Proceedings of the 55th Annual Coccidioidomycosis Study Group Meeting

2011

April 2, 2011 • University of California Davis • Davis, California

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Meeting Number 55
April 2, 2011
University of California Davis
Davis, California

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Meeting Program

7:00 am.	Breakfast and Registration
8:00 - 8:15.	**Welcome**
8:15 am.	**Epidemiology** Moderator: Rebecca Sunenshine
8:15 am.	Investigations of the *Coccidioides* spp. Endemic Zone in Southeastern Nevada, Southwestern Utah, and Northwestern Arizona. Fisher, F.S.*, Gettings, M.E., Johnson, S.M., Bultman, M.W., Pappagianis, D.
8:30 am.	Identification and Characterization of C. *immitis* Growth Sites in Kern County, CA, Using a Culture Independent Method and the Web Soil Survey Database of the U.S. Department of Agriculture. Lauer A.*, Baal J.C.H., Baal J.D.H., Chen J.M.
8:45 am.	Impact of Disseminated Coccidiodomycosis in Arizona, 2007-2008. Foley C.G., Tsang C.A.*, Christ C., Anderson S.M.
9:00 am.	Does 2010 Signal the Start of Another Coccidioidomycosis Epidemic in Kern County? Emery K.*, Hernandez K., Lancaster M., Constantine M., Jonah C., McMasters P., Morales P., Talamantes J.
9:15 am.	Cocci Cases and Deaths - California Prison Healthcare Services, 2005-2010. Schneider J.L., Pappagianis D., Leistikow B*., Mohle-Boetani, J.
9:30 am.	**Break and Poster Viewing**
10:00 am.	**Experimental** Moderator: Karl Clemons
10:00 am.	Multi-locus Sequence Analysis of Archived *Coccidioides* DNA. Johnson S.M.*, Carlson E.L., Pappagianis D.
10:15 am.	Detection of Coccidioidal Peptide Antigens in Plasma. Lake D.F.*, Blair J.E., Pitta T., Antwi K., Stolper R., Duffy S., Hanavan P.

Meeting Program

10:30 am.	Quantitative Comparative Proteomic Analyses of *Coccidioides posadasii* and Other Pathogenic Fungi. Hong T.B., Diaz-Arevalo D., Ito1 J.I., Liu M., Clemons K.V., Stevens D.A., Kalkum M.*
10:45 am.	Single-cell Analysis of the Responses of Human Neutrophils to *Coccidioides* Forms and Model Pathogens. Heinrich V.*, Lee C., Thompson G.R., Johnson S.M., Pappagianis D.
11:00 am.	Archived Pathology Material for Identification of Genetic Polymorphisms Associated with Disseminated Coccidioidomycosis – A Pilot Study. Wollersheim S.K., Adachi K., McGhee S., Krogstad P.*
11:15 am.	Lectin Receptors and Immunity to Coccidioidomycosis in Mice. Viriyakosol S., Fierer J.*
11:30 am.	**Posters with Poster Authors**
12:00 pm	**Lunch** **Optional Tour of Veterinary School (Autumn Davidson)**
1:00 pm	**Veterinary** Moderator: Autumn Davidson
1:00 pm.	Central Nervous System Coccidioidomycosis in Dogs and Cats. Lavely J.
1:15 pm.	Peritoneal Coccidiodomycosis in a California Sea Lion (Zalophus californianus)". Church M.
1:30 pm.	Bear Coccidioidomycosis. Woods L.*, Swift P.
1:45 pm.	Nikkomycin Z Treatment of Client-Owned Dogs with Coccidioidomycosis: Preliminary Results. Shubitz L.F.*, Nix D.E., Butkiewicz C.D., Galgiani J.N.
2:00 pm.	**Clinical Manifestations, Diagnostics & Therapy** Moderator: John Galgiani

Meeting Program

2:00 pm. PET Scans are Frequently Positive in Solitary Pulmonary Nodules Due to Coccidioidomycosis. Ampel N.M.*, Onadeko W., Knox K.S.

2:15 pm. Relative Performance of Immunodiffusion Methods and Complement Fixation for Detection and Quantitation of Coccidioides Specific IGG. Oubsuntia, V*., Lancaster, M.

2:30 pm. Specificity of Enzyme Immunoassay for Serologic Coccidioidomycosis Diagnosis Compared to Immunodiffusion with Subsequent Medical Record Review of "False Positive" Results. Petein N.*, Erhart L., Ryan F., Tsang C., Sunenshine R.

2:45 pm. Miltefosine, a Broad-spectrum Antifungal and Antiparasitic Phosphocholine Lipid Drug, In Vitro and In Vivo against *Coccidioides*. Shubitz L.F., Nix D.E., Martinez M., Chen V., Galgiani J.N., Stevens D.A.*

3:00 pm. Does the Presence of Mediastinal Adenopathy Confer a Risk for Disseminated Infection in Non-immunocompromised Persons with Pulmonary Coccidioidomycosis? Mayer A.P.*, Morris M.F., Panse P.F., Ko M.G., Files J.A., Ruddy B.E., Blair J.E.

3:15 pm. Studies with Nikkomycin Z in Mice with Experimental Coccidioidal Pneumonia. Nix D.E.*, Shubitz L.F., Trinh H., Perrill B., Hanan N., Thompson C.M., Galgiani J.N.

3:30 pm. Intensive Study of 6 Patients with Primary Pulmonary Coccidioidomycosis. Hoover S.E.*, Chavez S., Galgiani J.N., Nix D.E.

3:45 pm. Cerebrospinal Fluid Complement Fixation Titers as a Predictor of Outcome in Coccidioidal Meningitis. Karno G.*, Heidari A., Johnson R., Chandrasekaran V., Khurana J., Spinello I.

4:00 pm. Cure of Coccidioidal Meningitis, A Case Report. Kuberski T.

4:15 pm. Break

4:30 pm. Unusual Cases Presentation. Lanaido-Laborin R.

7:00 pm. Dinner and Business Meeting

Poster Session

Estimated Incidence of Coccidioidomycosis by Date of Onset in Kings County, California, 2007-2010. MacLean M.

Mapping Potential *Coccidioides* Growth Sites Based on Satellite Imagery and Molecular Biology. Talamantes J.*, Lauer A., Emery K., Castañón L.

Coccidioidomycosis Incidence in San Joaquin Valley Prisons. Leistikow B.*, Schneider J., Mohle-Boetani J.

A Second Look at *Coccidioides*' Cupin Protein. Carlson E.L.*, Johnson S.M., Pappagianis D.

Quantitative Comparison of Phagocytosis by Neutrophils from Healthy Donors and Patients with Chronic Coccidioidal Infection. Lee C.*, Thompson G.R., Mankovich A., Heinrich V.

Voriconazole and Posaconazole for the Treatment of Refractory Coccidioidomycosis: A Retrospective Review. Kim M.*, Blair J.E

Induction of Chitinolytic Enzymes during Spherule-endospore Phase of *Coccidioides posadasii*. Lunetta J.M.* and Pappagianis D.

Early Post-Infection Detection of *Coccidioides* in Intranasally Infected Mice. Shubitz LF*, Perrill R, Lewis ML, Dial SM, Galgiani JN.

Coccidioidomycosis in California State Correctional Institutions with a Seasonal Surge – 2010. Pappagianis D*, Davis D, Einstein J, and the Coccidioidomycosis Serology Laboratory

Assessing Erosion Potential and *Coccidiodes immitis* Probability Using Existing Geologic and Soils Data. Harris W.*, Roffers P.

Diagnosing Coccidioidomycosis using IL-17 in Bronchoalveolar Lavage and Peripheral Blood. Ampel N.M.*, Nesbit L., Knox K.S.

Coccidioidomycosis in 1300 Patients: Spectrum of Radiologic Findings. Mamlouk M, Heidari A, VanSonnenberg E., Yazdanshenas M, Naderi J., Osei K., Johnson R.

Investigations of the *Coccidioides* spp. Endemic Zone in Southeastern Nevada, Southwestern Utah and Northwestern Arizona

Fisher, F.S., Gettings, M.E., Johnson, S.M., Bultman, M.W., Pappagianis, D.

The areas between St. George, Utah and Mesquite, Nevada, and also the region locally known as the "Arizona Strip" (that part of Arizona lying north of the Colorado River) are believed to be endemic for *Coccidioides* spp. The endemicity of these areas is based on; **1**) the identification of coccidioidomycosis in soil dwelling *Chaetodipus formosus* (Long-Tailed Pocket Mice) and *Citellus leucurus* (ground squirrels) collected from the St. George area; **2**) relatively continuous numbers of human cases of coccidioidomycosis reported each year from Washington County, UT (av. = 13); Mojave County, AZ (av. = 98); Coconino County, AZ (av. = 36); and **3**) *Coccidioides* positive blood serum tests from dogs residing in all of the above counties. Three major physiographic regions (the Mojave Desert, the Great Basin Desert, and the Colorado Plateau) are juxtaposed this region, each providing distinctive ecological characteristics in their soils, vegetation, and animal species. Annual precipitation ranges from 15 to 25 cm throughout much of the region with greater amounts occurring in the higher parts of the Colorado Plateau. The boundary between warmer thermic soils and cooler mesic soils delineates the northern and northeastern margins of the *Coccidioides* Endemic Zone in Nevada and Utah. Ongoing field studies focused on the number, distribution, and soil characteristics of *Coccidioides* growth sites in this region are providing data concerning the expansion of the endemic zone northward as a result of warming soils due to climate change, and also the threat of infectious dust from major storms being carried into Colorado with the consequent exposure and infection of non-immune populations outside of known *Coccidioides* endemic zones.

