PROCEEDINGS OF THE 60th ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

April 8-9, 2016

Fresno, CA

Proceedings of the 60th Annual

Coccidioidomycosis Study Group

Meeting Number 60

April 8-9, 2016

University of California, San Francisco-Fresno

Community Regional Medical Center

Fresno, California

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Guidelines to the Content of the
CSG-60 Proceedings

I. 2016 CSG–60 Satellite Meeting: Coccidioidomycosis and the Environment

II. 2016 CSG-60 Satellite Meeting: Coccidioidomycosis and Occupational Health

III. COCCI STUDY GROUP 60TH ANNUAL MEETING

2016 CSG–60 Satellite Meeting: Coccidioidomycosis and the Environment
U.C.S.F.-Fresno campus, Room 136
Fresno and R Streets
Fresno, CA 93721
April 8, 2016; 1-5 P.M.

12:30-1:00 **Registration** (no added cost when registered to attend the CSG 60th Annual Meeting April 9, 2016 at U.C.S.F.-Fresno)

1:00-1:15 P.M. **Welcome Address: Bridget Barker (Moderator)**

1:15-1:35

DIRECT DETECTION OF *COCCIDIOIDES* FROM ARIZONA SOILS WITH A NEW REAL-TIME PCR ASSAY
Parise K, Bowers R, Kelly E, Rivas S, Doyle A, Hilsabeck R, Krohn A, Lewis E, Schupp J, Driebe E, Engelthaler D, Keim P, Barker B

1:35-1:55

DEVELOPING METHODS FOR DETECTION OF *COCCIDIOIDES* USING TARGETED AND SHOTGUN METAGENOMIC SEQUENCING OF ENVIRONMENTAL SAMPLES
Chow N, Gade L, Litvintseva A

1:55-2:15

STANDARDIZATION OF NESTED PCR FOR *COCCIDIOIDES SP.* DNA DETECTION IN SOIL SAMPLES
Morales-Flores G, Sandoval G, Ortega-Larrocea P, Suárez-Quijada I, Lauer A, Castañón-Olivares L

2:15-2:45 **Coffee Break**

2:45-3:05

REGIONAL ENVIRONMENTAL SOIL AND AIR SAMPLING FOR *COCCIDIOIDES SP.* AND AIRBORNE FUNGAL SPORE DISTRIBUTION PATTERNS
Cat L, Gorris M, Randerson J, Treseder K

3:05-3:25

GROWTH OF *COCCIDIOIDES* IN SOIL
Hurst S, Gade L, Plumlee G, Litvintseva A

3:25-3:45

INCREASED INCIDENCES OF COCCIDIOIDOMYCOSIS CORRELATED WITH LARGE SCALE LAND DEVELOPMENT IN THE ANTELOPE VALLEY
Colson A, Guevara R, Vredenburgh L, Lauer A

3:45-4:00	Break
4:00-5:00	**Forum Discussion**: Roundtable with speakers and final thoughts, Questions and Answers

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Dinner (on your own)

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DIRECT DETECTION OF *COCCIDIOIDES* FROM ARIZONA SOILS WITH A NEW REAL-TIME PCR ASSAY

Parise, K.L.[1], Bowers, J.R.[2], Kelly, E.[2], Rivas, S.M.[1], Doyle, A.L.[2], Hilsabeck, R.[2], Krohn, A.[3], Lewis, E.R.G.[2], Schupp, J.[2], Driebe, E.M.[2], Engelthaler, D.M.[2], Keim, P.[1,2], and Barker, Bridget M.[1,2]

[1]Center for Microbial Genetics and Genomics, Northern Arizona University, Flagstaff, AZ
[2]Pathogen Genomics Division, The Translational Genomics Research Institute (TGen-North), Flagstaff, AZ
[3]Center for Environmental Genetics and Genomics, Northern Arizona University, Flagstaff, AZ

INTRODUCTION

Current methods of detection of living Coccidioides in the environment rely on standard culture plate methods to grow the fungus directly from soils, or passaging soil solutions in mice susceptible to coccidioidomycosis. Molecular based methods have been proposed as a useful method to screen soils for the presence of Coccidioides. Several groups have worked to develop a method based on nested PCR applications, targeting the multi-copy internal transcribed spacer (ITS) region common to many fungal species. All of these methods have limitations, thus we sought to streamline screening of soils. We developed a single probe TaqMan PCR assay we named CocciEnv, which is based on the CocciDxQ assay, originally validated as a coccidioidomycosis diagnostic.

