 2002) and it was found that the mortality of the historical group (37.5%) was higher than our cases (25%).

CONCLUSION 1)There does not appear to be any deleterious effects from steroid use in severe pulmonary coccidioidomycosis 2) Improvement in hypoxia is noted in seven days or longer 3) Compared to historical controls a survival benefit is suggested in the current patient population.

9. Experience with Liposomal Amphotericin B in the Treatment of *Coccidioides immitis* Meningitis

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Coccidioides immitis meningitis (CM) is generally fatal if untreated.

The currently available treatments for this disease are not curative. Liposomal amphotericin B (LAB) has been shown to be associated with less toxicity in the treatment of systemic fungal infections and specifically reported to be effective in systemic coccidioidomycosis. There are data also which suggest LAB may have better penetration into the central nervous system than other ampthotericin B preparations. In addition, in a CM animal model LAB may have curative activity.

It is unlikely a controlled study comparing the various potential treatments in CM will be done. Between 2001 and 2002 six consecutive patients with CM were treated with LAB. A target dose of 5,000 mg of LAB was used with a treatment dose of 10 mg/kg. The total dose of LAB in these patients ranged between 6,300 and 17,549 mg. LAB was generally well tolerated and the usual toxicities associated with amphotericin B were less. Azotemia and hypokalemia were the most common complications, but reversible. All six patients were alive, well and maintained on oral azoles after 12-18 months follow up. It is not known whether any of the patients were cured of their CM.

10. Voriconazole Treatment in Coccidioidomycosis: An Initial Experience

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Treatment of disease caused by *Coccidioides immitis* may be difficult. Voriconazole is a new azole, antifungal drug, which has potential for treatment of coccidioidomycosis. In-vivo studies of this compound in the treatment of coccidioidomycosis are very limited. In patients who failed other modalities voriconazole has been used. We performed retrospective chart review of cases of both meningeal and non-meningeal Coccidioidomycosis. Eleven cases were analyzed. Patients were screened for a period ranging from 1 to 12 months (7.5 months average length of treatment) and their response to voriconazole was monitored with MSG (Mycoses Study Group) scoring system.

All patients in the non-meningeal group showed clinical improvement, 2/5 had a >50% score reduction (responders per MSG score). 67% of the patients in the meningeal group showed clinical improvement, 3/6 showed >40% score reduction (responders per MSG score). This review suggests that voriconazole may be an effective antifungal agent in the treatment of both meningeal as well as non-meningeal, disseminated infection caused by *Coccidioides immitis.*

11. Use of Posaconazole in the Treatment of Coccidioidomycosis

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Vice President Clinical Research Anti-Infectives
Schering-Plough Research Institute

Posaconazole (SCH 56592) is a broad-spectrum triazole antifungal that has been developed for the treatment of invasive fungal infections. In pre-clinical studies in over 18,000 strains of microorganisms, posaconazole showed substantially greater in vitro activity than many other antifungal drugs against a range of pathogenic fungi, including moulds (eg. Aspergillus, Zygomycetes, Fusarium, and dematiaceous moulds), dimorphic fungi (eg. Coccidioides) and yeasts (eg. Candida). Against Coccidioides, posaconazole has been show *in vitro* to be more potent than amphotericin and itraconazole and in animal models to be fungicidal and more potent than itraconazole and fluconazole based on organ clearance and animal survival.

The clinical efficacy of posaconazole in the primary treatment of non-meningeal coccidioidomycosis was shown in 15 clinically evaluable patients enrolled in an open-label, non comparative trial to receive posaconazole 400 mg daily for up to 6 months. Most patients were otherwise healthy and had infection at a variety of sites. A satisfactory response (defined as an improvement of at least 50% of the Cocci score as defined by the Bacteriology and Mycology Study Group –BAMSG- Coccidioidomycosis study group) was seen in 12 of 15 patients (80%) after an average of 4 months of posaconazole treatment. In a separate open-label, non-comparative study, the safety and efficacy of posaconazole 400 mg BID was assessed in 16 patients with coccidioidomycosis infection refractory to standard treatment. Most had been treated with amphotericin B (including lipid formulations) and/or itraconazole or fluconazole for months to years prior to posaconazole treatment. At the end of treatment with posaconazole, a satisfactory response (complete or partial resolution of signs and symptoms present at baseline) as determined by an independent panel was achieved for 11/16 (69%) of patients. One patient with CNS disease that had failed fluconazole therapy had a successful outcome following 12 months of posaconazole therapy.