Identification and Characterization of *C. immitis* Growth Sites in Kern County, CA, Using a Culture Independent Method and the WebSoilSurvey Database of the US Department of Agriculture

Antje Lauer, Jed Cyril Hugo Baal, Joe Darryl Hugo Baal, and Jeffrey M. Chen

California State University Bakersfield, Department of Biology, 9001 Stockdale Highway, 61 SCI, Bakersfield, CA 93311-1022

Coccidioides immitis is a fungal pathogen endemic to semi-arid soils in Southern California. The inhalation of its spores can cause coccidioidomycosis, a disease also known as Valley Fever. Results of culture dependent detection of *C. immitis* in the past indicated a spotty distribution and unreliable prediction of *C. immitis* growth sites and accumulation sites. In this project, we investigated bulk soil samples for the presence of the pathogen in non-agricultural loamy soils at nine different locations (three depths) around Bakersfield, Kern County, CA, over an almost two year period (2008-2009). To detect the pathogen, we used the multiplex PCR method first published by Greene et al. (2004), but optimized soil storage, DNA extraction and PCR protocol. With this method, we were able to detect *C. immitis* in 8.25 % of our samples in 2008, mostly from early spring to early summer. In 2009, however, the percentage of samples positive for *C. immitis* declined to 2.5 %. We clearly distinguished *C. immitis* growth sites from accumulation sites. Furthermore, we used the websoilsurvey database of the US Department of Agriculture (USDA) to obtain information about physical and chemical parameters of the *C. immitis* growth sites and beyond. Interestingly, a site not known before to support the growth of *C. immitis*, which is close to a recreation area (Lake Webb), turned out to be a strong growth site of the fungus. The cultivation independent method used in this study together with information from the USDA websoilsurvey database can be used to predict and confirm *C. immitis* growth sites in the future and might be a valuable tool for public health institutions.

Impact of Disseminated Coccidioidomycosis in Arizona, 2007-2008

Catherine G. Foley, MPH, MA; Clarisse A. Tsang, MPH; Cara Christ, MD, MS; Shoana M. Anderson, MPH

Arizona Department of Health Services

Background: Arizona represents approximately 60% of the nationally reported coccidioidomycosis cases each year. In 2007, the Arizona Department of Health Services (ADHS) sought to understand the impact of coccidioidomycosis in Arizona by conducting extensive patient interviews (enhanced surveillance). In addition, we reviewed medical records to confirm data reported by patients, and to better characterize symptoms and site of infection. Using these data, we aimed to better understand the impact of disseminated coccidioidomycosis in Arizona.

Methods: From January 2007 to February 2008, every tenth reported coccidioidomycosis case was contacted for an interview. Enrolled persons were asked about their symptoms, site of infection, healthcare-seeking behavior, medical history, and demographic information. Medical records were requested for all individuals interviewed during enhanced surveillance. Records were reviewed to examine previous medical history, including medications prescribed and site of infection, and were used to classify cases as having either pulmonary-only or disseminated disease. Dissemination was defined as having clinical or radiological evidence of *Coccidioides* spp. outside the lung.

Results: Data from 324 (65.7%) patients were included in the analysis. Of these, 26 (8.0%) had evidence of dissemination. Males comprised a higher proportion of the disseminated group (69% vs. 50%), and there was no difference in age when comparing the groups. Patients reporting their race as black were more likely to have dissemination (p=0.02), while those reporting their race as white tended to have pulmonary-only disease (p=0.02). Also, patients with dissemination were more likely to report being infected with HIV (p=0.02), or requiring hospitalization for their disease (p<.0001). Despite those with disseminated disease having a significantly longer symptom duration on average (p=0.02), there was no difference in the amount of reported time missed from daily activities due to this disease. Additionally, 65% of the disseminated disease group reported having a job or performing daily activities involving dust exposure.

Conclusions: Based on the findings of this study, clinicians should recognize the impact coccidioidomycosis has on all patients, not only those with disseminated disease.

Does 2010 Signal the Start of Another Coccidioidomycosis Epidemic in Kern County?

Emery K (1), Hernandez K (1), Lancaster M (1), Constantine M (1), Jonah C (1), McMasters P (1), Morales P (1), Talamantes J (2)

(1) Kern County Public Health Services Department
(2) Department of Physics, California State University, Bakersfield

Coccidioidomycosis is caused by the fungus *Coccidioides immitis*. Kern County, in the southern San Joaquin Valley of California, has long been recognized as a highly endemic county for this fungus. During endemic years (1980-1990, 1995-2000), the Kern County Public Health Services Department received an average of 300 case reports (range: 206-523; SD=100) per year. Endemic years have reported an average incidence rate of 55.9 cases per 100,000 residents (range: 33.6-84.8; SD=12.8) per year. During the 1991-1994 epidemic and the 2001-2008 resurgence, the average number of cases reported per year was 2,109 and 1,237, respectively. The corresponding average incidence rates for these epidemic periods were 356.0 and 163.9 per 100,000 residents, respectively. In 2010, Kern County expects to report approximately 2,000 cases for an average incidence rate=272.2 per 100,000 residents. This clearly signals a change in the number of cases reported in Kern County since the 1991-1994 epidemic. This presentation will characterize the 2010 reported cases, explain the impact that adding “cocci” to the list of laboratory reportable diseases in California has made in Kern County, and utilize a geographic information system to perform geospatial statistics on these data. It is our hope that we may further the understanding of the distribution of cases reported in Kern County, perhaps at the beginning of a second epidemic, and hopefully add additional knowledge to predictive models that may be utilized to improve the health of our residents by enhancing targeted education, awareness, and prevention efforts.

Coccidioidomycosis Cases and Deaths - California Prison Healthcare Services, 2005-2010

JL Schneider, D Pappagianis, B Leistikow, J Mohle-Boetani

Since 2007 California Prison Healthcare Services (CPHCS) Public Health Nurses (PHN) have systematically reported cases of coccidioidomycosis to the Public Health Unit.

Methods: We calculated annual coccidioidomycosis rates for 2007-2010 for institutions in located in hyperendemic CA counties. Additionally, we obtained data on coccidioidomycosis deaths, deaths reviewed by a panel for 2007-2010 and deaths for 2005-2006, in order to determine the severity of disease in the adult prisons. Rate ratios, comparing death among inmates to death among the CA general population were calculated. The rate for the general population was calculated using death data from CDC Wonder, the referent group was CA males aged 15 and greater for 2005-2007. Mid-year populations, per Offender Information Services Branch reports, were averaged and used as the denominator for the prison rate.

Results: A review of the first four years of data collection indicates that the majority of coccidioidomycosis activity among prisons in the hyperendemic counties occurs at Pleasant Valley State Prison (PVSP) and Avenal State Prison (ASP). The average annual incidence rates observed at ASP and PVSP were 1156/100,000 and 3754/100,000, respectively. The average annual incidence rate at ASP was 16 times greater than the rate in Kings County and the rate at PVSP was 123 times greater than that observed in Fresno County for the time period of 2001 to 2008[1].

There were 26 deaths due to coccidioidomycosis in the adult institutions from 2005-2010; there were 114 male coccidioidomycosis deaths in persons aged 15 or greater in 2005-2007 in California. The RR for death due to coccidioidomycosis in adult institutions compared to males in all of CA is 9.7 (95% CI 6.2-15.1).

Conclusions: Data available from the PHU surveillance system show that rates of disease are highest at PVSP and ASP, and much higher than rates observed in Kings and Fresno Counties. The risk of dying from coccidioidomycosis is much greater among inmates than the general population.

1Epidemiologic Summary of Coccidioidomycosis in California, 2001-2008.
Located at: http://www.cdph.ca.gov/data/statistics/Pages/EpiSummariesCDsCA-01-08.aspx

Multilocus Sequence Analysis of Archived *Coccidioides* DNA

Suzanne M. Johnson, Erin L. Carlson, D. Pappagianis

University of California, Davis, CA

Background: In 1994, our lab reported[1] differentiation of *Coccidioides* isolates into two groups using DNA restriction fragment length polymorphisms (RFLP). Of the 15 isolates examined, 2 were assigned to Group I (strain Silveira and the California isolate K-727) and the remaining to Group II. These, later labeled non-Californian and Californian types[2], have been subsequently recognized as *C. posadasii* and *C. immitis* respectively[3]. Studies regarding the differentiation of *Coccidioides* isolates using sequences of PCR amplified ribosomal internal transcribed spacer (ITS) region and other genes have recently been published. The purpose of this study is to compare the historical RFLP results with nucleotide sequences of amplified products using archived DNA.

Methods: PCR amplification of archived DNA used for RFLP analysis was performed using separate primer sets designed to amplify the ITS region, deoxygenase, serine proteinase, and urease genes. Sequences of the PCR products were determined and compared. Sequences were obtained from a minimum of two independent amplifications.

Results: Nucleotide sequences of the PCR products from the genes deoxygenase, serine proteinase, and urease were obtained. There were between 5 and 7 phylogenetically informative sites within each gene and the base composition was unique for the Silveira strain with one exception. At this site, within the urease gene, strain K-727 and Silveira were the same. Within the ITS region there was overall more sequence variation although there were 6 phylogenetically informative sites. All 12 isolates of the RFLP Group II appear to be *C. immitis*. Although K-727 has the same RFLP pattern as strain Silveira (Group I), it does not appear to be *C. posadasii*.

Conclusions: While isolates whose DNA belonged to RFLP Group II had sequence variations that indicated they were *C. immitis*, only 1 isolate of RFLP Group I was *C. posadasii*. Furthermore, analysis of the amplified products from the genes deoxygenase, serine proteinase, and urease provided information sufficient to assign the appropriate species.

References:

1. Zimmermann CR et al. J Clin Microbiol 1994
2. Koufopanou V et al. Proc Natl Acad Sci 1997
3. Fisher MC et al. Mycologia 2002

Identification of Peptides in Plasma from Coccidioides by Mass Spectrometry

Lake D.F., Blair J.E., Pitta T., Antwi K., Stolper R., Duffy S., Hanavan P.*

Currently available tests to distinguish Coccidioidomycosis from other community acquired pneumoniae, are based on the ability of patients to mount an antibody response to the fungus. Unfortunately, the antibody-based tests are inadequate for many patients because it may take weeks to months to develop such an antibody response (leading to delayed diagnosis), and many immunocompromised patients are unable to mount any antibody response at all. Therefore a blood test to detect coccidioidal proteins would allow a definitive diagnosis to be made even if serology is negative. Plasma is an ideal source to detect markers of infection because blood circulates through every organ, including lungs. We subjected plasma to ultrafiltration followed by mass spectrometry (LC-MS/MS) to identify coccidioidal peptides in plasma from patients with coccidioidomycosis. Mass spectra derived from patient plasma was searched using coccidioides_posadasii_str._silveira_1 protein database. One peptide was identified that was in common among 5 patients with active disease within 8 weeks of diagnosis). The identity of the peptide was confirmed and validated by chemically synthesizing the same sequence, but with a heavy leucine making the peptide 7 daltons heavier by LC-MS/MS analysis. The peptide concentration ranged from 47-89 ng/ml in plasma. This peptide was not present in plasma from 5 healthy non-immune donors, but was present at a low level 47 ng/ml in 1 of 5 healthy immune donors. We are currently expanding analysis of patients with active disease, healthy non-immune and healthy immune donors to determine the frequency of this peptide in healthy immune donors. We are also correlating serology with levels of peptide in patients with active disease.