METHODS

Several areas in Tucson that were previously identified as positive for Coccidioides were used as positive controls in fall 2013 and spring 2014. Additionally, soil samples were collected in the fall of 2013 from rodent burrows in Phoenix and Flagstaff areas for comparison. Each site was collected as a composite sample. Implements were decontaminated with 10% bleach and rinsed with distilled water between collections. Cell lysis and DNA extraction were conducted using a PowerSoil® DNA Isolation Kit (MO BIO, Carlsbad, CA). With the recent database deposition of new Coccidioides genome sequences, we compiled hundreds of alleles of the highly repetitive CocciDxQ target. We designed several new primers to increase the number of alleles of the target captured by the assay, and refer to the enhanced assay as CocciEnv. We employed Sanger sequencing to confirm the target when we detected PCR amplification in a soil sample. We employed amplicon sequencing of the ITS target for further validation. Soil DNA samples were PCR amplified in triplicate with primers targeting the ITS2 region, pooled and quantified. The final pool was bead-purified and quantified by qPCR against Illumina Library Quantification Standards and sequenced in 2x250 mode on an Illumina MiSeq Desktop Sequencer.

RESULTS

Comparing our new assay, CocciEnv, with the clinical assay, we have shown in increase in sensitivity based on cycle threshold values. We further validated the amplicon target as Coccidioides specific using traditional Sanger sequencing. Finally, we detected Coccidioides DNA using amplicon sequencing in our real time PCR positive samples.

CONCLUSIONS

We propose that the CocciEnv assay is a robust method to detect Coccidioides DNA in environmental samples, and will be a useful tool for understanding the ecology of this understudied pathogen.

DEVELOPING METHODS FOR DETECTION OF *COCCIDIOIDES* USING TARGETED AND SHOTGUN METAGENOMIC SEQUENCING OF ENVIRONMENTAL SAMPLES

Chow NA[1], Gade L[1], and Litvintseva AP[1]

[1] Mycotic Diseases Branch, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta GA

INTRODUCTION

Next-generation sequencing (NGS), whether targeted or shotgun metagenomic sequencing, can be utilized to answer a variety of questions that pertain to the habitat and life-cycle of *Coccidioides*. In addition, these methods can be used in environmental surveillance to confirm qPCR detection of *Coccidioides* in soil samples when culturing methods fail or prove too difficult. However, analysis of NGS data for environmental samples is challenging due to their vast microbial diversity. In addition, characterization of the fungal community composition, as compared to that of bacteria, is addressed less in bioinformatics thereby resulting in fewer fungal databases and software tools for fungal classification.

RESULTS

We have tested several blast- and kmer-based methods against a variety of microbial DNA databases to standardize an approach for targeted sequencing using the ITS amplicon and shotgun metagenomic sequencing. We tested our methods on soil samples found to be either positive or negative for *Coccidioides* by qPCR detection, and in both targeted and shotgun metagenomic sequencing, we were able to detect *Coccidioides* and neighboring bacterial and fungal species. We have gained insights in how best to perform quality control, taxonomic classification, genome mapping, and data visualization when performing fungal classification, especially for *Coccidioides* research and environmental surveillance.

CONCLUSIONS

Using these methods, we are now able to ask specific biological questions relevant to *Coccidioides* and the Valley Fever field. We plan to investigate sites positive for *Coccidioides* and identify microbial signatures that correlate with its presence. We also plan to pair this data with geochemical data for a robust analysis of potential 'predictors' for sites positive for *Coccidioides.*

STANDARDIZATION OF NESTED PCR FOR *COCCIDIOIDES SPP*. DNA DETECTION IN SOIL SAMPLES

Morales-Flores G[1], Sandoval G[1], Ortega-Larrocea P[1], Suárez-Quijada I[1], Lauer A[2], Castañón-Olivares LR[1]

[1]Universidad Nacional Autónoma de México.
[2]Biology Department Faculty, California State University, Bakersfield.