In summary, posaconazole may represent a valid alternative to the currently available standard treatment of coccidioidomycosis.

12. Comparison of *in vitro* Interferon-gamma Response by QuantiFERON and CD69 Reactivity to Clinical Outcome in Human Coccidioidomycosis

Ampel NM, Chavez S, Nelson D, Naus K, Herman A
University of Arizona, Southern Arizona Veterans Health Care System, Tucson, Arizona

Measurement of cellular immune response in human coccidioidomycosis has important diagnostic and prognostic implications. Typically measured by assessing delayed-type hypersensitivity (DTH), coccidioidal cellular immunity is not evaluable at this time since both coccidioidin and spherulin are not currently available in the United States. However, we have previously shown that in vitro tests of cellular immunity may serve a similar purpose. In previous work, we showed that measurement of the early antigen CD69 on peripheral blood T lymphocytes after incubation with the coccidioidal antigen preparation T27K, a kind gift from Dr. D. Pappagianis, was correlated to clinical severity in human coccidioidomycosis. In the current work, samples from 69 subjects with coccidioidomycosis were examined for their release of interferon-gamma (IFN-g), using the QuantiFERON¨ assay (Cellistis Limited). By multivariate analysis, an IFN-g concentration of ³5 IU/ml was correlated with benign pulmonary disease and no underlying condition. IFN-g was significantly correlated with a lower clinical severity score within the first 5 months of diagnosis. Finally, IFN-g concentrations were significantly correlated with CD69 results. These data suggest that the QuantiFERON¨ assay using T27K as the stimulatory antigen could serve as a useful clinical assay for the measurement of human coccidioidal cellular immunity.

List of Annual Meetings

MEETING	DATE	LOCATION	
1	07/18/56	San Francisco	
2	12/5 – 6/57	Los Angeles	
3	12/4 – 5/58	Los Angeles	
4	12/3 – 4/59	Los Angeles	
5	12/8 - 9/60	Los Angeles	
6	11/30 -12/1/61	Los Angeles	
7	11/29 - 30/62	Los Angeles	
8	12/5 – 6/63	Los Angeles	
9	12/10 – 11/64	Los Angeles	CTS*
10	12/07/65	Phoenix – 2nd Coccidioidomycosis Conference	
11	4/19/67	Palm Springs	CTS*
12	5/01/68	Fresno	CTS*
13	4/15/69	San Diego	CTS*
14	4/01/70	San Francisco	CTS*
15	4/06/73	Newport Beach	CTS*
16	4/05/74	Sacramento	CTS*
17	9/30/74	San Francisco	CCTG*
18	04/02/75	San Diego	CTS*
19	7/31/75	San Diego	CCTG*
20	1/14 – 15/76	San Diego	CCTG*
21	4/07/76	Palo Alto	CTS*
22	5/18/77	San Francisco	ALA*
23	4/05/78	Beverly Hills	CTS*
24	5/15/79	Las Vegas	ALA*
25	4/11/80	Sacramento	CTS*
26	3/28/81	San Francisco	CTS*
27	5/15/82	Los Angeles	ALA*
28	3/20/83	La Jolla	CTS*
29	3/14-17/84	San Diego – 4th Coccidioidomycosis Conference	
30	3/08/86	Santa Barbara	
31	04/04/87	Los Angeles	
32	04/09/88	Los Angeles	
33	04/08/89	San Jose	
34	04/07/90	Berkeley	
35	04/06/91	Tucson	
36	04/04/92	Fresno	
37	04/03/93	Tucson	
38	8/24-27/94	Stanford – 5th Cocci “Centennial” Conference	
39	04/01/95	Bakersfield	
40	3/30/96	Scottsdale	
41	03/05/97	San Diego	
42	04/04/98	Visalia	
43	03/20/99	Tijuana, BC, Mexico	
44	04/01/2000	Berkeley	
45	03/31/2001	Tucson, AZ	
46	04/06/2002	Davis, CA	
47	04/05/2003	Scottsdale, AZ	
48	04/03/2004	Rosarito Beach, Mexico	

Conferences held in conjunction with:

- CTS = California Thoracic Society
- CCTG = Coccidi CooperativeTreatment Group,
- ALA = American Lung Association