Quantitative Comparative Proteomic Analyses of *Coccidioides posadasii* and Other Pathogenic Fungi

Teresa B. Hong[1], Diana Diaz-Arevalo[1], James I. Ito[1], Min Liu[2], Karl V. Clemons[2], David A. Stevens[2] and Markus Kalkum[1]

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A whole cell *Saccharomyces cerevisiae* vaccine has shown protection against *Aspergillus fumigatus*, *Coccidioides*, and other opportunistic fungi. In initial studies we found antibodies from *C. posadasii*-infected rabbits cross-reacted with several protein antigens from other fungi, such as the mould *A. fumigatus* or the yeast *S. cerevisiae* on Western blots. Similarly, antibodies from mice immunized with hyphal extracts from *A. fumigatus* or with heat-killed yeast cross reacted with several antigens from *C. posadasii* and *S. cerevisiae*. This cross reactivity suggests the presence of structural similarities among protein antigens from different fungal species that could potentially be exploited for the generation of broad-spectrum antifungal vaccines and for diagnostics. Structural homology may be manifested in sequence similarities or homologous posttranslational décor – possibly glycosylations. It is conceivable that potential vaccine candidates that would provide protection against a number of fungal species would be proteins that are a) highly expressed, b) have high degree of sequence and structural homology, and c) are sufficiently immunogenic.

As a first step, we have quantitatively analyzed and compared the hyphal proteome of *C. posadasii* with that of *A. fumigatus* using a combined liquid chromatography and mass spectrometric (MS) approach. C. posadasii and *A. fumigatus* were cultured in Converse or Czapek-Dox medium, respectively; hyphae were homogenized, debris pelleted by centrifugation and supernatant proteins recovered. Two µg of protein per sample were alkylated and trypsin digested in solution using 2,2,2- trifluoroethanol and urea as chaotropic agents to guarantee complete digestion of the fungal proteins. The resulting peptides were analyzed using a novel mass spectrometric method, named MS^E, on a Synapt G2 mass spectrometer (Waters) with two-dimensional Ultra Performance Liquid Chromatography. A spiked-in standard of peptides from a trypsin digest of equine cytochrome C was used for label-free MS^E protein quantification. The MS^E data sets were analyzed with Protein Lynx Global Server and Scaffold software for protein identification and quantification. A total of 359 proteins from *C. posadasii* and 473 proteins from *A. fumigatus* could be identified and quantified. Seven of the 20 most abundant proteins of each species had

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The MS^E data sets were analyzed with Protein Lynx Global Server and Scaffold software for protein identification and quantification. A total of 359 proteins from *C. posadasii* and 473 proteins from *A. fumigatus* could be identified and quantified. Seven of the 20 most abundant proteins of each species had more than 50% inter-species sequence identity. For example, the peroxisomal vaccine candidate protein Pmp1 from C. posadasii and its homologue Asp f3 from A. fumigatus were the fourth and fifth most abundant proteins by mass, respectively, and share 69% identical sequence. Other highly homologous proteins were enolase, glyceraldehyde 3-phosphate dehydrogenase, elongation factor 1 alpha, HSP70, elongation factor 2, and mitochondrial heat shock protein SSC1.

We are currently investigating the abundant homologous proteins that *C. posadasii* and *S. cerevisiae* have in common, and are further refining our MSE analysis to also map glycosylation sites. Our objective is to provide a list of highly abundant homologous proteins that could be tested as potential cross-protective vaccine candidates.

Single-cell Analysis of the Responses of Human Neutrophils to *Coccidioides* Forms and Model Pathogens

Volkmar Heinrich, Cheng-Yuk Lee, George R. Thompson, Suzanne M. Johnson, Demosthenes Pappagianis*

University of California, Davis

Although neutrophils, monocytes, and macrophages are the first host cells reacting in a pre-programmed manner to pathogenic invaders, interest in the innate immune system has long been outshone by a stronger research emphasis on its adaptive counterpart. However, technological advances and emerging cross-disciplinary research alliances recently have bolstered interest in the chemotactic and phagocytic behavior of innate immune cells. Contributing to this development, we have implemented and validated an immunophysical approach that is based on dual-micropipette manipulation of individual cells and targets, providing us with tight control over their mutual encounters, as well as with a unique live view of their "one-on-one" interactions. We here demonstrate how single-cell/single-target experiments reveal a wealth of quantitative information about the responses of human neutrophils to antibody-coated microspheres ("Fc beads"), zymosan particles, and inactivated *Coccidioides* forms. Our results show, for example, that heat treatment of serum suppresses neutrophil chemotaxis toward, but not phagocytosis of, fungal targets (zymosan, *Coccidioides*). Quantitative comparison of the phagocytosis of fungal targets and of Fc beads exposes a surprising difference between these two pathways. Unlike the efficient uptake of 3-μm Fc beads (within ~66 s), the engulfment of similarly sized fungal targets is significantly slower, mainly due to the formation of a characteristic cellular pedestal that initially pushes the latter particle outwards by ~1 μm. Drug inhibition shows that an intact actin cytoskeleton is required to suppress, in antibody-mediated phagocytosis, the initially protrusive deformation that distinguishes the neutrophil response to zymosan and *Coccidioides*. We thus attribute the observed difference to distinct structural interactions between the cytoskeleton and the membrane patch adherent to a specific target. Such mechanistic insight not only deepens our fundamental grasp of innate immunity, but also provides new ground for bottom-up approaches to diagnosis and treatment of infectious diseases.

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Archived Pathology Material for Identification of Genetic Polymorphisms Associated with Disseminated Coccidioidomycosis – A Pilot Study

Susan K. Wollersheim MD, Kristina Adachi MD, Sean McGhee MD, Paul Krogstad, MD.*

Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Dissemination of coccidioidomycosis occurs at an elevated rate among otherwise healthy African Americans and Filipinos, suggesting genetic predisposing factors may be present. The elevated risk is sufficiently large to warrant examination in a genome-wide association study, if DNA specimens from a sufficient number of patients can be accrued.

Objective: In anticipation of a larger, multicenter collaborative study, a pilot study is being performed at UCLA to determine the feasibility of using archived pathology specimens for genetic analysis.

Design/Methods: With approval from the Office for Protection of Research subjects, clinical laboratory and pathology records from UCLA/Ronald Reagan Medical Center were reviewed and cross-referenced to identify cases of histologically and microbiologically confirmed extra-pulmonary coccidioidomycosis. Chart reviews were conducted to exclude cases occurring in patients with immunocompromising states (HIV infection, organ transplantation, cancer etc.).

Results: 140 positive cultures from 90 different patients were identified in the study period, as well as 156 non-pulmonary biopsy specimens from 123 different patients that revealed evidence of disseminated Coccidiodes infection (DCI). After excluding cases of isolated pulmonary infection, children below the age of 7, and those with immunocompromising conditions, 51 cases were identified that had electronic medical records available for review. White and black patients were equally represented (27.5% each); individuals of Asian descent represented another 13.7% (n=17). Bony sites, including the spine, and coccidioidal meningitis were the primary foci of disseminated infection. Tissue blocks were obtained from pathology archives from 7 patients; useful amounts of DNA were obtained from most (6) and are currently being subjected to amplification for analysis of single nucleotide polymorphisms.

Conclusions: Analysis of archived pathology specimens may facilitate genetic studies to augment our understanding of genetic polymorphisms associated with an elevated risk of DCI.

*presenter

Dectin-1 (*Clec7a*) in Murine Coccidioidomycosis

Joshua Fierer, Suganya Viriyakasol

VA Healthcare San Diego and UC San Diego School of Medicine

Dectin-1 is a C-type lectin expressed on myeloid cells in people and mice. We have previously shown that it is involved in the macrophage response to live and formalin-killed spherules (FKS). We now investigated the role of Dectin-1 in dendritic cell (DC) recognition and response to spherules, and in resistance to infection. We found that adherence to DC from Dectin-1 KO mice was reduced by 75% and that TNFαå and IL-6 secretion was entirely Dectin-1 dependent in vitro. IL-1ß and IL-10 secretion was reduce by 2/3, but IL-12 p40 was unaffected. Importantly, Dectin-1 KO mice were more susceptible to infection with C. *immitis* RS than control C57BL/6 mice. Thus Dectin-1 plays a non-redundant role in resistance to C. *immitis*.

Central Nervous System Coccidioidomycosis in Dogs and Cats

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Coccidioidomycosis involving the central nervous system (CNS) is rarely reported in dogs and cats. Central nervous system involvement results from hematogenous spread. Systemic abnormalities are common in dogs and cats with disseminated coccidioidomycosis. Thoracic radiographs commonly identify pleural disease in cats and an interstitial pattern in dogs. Osseous lesions occur in 65% of dogs with disseminated coccidioidomycosis. Osseous proliferation can be identifiable on spinal radiographs when vertebral involvement is present. CNS signs are dependent on lesion location. Magnetic resonance imaging (MRI) can identify a granulomatous lesion in dogs compared to contrast enhancement of the meninges in humans. Cerebrospinal fluid (CSF) evaluation can indicate a neutrophilic or mixed pleocytosis and increased protein concentration. Diagnosis can be supported by serology and confirmed via fine needle aspirate of disseminated lesions, histopathology or culture of biopsied tissue. Surgical decompression is indicated with focal compressive spinal lesions. If accessible, surgical debridement can be considered with focal intracranial disease. Azole therapy has been the mainstay of medical therapy in dogs and cats. Fluconazole's ability to penetrate the CSF makes it an optimal choice for brain involvement. Itraconazole is considered superior with osseous lesions. Concurrent short term corticosteroid therapy can be of benefit in treating inflammation and edema within the CNS. Anti-inflammatory doses of corticosteroids should be considered when significant edema is identified via MRI, CSF indicates a significant inflammatory response or if rapidly deteriorating neurological signs are present. High dosages of corticosteroids or long term use should be avoided, due to the potential for compromising cell mediated clearance of the organism.