INTRODUCTION

The isolation of *Coccidioides spp* or its DNA finding from soil samples have been difficult through microbiological or molecular techniques. The hypotheses explaining this short success in determining the fungus habitat are based in the low concentration of fungal particles, the presence of competitors, the low spreading of the fungus and possible the fact that possibly this organism is highly adapted to parasitism with low free life prevalence. The consulted references state that sensibility and specificity of the DNA amplification increase in the semi nested or nested PCR detection techniques. The aim of this work was to standardize a sensitive and reliable nested PCR (PCR-n) technique for the detection of *Coccidioides spp* DNA from soil samples.

METHODS

A couple of external and internal primers were designed from sequences presenting the rDNA gene complex of *Coccidioides spp.* stored in GenBank. DNA was extracted from *Coccidioides immitis*, *Candida albicans*, *Blastomyces dermatitidis*, *Malbranchea* spp. and *Trichophyton rubrum.* A standardization of the PCR-n was performed with the proposed oligonucleotides. Simultaneously, there was an inoculation in non-disturbed soil samples with arthroconidia of *Coccidioides immitis*, in order to obtain DNA and amplify it by the experienced conditions.

RESULTS

The performed trials demonstrate that the minimum concentration required for amplification of *Coccidioides* DNA from soil inoculated with arthroconidia, was 10 ng/µL. Furthermore, the specificity of the designed PCR technique is considered as successful since DNA from other ascomycetes, close or distant phylogenetically from *Coccidioides* spp. was not amplified,

CONCLUSIONS

Due to the sensitivity and the specificity shown, the designed technique is recommended for its use in the identification of *Coccidioides spp.* from natural substratum, which can be reservoir or vector for this fungus.

REGIONAL ENVIRONMENTAL SOIL AND AIR SAMPLING FOR *COCCIDIOIDES SPP.* AND AIRBORNE FUNGAL SPORE DISTRIBUTION PATTERNS

Cat, Linh Anh[1], Gorris, Morgan E.[2], Randerson, James T.[2], Treseder, Kathleen K.[1]

[1]Ecology and Evolutionary Biology, University of California, Irvine, Irvine, CA 92697
[2]Earth System Science, University of California, Irvine, Irvine, CA 92697

INTRODUCTION

The drivers of *Coccidiodes* distribution in the soil and air of the U.S. Southwest are poorly understood. *Coccidioides'* range may be determined by air dispersal limitations, environmental filtering, or both. Climate change likely plays a role in the dramatic increase of valley fever incidence due to the environmental pressures on *Coccidioides* fungal spores before human infection. Regional climate models predict more severe droughts along with less frequent, heavier rainstorms, which may encourage an increased amount of spores. Understanding limiting factors on *Coccidioides* distribution is crucial to anticipating public health impacts. This study will examine *Coccidioides* presence-absence in both the soil and air as well as airborne fungal spore distribution patterns.

METHODS

120 soil samples and 60 air samples were taken along north-south and east-west transects, covering five states (CA, AZ, NM, NV, UT). The sampling range spanned the endemic range of *Coccidioides* and beyond. Soil samples were taken in duplicate at 60 sites located away from major roadways. Simultaneously, air samples were taken using a BioImpactor sampler, which impinges spores onto an agar dish. DNA was extracted for species-specific PCR analysis using the method outlined in Vargas-Gastelum 2015. Spore counts were performed on the air samples and classified by spore size (1-5 microns, 5-10 microns, 10-20 microns, 20-50 microns). Fungal community composition is being determined using ITS2 region on the Illumina Mi-Seq platform. Standard physical soil measurements were determined (pH, density, water content) for environmental analysis.

RESULTS

Spore distribution by size class was found to vary significantly with elevation and longitude (as a proxy for ecosystem type) ($p=0.005$). This trend was found for all spore size classes except for the smallest (1-5 microns), which includes *Coccidioides* spores. All soil and air samples were negative for *Coccidioides* presence using species-specific PCR. Samples are currently being sequenced to check for presence-absence and results are expected by late March.