Coccidioidomycosis in a California Sea Lion *(Zalophus californianus)*

M Church

Cases of coccidioidomycosis have been reported previously in marine mammals at the Veterinary Medical Teaching Hospital (VMTH) at UC Davis. This is a report of systemic coccidioidomycosis in a subadult male California sea lion (*Zalophus californianus*).

He stranded 4 July 2010 in Monterey, and was transported to the Monterey field station of Marine Mammal Center the next day. He died at the center and necropsy revealed severe atrophy of skeletal muscle and adipose tissue throughout the body. The peritoneal cavity contained 2 L of opaque, yellowish fluid. The omentum and mesentery were congested and thickened by multifocal, coalescing nodules measuring 1 – 5 mm in diameter that were also present on the serosal surface of the bladder, the peritoneal surface of the abdominal body wall, and the capsular surface of the liver and kidney. Gastric lymph nodes were markedly enlarged. Histologically, the nodules corresponded to aggregates of intact and fragmented neutrophils with plump epithelioid macrophages and multinucleated giant cells. Lymphocytes, plasma cells and fibroblasts surrounded these aggregates. The centers of many of these nodules contained spherules characteristic of *Coccidioides immitis* (25 to 45 um diameter with a double contoured wall; containing granular basophilic material or round endospores approximately 5 um in diameter). Ten of the 833 sea lions examined post mortem at UCD VMTH since 1983 were diagnosed with coccidioidomycosis, which represents approximately 1% of the cases seen. In most of the cases, there was often involvement of the abdominal cavity. Of the ten cases we have seen at the UCD VMTH, only two cases had disease limited to the thoracic cavity; gastric lymph node enlargement and granulomatous peritonitis are commonly seen in these cases. Given the frequent peritoneal distribution of lesions, especially the frequent enlargement of gastric lymph nodes, sometimes in the absence of thoracic lesions, perhaps ingestion could be a significant mode of transmission involved with disease development in this species. Possible further studies to determine transmission and pathogenesis of coccidioidomycosis in sea lions include serosurvey of sea lions on rookeries in addition to those at rehabilitation centers to account for the skewed sample at the UC VMTH, and to expand the population of samples to include sea lions in southern California.

Coccidioidomycosis in an American Black Bear *(Ursus americanus)*

Leslie Woods, Pam Swift

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In February of 2011, a biopsy of a pleural mass from an American Black bear (*Ursus americanus*) was submitted to the California Animal Health and Food Safety Laboratory System at the University of California, Davis. Microscopically, the mass was diagnosed as a *Coccidioides immitis* pyogranuloma. The bear was a trophy bear that was harvested by a hunter in the San Joaquin Valley in the central valley of California in December 2010. After dressing out the bear, the hunter's friends and family ate the heart and liver. The hunter skinned the bear and submitted the skull and hide to the taxidermist and the remainder of the carcass to the meat processor. The taxidermist froze the skull upon receiving it. He scraped the hide, salted and pickled the hide for 14 days in water/citric acid (pH 1.5) and then froze it. After sawing the chest open, the meat processor observed large numbers of white, nodular, firm masses, 2-10 cm in diameter, on the parietal pleura of the thoracic wall. He contacted a biologist at the California Department of Fish and Game who sent the mass to the Wildlife Investigations Laboratory and advised the meat processor to discard the carcass. The mass was submitted to CAHFS in formalin a few months later at which time a diagnosis of coccidioidomycosis was made. Upon questioning, the hunter indicated he did not notice that any of the other tissues appeared to be affected when he eviscerated the carcass. No persons at risk of exposure, including the hunter, family, friends, taxidermist and meat processor reported any illness from the time of exposure until the diagnosis was made.

Nikkomycin Z Treatment of Client-Owned Dogs with Coccidioidomycosis: Preliminary Results

Lisa F. Shubitz[1,3], David E. Nix[2], Michael E. Roy[4], John N. Galgiani[3]

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Current drug therapies for coccidioidomycosis are not always effective at either alleviating the illness or curing the infection. There is ongoing need for new antifungal drugs to treat this difficult fungus.

Nikkomycin Z (NikZ) is a chitin synthase inhibitor that has been shown to reduce fungal burden in mice to undetectable levels after lethal challenge. In addition, the drug appears to have little or no toxicity in dogs and rats, and to be well-tolerated after oral administration in humans. A small preclinical trial in client owned dogs (n=12) was designed to provide a first look at efficacy of NikZ in natural disease. Dogs between 5-15 kg (11–33 lbs) with radiographic and clinical pathology changes consistent with coccidioidal pneumonia were enrolled to receive 250 mg (16.7-50 mg/kg) NikZ twice daily for 60 days. Between days 21-30 of treatment, dogs were hospitalized for one day and plasma was collected at specified intervals after drug administration for pharmacokinetic analysis.

After one year, 7 dogs have been enrolled in the trial. Two were removed from study after 6 and 8 days, and 5 completed treatment for 60 days. Dogs completing treatment improved clinically during the study, though it took approximately three weeks before owners reported less coughing and improved appetite and energy. Owners reported no GI or other adverse effects from the medication. Radiographic improvement of lung lesions was observed in all 5 dogs, with resolution in 1, near resolution in 2, and greater than 50% improvement in 2. Four of 5 dogs entered the study having not responded to fluconazole; the fifth was naïve to treatment. Follow up is available on 3 dogs at this time. One dog remains well on no medication after NikZ treatment (failed fluconazole); one dog took 60 days of fluconazole after NikZ and is well on no further medication after 6 months. One dog failing fluconazole and with 50% improvement of lung lesion on NikZ had elevation of titer and white blood cell count after returning to fluconazole, but 8 months after NikZ treatment has near resolution of the lung lesion with ongoing high dose (12 mg/kg BID) fluconazole therapy.

Positron Emission Tomography (PET) Scans are Frequently Positive in Solitary Pulmonary Nodules Due to Coccidioidomycosis

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Solitary pulmonary nodules (SPN) due to coccidioidomycosis are a common finding among patients living in the coccidioidal endemic region and are difficult to distinguish from malignancies using radiographic methods. Uptake of ^{18}fluorodexoglucose (^{18}FDG) by positron emission tomography (PET) has been used to assess whether SPN are malignant but significant uptake may occur in lesions due to infectious causes. The purpose of this study was to assess ^{18}FDG uptake by PET among SPN shown to be either coccidioidal or granulomatous in etiology among patients living in the coccidioidal endemic region. To do this, we retrospectively reviewed all solitary pulmonary nodules found to be either coccidioidal or granulomatous based on lung biopsy at SAVAHCS between January 2008 and April 2010. Patients who underwent PET were further analyzed. Among 173 diagnostic biopsies, 20 (11.6%) were either coccidioidal (14) or granulomatous without an identified organism (6). PET was performed in 10 of these cases. Of the seven in the coccidioidal group, six were positive for ^{18}FDG uptake (86%), while two of the three (67%) in the granuloma group were positive. Of the six with positive PET in the coccidioidomycosis group, four (67%) had ^{18}FDG uptake both in the lung and mediastinum while two patients (23%) had ^{18}FDG uptake in the nodule only. Among the two with ^{18}FDG uptake in the granuloma group, one had ^{18}FDG uptake in the lung only while the other had ^{18}FDG uptake only in the mediastinum. The mean ± SEM uptake in standard uptake values (SUV) in the lung of those with positive scans was 3.2 ± 0.3 and was 2.3 ± 0.9 in the mediastinum, values that are considered consistent with a possible malignancy. In conclusion, coccidioidal and granulomatous pulmonary nodules frequently take up clinically detectable amounts of ^{18}FDG. PET does not reliably distinguish malignancy from coccidioidomycosis in patients with SPN.

Relative Performance of Immunodiffusion Methods and Complement Fixation for Detection and Quantitation of *Coccidioides* Specific IGG

Oubsuntia V, Lancaster M

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Background: The objective of this study was to determine the relative performance of microdilution Coccidioides antigen specific complement fixation CF), classic (routine) Ouchterlony double diffusion (RID), a high sensitivity modification of Ouchterlony double immunodiffusion (KID), and a further modification to provide quantitative immunodiffusion (QID) results. Earlier studies have suggested that QID could be used in place of the CF test. Our laboratory was interested in investigating the utility of incorporating an alternative antibody quantitation method into our testing procedures.

Methods: Serum samples were those presented for routine serologic analysis for *Coccidioides* infection in our laboratory. Samples were evaluated for evidence of IgG using both RID and KID. Immunodiffusion precipitin intensity was graded on a three point scale: Negative, Weakly Reactive, and Reactive. All samples were also tested by microdilution CF with complement fixation overnight at 4ºC. An additional set of samples were also tested in parallel using QID and CF methods.

Results: A series of 893 serum specimens representing an approximate distribution of IgG reactivity in our community were evaluated for IgG reactivity by RID, KID and CF tests. A second study evaluated 5031 (including the aforementioned 893 samples) sera were evaluated to focus on relative performance at the lower end of the dilution range; titers of <1:1 to 1:4. A third study evaluated correspondence of antibody titers determined by both QID and CF methods. Good agreement for detection of IgG exists between RID and KID. KID method detected only an additional 5 of 334 IgG positive samples. Our conclusion is that KID may not be necessary for routine detection of IgG. A high level of correspondence exists between both RID and KID and CF testing when using a three point semi-quantitative grading criteria and a high level of correspondence between antibody titers derived using QID and CF methods.

Conclusions: This study suggests that QID may be suitable for use as an alternative to the CF test to quantitate *Coccidioides* specific antibodies in serum.

Specificity of Enzyme Immunoassay for Serologic Coccidioidomycosis Diagnosis Compared to Immunodiffusion

Nathalie Petein, Laura Erhart, Rebecca Sunenshine

Background: Serologic testing for coccidioidomycosis challenges clinicians due to conflicting small studies regarding the sensitivity and specificity of newer enzyme immunoassay (EIA) tests and the lack of a true gold standard diagnostic test for comparison.

Methods: We analyzed all Lab Corp coccidioidomycosis serological test results from February 2008 through February 2009 and calculated the sensitivity, specificity, and positive/negative predictive values of EIA immunoglobulin (Ig)M and IgG. Immunodiffusion IgM and IgG (ID), complement fixation titers (CF), and tissue/culture diagnosis were used as tests for comparison. The comparison test (CT) was considered positive if any comparison test was positive the day of EIA collection or if tissue/culture diagnosis occurred during the time period. Cases required EIA IgM and IgG and ≥ 2 comparison tests performed the same day for inclusion. Medical records associated with positive EIA and negative comparison test results were reviewed for coccidioidomycosis symptoms, physician diagnosis, and subsequent positive comparison test results. Sensitivity, specificity, and predictive values were calculated, including those with subsequent positive comparison test results.

Results: A total of 1445 laboratory test sets were identified. EIA sensitivity and specificity were 83.8% and 92.6%, respectively. Positive and negative predictive values were 61.5% and 97.6%, respectively. Of 94 “false positive” EIA results, 92 (97.9%) were associated with documented coccidioidomycosis symptoms and 81% with coccidioidomycosis physician diagnosis.

Conclusion: Based on the largest study of sensitivity and specificity calculated from laboratory surveillance data, EIA sensitivity and specificity for coccidioidomycosis diagnosis are lower than previously reported using only coccidioidomycosis laboratory tests as a comparison. However, association of “false positive” EIA results with coccidioidomycosis symptoms and physician diagnosis suggests that ID and CF laboratory tests alone are not a sufficient confirmation test for diagnosis.

Miltefosine (MF) in vitro and in vivo against *Coccidioides*.

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Background: MF is a phosphocholine lipid used in Rx leishmaniasis. It may act on Na+-ATPase, via inhibiting phosphatidylcholine synthesis, altering phospholipids, and thus changing membrane phospholipid interaction with enzymes, or by inhibiting protein kinase C, which activates Na+-ATPase by phosphorylation. It is a broad-spectrum antifungal in vitro, efficacious PO in murine cryptococcosis, and studied in resistant human mycoses cases.

Methods: We tested *Coccidioides* mycelia in vitro via broth macrodilution. Six groups of 6 Swiss-Webster 8-wk-old mice were challenged intranasally with 485 *Coccidioides* arthroconidia. Mice were Rx 7 days with 7.2 (dose effective vs. cryptococcosis, and at drug solubility limits) or 3.6 mg/kg MF in water QD via gavage, starting 120h post-challenge, to allow establishment of parasitic-form infection. A group received 7.2 mg/kg starting 48h. Fluconazole (FZ) 25 mg/kg BID, a suboptimal dose, was given groups +/- MF. Controls were given saline. Two days after Rx, infection was quantitated.

Results: MF was cidal to 8 clinical *Coccidioides* isolates (MICs and MFCs ≤2 mcg/ml) in vitro. In vivo, lung CFU were *higher* ($p \leq 0.01$) in 7.2 mg/kg group than all 5 others. MF 3.6 mg/kg was less efficacious than FCZ ($p=0.01$), and didn’t potentiate FZ. Starting MF at 48h gave superior results to 120h ($p=0.006$), but not controls. Spleen cultures gave identical conclusions. MF 7.2 mg/kg appeared poorly tolerated.

Conclusion: MF inefficacy could be related to suppression of host immunity, toxicity; different susceptibility of parasitic (vivo) vs. saprophytic (vitro) forms, or enhancement of spherule growth; and/or poor penetration into coccidioidal infection.

Does the Presence of Mediastinal Adenopathy Confer a Risk for Disseminated Infection in Non-immunocompromised Persons with Pulmonary Coccidioidomycosis?

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Background: Pulmonary coccidioidomycosis is caused by inhaling airborne arthroconidia of *Coccidioides*, a soil-dwelling fungus endemic to the desert southwestern United States. Although uncommon, disseminated coccidioidal infection can be associated with well-defined risk factors such as cell mediated immunodeficiency, certain races such as African or Filipino, male sex, or pregnancy. Prior to widespread use of computed tomography (CT), the presence or persistence of mediastinal lymphadenopathy in conjunction with pulmonary infiltrate (as identified on chest radiographs) was suggested to be a risk factor for disseminated infection, but this possibility was not subjected to formal scientific investigation.

Methods: We performed a retrospective review of patients with pulmonary coccidioidomycosis who were evaluated by chest CT. Two radiologists independently interpreted 157 CT scans from patients with pulmonary coccidioidomycosis: 52 patients had mediastinal lymphadenopathy by CT criteria, and 105 patients did not have such mediastinal lymphadenopathy.

Results: Disseminated coccidioidal infection was seen in 7 (13.5%) of 52 patients with mediastinal lymphadenopathy, and in 6 of 105 (5.7%, p=0.12)) without such adenopathy.

Conclusion: Among immunocompetent patients, mediastinal lymphadenopathy, as defined by chest computed tomography, does not portend an increased risk of disseminated coccidioidomycosis.

Studies with Nikkomycin Z in Mice with Experimental Coccidioidal Pneumonia.

Nix D.E., Shubitz L.F., Trinh H., Perrill B., Hanan N., Thompson C.M., Galgiani J.N.*

Presented but abstract not available

Intensive Study of Six Patients with Primary Pulmonary Coccidioidomycosis

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Six patients with symptoms of confirmed pulmonary coccidioidomycosis of between 8 and 25 days' duration were enrolled in a randomized double-blind study of nikkomycin Z versus placebo. Four patients received nikkomycin Z at 50 mg bid, a dose predicted to have little effect based on animal studies. One patient received 250 mg bid, and one received placebo. Study procedures included assessment of symptoms and laboratory testing every few days over a 28-day period, as well as a chest CT scan at baseline and after 2 or 4 weeks. In 2 of 4 patients where sputum was obtained at enrollment, Coccidioides was recovered. At end of study, sputum from one patient whose lesion became cavitary again yielded the fungus in culture. ESR was normal in 5/6 patients. CRP was mildly elevated in 4/6 patients and declined during the study period. Eosinophil count was elevated at some time during the study period in 5/6 patients. CT scans showed single pulmonary masses in 4/6 patients, with modest decrease in size over a 14 or 28-day period, and development of cavitation in 2/4. One patient had a thin walled pulmonary cavity that persisted. One patient with mild symptoms had multilobar nodular disease on CT scan that was not appreciable on chest X-ray. All patients did well clinically, with most symptoms resolved by day 28. We conclude that 1) simple sputum cultures for fungus in patients with even mild illness may be diagnostically useful and 2) despite revealing more extensive disease, CT scans did not contribute significantly to altering management or outcome assessment.

Cerebrospinal Fluid Complement Fixation Titer as a Predictor of Outcome in Coccidioidal Meningitis

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Background: Cerebrospinal fluid (CSF) pleocytosis, differential, protein, glucose and complement fixation titers have traditionally been used in the diagnosis and prognosis of coccidioidal meningitis (CM). Prior studies have evaluated the significance of CSF pleocytosis and protein as risk factors for morbidity and mortality. The objective of this study is to evaluate the complement fixation (CF) titer of CSF as a predictor of outcome.

Method: This is a retrospective review of 148 medical records of CM patients that were registered in coccidioidomycosis clinic at Kern Medical Center (KMC) between 1987 and 2010. Twenty-nine patients were excluded due to unavailability of initial CF titers. Patients were followed for an average of 102 months (2 - 281). After conversion of titers to 2^n log and analysis with One-way ANOVA test by SAS® JMP® 8.0, titers were correlated with patient incidence of hydrocephalus, cerebrovascular infarction, arachnoiditis, seizures, cerebral hemorrhage and mortality. Individual CF titers by mortality were assessed with Epi Info™ for chi square.

Results: Mean age was 34 (14-74) with 73% Hispanic, 14% African American, 11% Caucasian, and 2% others. The overall ratio of male to female was 69% to 31 %. (n=119)

Mortality was lower in CM patients with initial CSF CF titers of ≤1:4. This association was statistically significant. [OR: 6.25, CI 95(1.63-26.0); *P*=0.0017].

Mortality, on the other hand was higher in patients with initial CSF CF titers of ≥1:64. This association was also statistically significant. [Mean $2^{6.7}(2^{5.6} – 2^{7.9})$; *P*=0.0497]. (Figure 1)

Incidence of hydrocephalus [Mean $2^{5.8}(2^{5.2} – 2^{6.5})$; *P*=0.18] and cerebrovascular infarction [Mean $2^{6.0}(2^{5.3} – 2^{6.9})$; *P*=0.12] were increased in patients with higher initial CF titers, but were not statistically significant.

(Continued)

Cerebrospinal Fluid Complement Fixation Titer as a Predictor of Outcome in Coccidioidal Meningitis

Grant Karno[1], Arash Heidari[1,2], Royce Johnson[1,2], Vinutha Chandrasekaran[1], Jasjit Khurana[1], Irene Spinello[1]

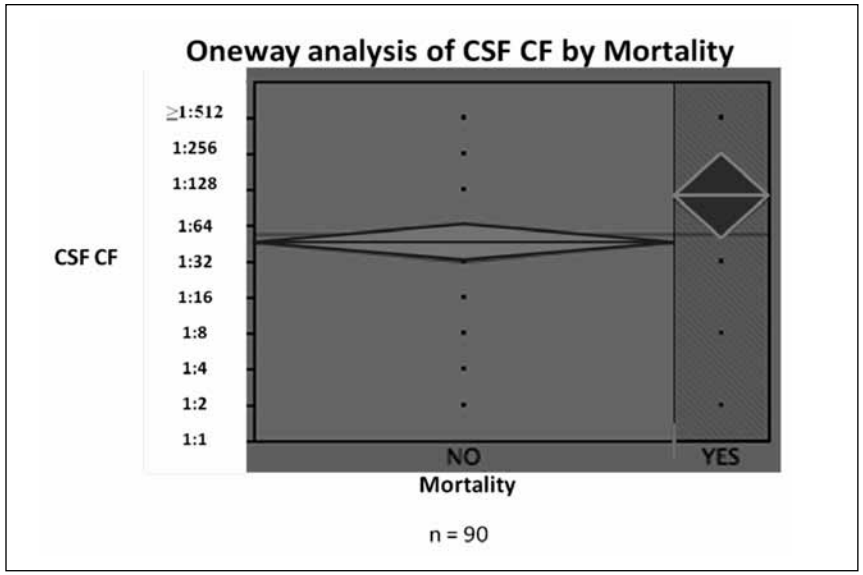

Figure 1.

Conclusions: Cerebrospinal fluid complement fixation titer is a predictor of mortality. There is a trend for increased incidence of hydrocephalus and cerebrovascular infarction with higher CF titers.

Cure of Coccidioidal Meningitis A Case Report

Tim Kuberski, MD, FIDSA

If untreated coccidioidal meningitis (CM) is fatal. The advent of antifungal agents improved the prognosis for this infection, but a cure is extremely uncommon. Fluconazole has been shown to be effective in controlling the disease, but it is not curative. If the fluconazole is stopped in the course of therapy, the CM will relapse. There is some evidence in an experimental animal model that CM can be cured by using parenteral liposomal amphotericin B (LAB). It is unlikely that any controlled studies will be done on the use of LAB in humans with CM. This case report details the clinical findings, treatment and outcome of a patient with CM treated with LAB as the primary agent of therapy.

The patient is a Caucasian male who was 61 years old when he presented in 2001 with fever and mental status changes evolving over several weeks. Several months prior to becoming ill the patient was treated with antibiotics for a pneumonia of unknown cause. On examination he was confused with no focal neurological findings. His lumbar puncture revealed: WBC 1688/ mm^3; 9% PMN's, 58% mononuclear cells and 33% eosinophils; CSF glucose 10 mg/dl and protein 152 mg/dl. *Coccidioides* grew from the CSF. MRI of the brain, with contrast, did not show meningeal enhancement. His serum and CSF complement fixation (CF) titer to *Coccidioides* was 1:8. The patient received a total dose of 8300 mg of intravenous LAB, titrating the infused dose between 5-7 mg/kg depending on tolerance and laboratory parameters. The total dose of LAB was given over 4 weeks. In the last week of the LAB he was started on oral fluconazole, 400 mg, once daily. The fluconazole was discontinued in 2007 when the patient's serum CF tests were negative for 18 months and the patient was doing well. He remains asymptomatic, functions normally and his serum CF serology remains negative.

Why does this patient appear to be cured? Factors to be considered: Caucasian race, presenting mental changes were relatively mild, marked eosinophilic CSF pleocytosis, relatively low acute CF titer, no corticosteroids, compliant about LAB and fluconazole. This is the type of patient who would be given oral fluconazole indefinitely upon presentation by most experts, however he might be the kind of patient who has the best chance of being cured if treated aggressively with LAB.

Estimated Incidence of Coccidioidomycosis by Date of Onset in Kings County, California, 2007-2010

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Health Officer, Kings County, California

Kings County is a small, coccidioidomycosis-endemic county in the southern San Joaquin Valley of California. Prior to 2007 Kings County reported cases to the state if a medical provider completed a Confidential Morbidity Report. The date of onset for the illness was often missing or was the same date as the date of diagnosis. In an attempt to track the incidence by month, the health officer mandated additional reporting requirements. As of 1/1/07 providers were required to submit on the reporting form a date of onset and the presenting illness. Providers were also required to submit a copy of the supporting laboratories. The health officer then reviewed the materials to determine whether the diagnosis and the date of onset were reasonable. If the date of onset were questionable additional medical records were requested and reviewed. Some the cases were interviewed about the date of onset of their illness. Confirmed cases with a reasonable date of onset are termed incident cases. Confirmed cases without a reasonable date of onset are termed non-incident cases. No set criteria for reasonableness were used except that no case was confirmed based solely on a positive ELISA IgM. Examples of reasonableness decisions will be provided. We will present four years of incident and non-incident Kings County data, approximately 600 cases. The incident cases per month will be graphed by date of onset. The non-incident cases per month will be graphed by date of diagnosis. Additionally, the data will show that risk by place of residence is not uniformly distributed in the county and that state prisoners are at an apparent increased risk for coccidioidomycosis compared with the population of the county who aren't incarcerated by the state.

Mapping Potential *Coccidioides* Growth Sites Based on Satellite Imagery and Molecular Biology

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We present preliminary results on a method we are developing to map out areas in the San Joaquin Valley portion of Kern County, California (our Region of Interest, or ROI) where one might find *Coccidioides immitis*. The technique utilizes multispectral satellite images of a section of Shark Tooth Hill (STH). This location has been reported in the literature as a site well-known for its ability to consistently harbor *C. immitis* –even with the spotty distribution this fungus exhibits. Our approach utilizes the spectral signature found at STH to train a Maximum Likelihood Classification algorithm to find other locations in the ROI with similar characteristics. The method is somewhat akin to using vegetation type as a marker. This way, we characterize the growth sites by the vegetation that tends to grow in the same environment as *C. immitis*. This makes sense because vegetation type closely reflects the co-variation of the relevant biochemical, biophysical, and biological variables such as nutrients, temperature and energy environment, soil microorganisms and plants, etc. The implicit assumption is of course that the STH environment is the only *C. immitis*-supporting environment within the ROI. This is a safe assumption given that the ROI we consider is relatively small, and does not include a wide range of ecosystems. The final step in this study is to link the results of the satellite imagery to results of molecular biological studies in order to identify *C. immitis* growth sites using a culture independent method. We use this step to check for consistency with the computer results (i.e. this step provides ground truth).

One of the main goals is to generate a model that identifies the most likely niche for *Coccidioides* growth in the ROI. This technology may help establish a more systematic method of prioritizing field-sampling strategies and thus allow a more thourough understanding of the ecological niche occupied by the fungus. A second goal is to use our resulting map to advise the public as to potentially dangerous areas. Finally, by observing changes in the spatial distribution of this signature over time, we hope to correlate changes in these maps with changes in coccidioidomycosis incidence.

Coccidioidomycosis Incidence in San Joaquin Valley Prisons

Leistikow B, Schneider J, Mohle-Boetani J.

California Prison Health Care Services

Background: Recent reports suggest that some California prisons (institutions) have a substantial coccidioidomycosis burden, but few of their incidence rates have been reported. We conducted a study to determine recent coccidioidomycosis incidence rates by institution using publically available data.

Methods: We used published coccidioidomycosis case counts by institution-year from the Kern and Fresno County Health Departments, who collect data through state mandated Confidential Morbidity Reports (CMRs) and identify prison residents by the addresses on the CMR cards. To calculate incidence rates (cases per 100,000 person-years) we divided the coccidioidomycosis case counts in each institution by the inmate population in that institution using data published by the state. We then compared these rates with published Kern County community rates. We investigated 5 institutions in Kern and Fresno counties for the years 2004-2008.

Results: We found an average incidence rate of 960 per 100,000 person-years across all the institution-years studied. Institution-year-specific incidence rates ranged from 0 to 12,000. Compared to the Kern community rate, incidence was consistently relatively low at the California Correctional Institution (CCI) and high at Pleasant Valley State Prison (PVSP). The five year average annual incidence rate per 100,000 by institution ranged from 50 at CCI to 5,500 at PVSP.

Discussion: Coccidioidomycosis incidence varied substantially by institution even within the area known to be endemic for coccidioidomycosis.

A Second Look at *Coccidioides*' Cupin Protein

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T27K is a multi-component vaccine shown to protect mice challenged with *Coccidioides*. Various methods have been utilized to identify individual proteins with the goal of discovering which constituents are immunoprotective. As previously reported, continuous elution electrophoresis was used to fractionate T27K and the eluted pools were tested for their ability to stimulate coccidioidal-immune human PBMCs. The stimulatory pools were analyzed using mass spectrometry which lead to the identification, cloning, and expression of the Coccidioides cupin protein 21 (CCP21). Here we report the further characterization of the purified recombinant CCP21 (rCCP21) from C. posadasii and glycoprotein analysis of the native protein.

The reactivity of human serum with rCCP21 was investigated using an ELISA. In a preliminary experiment, pools of serum containing either complement fixation (CF) IgG, precipitin (PPTN) IgM, or no detectable antibodies were studied. Reactivity between rCCP21 and CF positive serum was significantly greater than with negative serum when measuring human IgG. There was no detectable difference between PPTN positive and negative sera when an anti-human IgM antibody was used. In a second experiment, the reactivity of 30 individual sera was evaluated. While the number of samples used was too small to permit robust statistical analysis, the data suggests that CF positive patients generate IgG antibodies to CCP21. There is a minor trend correlating CF titer with rCCP21 reactivity, although it does not appear to be prognostically useful.

In an immunohistochemical analysis using paraffin embedded infected mouse lung tissue, sections were incubated with either prebleed or rCCP21 hyperimmunized rabbit serum and then detected using an Alexa Fluor 488 conjugated goat anti-rabbit antibody. The autofluorescence of the coccidioidal cell wall prevented a clear determination of the presence or absence of CCP21 in that area. However, intracellular staining was visible with the hyperimmunized serum incubated sections that was absent in the prebleed stained sections.

The lectins concanavalin A and wheat germ agglutinin were used to isolate glycoproteins from T27K. A western blot analysis of the fractions was performed using rabbit anti-rCCP21. Staining material at 21kDa was apparent in the eluate suggesting that native protein was glycosylated despite lacking a predicted signal sequence.

Quantitative Comparison of Phagocytosis by Neutrophils from Healthy Donors and Patients with Chronic Coccidioidal Infection

Cheng-Yuk Lee, George R. Thompson, Alexander Mankovich, and Volkmar Heinrich*

University of California, Davis

Our interdisciplinary study aims to illuminate the mechanisms employed by human neutrophils (from healthy donors and patients with chronic coccidioidomycosis) during the phagocytosis of various model pathogens, i.e., antibody-coated beads, zymosan particles, and inactivated *Coccidioides* forms. To this end we are performing in parallel single-live-cell/single-target experiments using dual-micropipette manipulation as well as bulk phagocytosis assays by flow cytometry. Our quantitative assessment of the time course of single-cell neutrophil phagocytosis reveals that generally, the cell morphology and cell mechanics during the uptake of the two types of fungal particles (i.e., zymosan and *Coccidioides*) are similar. This suggests that our recently reported results on zymosan phagocytosis readily carry over to neutrophil interactions with *Coccidioides* forms, in particular the clear difference between phagocytosis of fungal targets and antibody-coated particles. Furthermore, preliminary single-cell experiments comparing the behavior of neutrophils from healthy donors and coccidioidomycosis patients have shown that the neutrophil responses to *Coccidioides* forms are similar in the two cases. Intriguingly though, we have discovered a significant difference in the responses to antibody-coated targets, indicating that FcyR-mediated recognition of pathogens may be compromised in neutrophils from coccidioidomycosis patients. We are currently investigating possible origins of this behavior using bulk phagocytosis assays as well as measurements of the cell-surface expression of Fcy- and other phagocytic receptors by flow cytometry.

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Voriconazole and Posaconazole for the Treatment of Refractory Coccidioidomycosis: A Retrospective Review

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Background: Coccidioidomycosis is a fungal infection of the desert southwestern US. While many afflicted suffer a self-limited disease, others require antifungal therapy. Currently used triazoles such as fluconazole and itraconazole have largely supplanted the use of amphotericin B which was fraught with adverse effects. Voriconazole and posaconazole have shown benefit for patients with coccidioidomycosis refractory to the first line agents in limited case reports and small open label trials.

Methods: We conducted a retrospective review of all patients who were prescribed voriconazole or posaconazole for coccidioidomycosis at our institution between 1/1/2006 and 8/1/2010. We used both a retrospectively-applied Mycosis Study Group score (which includes a composite score for symptoms, serology and radiographic findings) and the documented impression of the treating medical practitioner to assess outcomes.

Results: Twenty one patients received voriconazole and 16 received posaconazole and met criteria for study inclusion. After a median duration of 6 treatment months, 14 of the 21 (67%) voriconazole recipients were improved in overall status, 5 were unchanged, and 2 patients were deemed voriconazole failures. After a median treatment duration of 17 months, 12 of 16 (75%) posaconazole recipients were improved, 1 was unchanged, and 3 patients failed treatment due to medication intolerance or relapsed infection. The cost of the medication (voriconazole or posaconazole) was a limiting factor for 4 patients who ultimately discontinued the medication.

Conclusions: Voriconazole and posaconazole are reasonable but not infallible options for salvage treatment of refractory coccidioidal infections. The high cost of these medications may limit a patient's ability to utilize such therapy. Prospective comparative trials are required to provide further insight into the efficacy and utility of one agent over the other.

Induction of Chitinolytic Enzymes during Spherule-endospore Phase of *Coccidioides posadasii*

Jennine M. Lunetta and Demosthenes Pappagianis

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School of Medicine, University of California, Davis, CA 95616, USA

Chitin is a homopolymer of ß(1,4)-linked N-acetylglucosamine (GlcNAc) and a major structural component of the fungal cell wall. Chitinolytic enzymes catalyze the cleavage of chitin and can be divided into two groups: chitinases (endo- and exo- depending on their cleavage patterns) and ß-N-acetylhexosaminidases. A number of studies have demonstrated that chitinolytic enzymes are inducible by chitin and/or chitin degradation products such as GlcNAc. Based on these studies, we investigated the effect of GlcNAc on the chitinolytic enzymes of C. posadasii during the in vitro growth of the spherule-endospore (SE) phase. Previously, we reported that the addition of GlcNAc to SE phase cultures at 24 hrs after inoculation resulted in an increase of ß-N-acetylhexosaminidase 1 protein (CpHEX1) and enzyme activity in the extracellular medium and an increase in the temporal expression of the CpHex1 transcript. Here we report on the effect of GlcNAc on chitinases of C. posadasii. More specifically, we evaluated chitinase 1 protein (CTS1) concentrations and exo- and endochitinase activities in the extracellular medium and the expression of multiple chitinase genes in SE phase cultures with and without supplemental GlcNAc. SE phase cells were grown in Converse medium at 37 °C and then GlcNAc or water was added directly to the cultures at 24 hrs after inoculation. Cells and culture filtrates were collected every 24 hrs through 96 hrs after inoculation. SDS-PAGE analysis of culture filtrates showed an increase in the concentration of CTS1 protein in the extracellular medium from cultures supplemented with GlcNAc at 72 and 96 hrs after inoculation (Fig. 1). In addition, an increase in chitinase enzyme activities was observed in the supplemented cultures at 96hrs after inoculation (Fig. 2). RT-PCR analysis with primers specific for the nine predicted chitinase genes of C. posadasii showed that some of the genes (e.g. cts1, cts3 and cts4) are inducible by GlcNAc (Fig. 3). In summary, individual chitinolytic enzymes of C. posadasii are inducible by the chitin monomer, GlcNAc during in vitro SE phase growth. Additional studies on the differential expression and induction patterns exhibited by chitinolytic enzymes during SE phase growth may provide insight into their biological roles.

(Continued)

Induction of Chitinolytic Enzymes during Spherule-endospore Phase of *Coccidioides posadasii*

Jennine M. Lunetta and Demosthenes Pappagianis

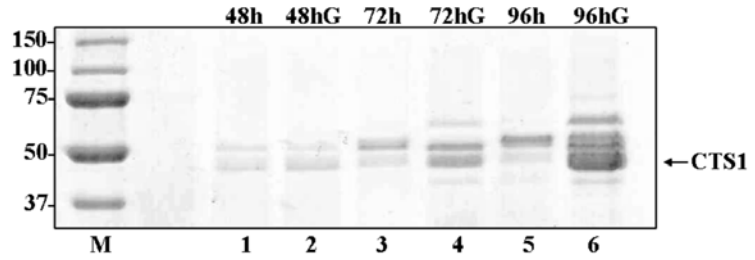

Fig. 1. The effect of GlcNAc (G) on the level of chitinase protein (CTS1) in the extracellular medium during *in vitro* SE phase growth. The Coomassie blue-stained SDS-PAGE gel shows culture filtrate proteins (20 µg per well) collected at 48, 72 and 96 hours after inoculation from cultures with and without GlcNAc.

Figure 1.

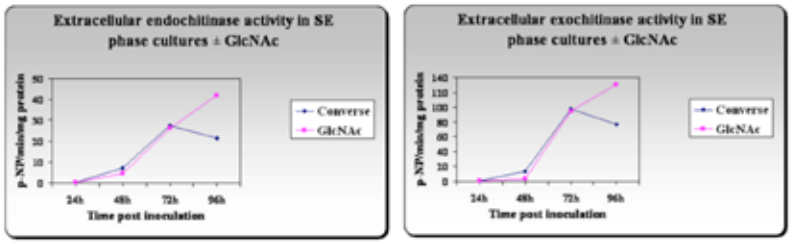

Fig. 2. The effect of GlcNAc on extracellular endochitinase and exochitinase enzyme activity during *in vitro* SE phase growth. The plots show enzyme activity in culture filtrates collected from SE phase cultures at 24h, 48h, 72h and 96h post-inoculation grown in Converse medium (♦) or Converse medium with 12.5 mM GlcNAc added directly to the culture at 24h post-inoculation (■).

Figure 2.

Early Post-Infection Detection of *Coccidioides* in Intranasally Infected Mice

Lisa F. Shubitz, Robert Perrill, Maria L. Lewis, Sharon M. Dial, John N. Galgiani

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Recent studies of fungal burden in lungs of mice treated with antifungal drugs has caused us to reassess the ability to detect very low numbers of fungal organisms in lungs of mice, and also to determine how early we can detect it. Swiss-Webster mice were infected with target doses of 500 arthroconidia and mice were sacrificed between days 3 and 6 post-infection (p.i.). Lungs were 1) sliced thinly and plated in their entirety on GYE plates; 2) homogenized in PBS and diluted 1:10, with plating of 100 ul, 900 ul, and 450 ul each of the undiluted volume on 4 GYE plates; 3) fixed in formalin and the entire lung prepared in 5-6 um slices on slides and stained with a cocci-specific immunohistochemistry stain on every third section. Lung homogenization studies were performed with and without Triton X-100, a detergent used to disperse fungal organisms from the tissue, in the initial homogenizing diluent

Results of homogenization and plating of entire lung on 4 GYE plates revealed that colony forming units can be detected 48 hrs p.i. The fraction of the inoculum applied to the nares that we detected as colony growth ranged from 3-13% (median 7%, n= 5 mice). By day 4 p.i., the number of colonies detected increased a hundred fold, most likely due to maturation and rupturing of spherules. Undiluted and 1:10 diluted homogenate solutions containing Triton X-100 grew few or no colonies; we confirmed with 48-hour in vitro spherules that 1% Triton X-100 caused no colonies to grow and 0.1% reduced colony counts by at least 50%.

Histopathology confirmed the results of the homogenized lung cultures. On days 3 and 4, approximately 20 maturing spherules were observed in the entire lungs. Surrounding the developing spherules was usually a few layers of macrophages. Overall, inflammation surrounding the spherules at days 3 and 4 was minimal. By day 5, spherules were observed to be rupturing and neutrophils became abundant mixed with the macrophages. About 20 spherules with spreading endospores were observed throughout all lung fields. By day 6, 1-1.5 mm lesions were seen grossly at necropsy. Neutrophils and other inflammatory cells increased at the sites of spherule rupture; many endospores exhibited enlargement and were further dispersed from the ruptured spherule. By day 6, inflammation and organisms were observed in the airways as well as parenchyma and airway destruction was present.

Coccidioidomycosis in California Prisons with Seasonal Surge, 2010

D. Pappagianis, D. Davis, J. Einstein

University of California Davis
Coccidioidomycosis Serology Laborator

Reports prior to and during this *Coccidioides* (coccy) Study Group have referred to the problem of coccy in California State Prisons (Pappagianis, et al 2007 Ann NY Acad Sci). Some prisons were constructed in endemic areas where inmates and employees can acquire Valley Fever. However, the associated clinical problem can also be encountered outside the endemic areas as infected inmates are reassigned. Even within endemic areas, the frequency of the disease is markedly varied (Table). “Hyperendemicity” is emphasized at Pleasant Valley, Coalinga and Avenal State Prison. A surge in cases in the latter months in these two institutions is shown in the table and Figure which shows monthly rainfall in Coalinga and coccidioidomycosis detected by month through serologic testing in 2010. In that year, increased numbers of cases were detected in California (4446

Table. Coccidioidal Infections for 2010 in California State Prisons

Institution*	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total	Population	Infections/ 100,000
Pleasant Valley SP	18	6	8	13	6	18	33	44	62	71	41	37	**357**	4647	7682
Avenal SP	5	3	3	4	7	10	9	41	49	52	27	6	**216**	5723	3774
Cal SP, Corcoran	4	2	1	1	0	2	1	1	4	5	4	3	**28**	4876	574
Cal Men's Colony, San Luis Obispo	1	0	2	1	0	2	0	0	4	6	5	2	**23**	6139	375
Cal SP, Los Angeles Co, Lancaster	3	0	1	0	3	5	3	0	2	2	3	0	**22**	4356	505
Kern Valley SP	0	3	1	1	1	0	1	4	3	4	1	0	**19**	4663	407
Cal Corr Ctr, Susanville	0	0	0	1	0	0	0	1	3	1	1	0	**7**	5460	128
Cal Corr Inst, Tehachapi	2	0	0	0	0	0	0	0	1	0	3	1	**7**	5519	127
Cal SATF and SP, Corcoran	0	1	1	0	1	0	0	0	1	1	2	0	**7**	6082	115
Corr Training Fac, Soledad	1	2	0	0	0	0	2	1	0	0	0	0	**6**	6538	92
Mule Creek SP	2	0	0	0	0	2	0	1	0	0	0	1	**6**	3523	170
Cal Rehab Ctr, Norco	0	0	0	2	0	0	1	0	0	0	1	0	**4**	4132	97
RJ Donovan Corr Fac, San Diego	2	0	0	0	0	0	0	2	0	0	0	0	**4**	4369	92
Sierra Conserv Ctr, Jamestown	0	0	0	0	0	0	1	1	0	2	0	0	**4**	5314	75
Deuel Vocational Inst, Tracy	0	0	1	0	0	0	0	0	0	2	0	0	**3**	3785	79
Cal Medical Fac, Vacaville	1	0	1	0	0	0	0	0	0	0	0	0	**2**	2737	73
High Desert SP, Susanville	0	0	1	0	0	0	0	0	0	0	0	1	**2**	4128	48
Cal Inst for Women, Corona	0	0	0	0	0	1	0	0	0	0	0	0	**1**	2071	48
Cal SP, Calipatria	0	0	0	0	0	0	0	0	0	1	0	0	**1**	4153	24
Cal SP, San Quentin	0	0	0	0	0	0	0	0	0	0	1	0	**1**	4983	20
Cal SP, Solano	0	1	0	0	0	0	0	0	0	0	0	0	**1**	5022	20
Chuckwalla Valley SP	0	0	0	0	0	0	0	0	1	0	0	0	**1**	3159	32
Valley SP, Chowchilla	0	0	0	0	0	0	0	0	0	0	0	0	0	3296	0
Totals:	**39**	**18**	**20**	**23**	**18**	**40**	**51**	**96**	**130**	**147**	**89**	**51**	**722**	**104675**	**14559**

Figure 1.

(Continued)

Coccidioidomycosis in California Prisons with Seasonal Surge, 2010

D. Pappagianis, D. Davis, J. Einstein

in 2010 compared with 2499 in 2009 and 2324 for 2008, Prison cases (Table) numbered 723, 16% of the total of the 4446 reported cases. The numbers are still somewhat crude and we hope to refine them with collaboration with Ann Alcarez, RN, BSN, PHN, Infection Control, Pleasant Valley State Prison.

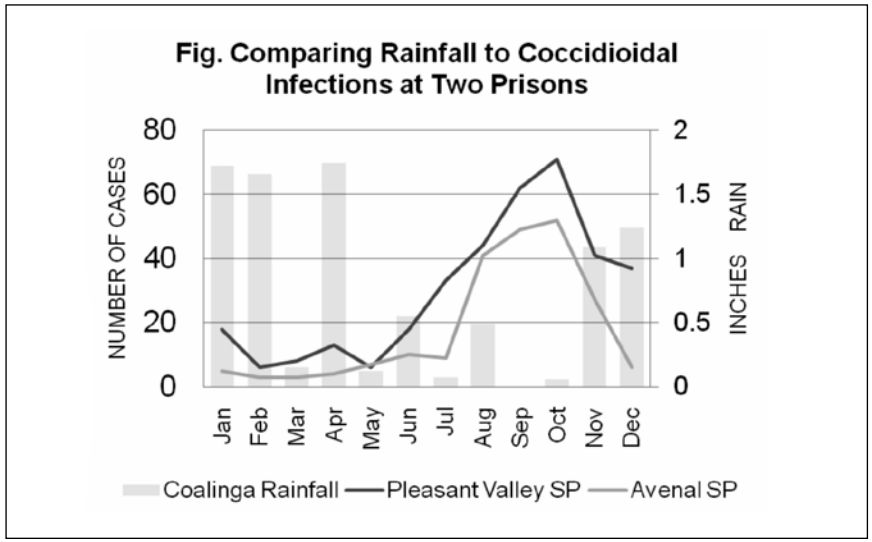

Figure 2.

Assessing Erosion Potential and Coccidiodes immitis Probability Using Existing Geologic and Soils Data.

Harris W., Roffers P.*

Presented but abstract not available

Diagnosing Coccidioidomycosis using IL-17 in Bronchoalveolar Lavage and Peripheral Blood.

Ampel N.M., Nesbit L., Knox K.S.*

Presented but abstract not available

Coccidioidomycosis in 1300 Patients: Spectrum of Radiologic Findings.

Mamlouk M, Heidari A, VanSonnenberg E., Yazdanshenas M, Naderi J., Osei K., Johnson R.

Presented but abstract not available

Annual Meetings of the Coccidioidomycosis Study Group

Number	Date(s)	Location	Held In Conjunction With
1.	July 18, 1956	San Francisco, CA	
2.	December 5-6, 1957	Los Angeles, CA	
3.	December 4-5, 1958	Los Angeles, CA	
4.	December 3-4, 1959	Los Angeles, CA	
5.	December 8-9, 1960	Los Angeles, CA	
6.	Nov. 30 – Dec. 1, 1961	Los Angeles, CA	
7.	November 29-30, 1962	Los Angeles, CA	
8.	December 5-6, 1963	Los Angeles, CA	
9.	December 10-11, 1964	Los Angeles, CA	California Thoracic Society
10.	December 7, 1965	Phoenix, AZ	2nd Coccidioidomycosis Conference
11.	April 19, 1967	Palm Springs, CA	California Thoracic Society
12.	May 1, 1968	Fresno, CA	California Thoracic Society
13.	April 15, 1969	San Diego, CA	California Thoracic Society
14.	April 1, 1970	San Francisco, CA	California Thoracic Society
15.	April 6, 1973	Newport Beach, CA	California Thoracic Society
16.	April 5, 1974	Sacramento, CA	California Thoracic Society
17.	September 30, 1974	San Francisco, CA	Coccidioidomycosis Cooperative Treatment Group
18.	April 2, 1975	San Diego, CA	California Thoracic Society
19.	July 31, 1975	San Diego, CA	Coccidioidomycosis Cooperative Treatment Group
20.	January 14-15, 1976	San Diego, CA	Coccidioidomycosis Cooperative Treatment Group
21.	April 7, 1976	Palo Alto, CA	California Thoracic Society
22.	May 18, 1977	San Francisco, CA	American Lung Association
23.	April 5, 1978	Beverly Hills, CA	California Thoracic Society
24.	May 15, 1979	Las Vegas, NV	American Lung Association
25.	April 11, 1980	Sacramento, CA	California Thoracic Society
26.	March 28, 1981	San Francisco, CA	California Thoracic Society
27.	May 15, 1982	Los Angeles, CA	American Lung Association
28.	March 20, 1983	La Jolla, CA	California Thoracic Society
29.	March 14-17, 1984	San Diego, CA	4th Coccidioidomycosis Conference

Annual Meetings of the Coccidioidomycosis Study Group

Number	Date(s)	Location	Held In Conjunction With
30.	March 8, 1986	Santa Barbara, CA	
31.	April 4, 1987	Los Angeles, CA	
32.	April 9, 1988	Los Angeles, CA	
33.	April 8, 1989	San Jose, CA	
34.	April 7, 1990	Berkeley, CA	
35.	April 6, 1991	Tucson, AZ	
36.	April 4, 1992	Fresno, CA	
37.	April 3, 1993	Tucson, AZ	
38.	August 24-27, 1994	Stanford, CA	5th Coccidioidomycosis “Centennial” Conference
39.	April 1, 1995	Bakersfield, CA	
40.	March 30, 1996	Scottsdale, AZ	
41.	March 5, 1997	San Diego, CA	
42.	April 4, 1998	Visalia, CA	
43.	March 20, 1999	Tijuana, BC, Mexico	
44.	April 1, 2000	Berkeley, CA	
45.	March 31, 2001	Tucson, AZ	
46.	April 6, 2002	Davis, CA	
47.	April 3, 2003	Scottsdale, AZ	
48.	April 31, 2004	Rosarito Beach, Mexico	
49.	April 2, 2005	Bass Lake, CA	
50.	August 23-26, 2006	Stanford, CA	6th International Symposium on Coccidioidomycosis
51.	March 29, 2007	Tempe, AZ	
52.	April 5, 2008	San Diego, CA	
53.	April 4, 2009	Bakersfield, CA	
54.	March 27, 2010	Surprise, CA	
55.	April 2, 2011	Davis, CA	

• Publishing courtesy of Mayo Clinic in Arizona •