CONCLUSIONS

The smallest spores will remain suspended in the air longer and are able to be transported further distance, therefore, their concentrations are much lower compared to spores 5 microns or bigger which exhibit a point source type of distribution. Since *Coccidioides* spores are 2-6 microns they are likely to travel far distances and be as cryptic to detect in the air as soil.

GROWTH OF *COCCIDIOIDES* IN SOIL

Steven Hurst[1], Lalitha Gade[1], Geoffrey Plumlee and Anastasia P. Litvintseva[1]

[1]Mycotic Diseases Branch, Centers for Diseases Control and Prevention (CDC), Atlanta, GA
[2] U. S. Geological Survey, Denver, CO

INTRODUCTION

Recent discovery of *Coccidioides immitis* in Washington State and Utah, outside of the established endemic region, raises a question about the mechanisms of dispersal of this fungus. *Coccidioides* is known to produce airborne arthroconidia that can be disseminated by winds and dust storms over large geographic areas. However, the ability of *Coccidioides* arthroconidia to colonize new sites has been put into question based on the genomic evidence, which suggests that this fungus is poorly adapted for the saprophytic growth in soil and likely requires animals or animals' fragments to grow. Specifically, it has been hypothesized that small mammals rather than abiotic factors, such as soil and wind, play the major roles in distribution and establishments of *Coccidioides*. To test this hypothesis, we investigated the ability of *Coccidioides* arthroconidia to colonize soils in the laboratory in the absence of the animal host.

METHODS

Soils were collected from Washington State from areas, where *Coccidioides* has been recently discovered. Only soils that were negative for *Coccidioides* by real-time PCR were selected from sites without visible rodent activity. Prior to the experiment, soils were inspected visually and no animal fur, droppings or bone fragments were detected. Soils were autoclaved, inoculated with approximately 1000 arthroconidia and incubated at 37°C for one month with weekly watering.

RESULTS AND CONCLUSIONS

After one month, more than 100X increase of *Coccidioides* biomass was detected by the real-time PCR, and numerous hyphae and arthroconidia were detected in soil by microscopy indicating successful colonization. In my presentation, I will discuss the implications and limitations of this experiment, as well as present our other recent attempts to characterize biotic and abiotic factors that enable *Coccidioides* to colonize soils.

INCREASED INCIDENCES OF COCCIDIOIDOMYCOSIS CORRELATED WITH LARGE SCALE LAND DEVELOPMENT IN THE ANTELOPE VALLEY

Colson Aaron[1], Guevara Ramon[2], Vredenburgh Larry[3] and Lauer Antje[1]

[1]California State University, Bakersfield, CA; [2]County of Los Angeles Department of Public Health, Los Angeles, CA; [3]Bureau of Land Management, Bakersfield, CA

INTRODUCTION

Increased fugitive dust emissions are a major concern for the population of the Western Mojave Desert, partially due to extensive soil disturbance for the construction of photovoltaic power plants. Our study area west of the city of Lancaster, lays where 6 solar ranches of varying sizes were planned, with construction beginning in 2014/15. Our area of interest is known for a significant increase in coccidioidomycosis, especially since 2011 when major soil disturbance led to an increase in fugitive dust emissions. It is well known that the emerging fungal pathogen Coccidioides immitis, the causative agent of coccidioidomycosis, can easily become airborne when soil is disturbed.

METHODS

In this project, soil samples (bulk soil) were collected from 6 sites (n=31) in our area of interest, which differed in regard to soil chemical and physical parameter, vegetation cover and degree of disturbance, but which could all be characterized as fine particulate soils (quaternary alluvium). We were able to detect the pathogen in 3 out of the 6 sites using a culture independent nested PCR approach on soil DNA extracts. We also obtained PM10 data (1996-2013) and used ArcGIS to show changes in land use between 2000 and 2011 in the Antelope Valley.

RESULTS

The PM10 data showed a positive correlation between reported incidences of coccidioidomycosis and land disturbance (RSQ= 0.41, Pearson=0.64)) for renewable energy projects construction, housing developments, and agricultural land use for field crops. Overall, 8 soil samples from 3 sites tested positive for C. immitis (25.8%). The site with the most positive individual samples was a non-disturbed site with natural vegetation dominated by Atriplex polycarpa.

CONCLUSION

Our findings implicate the need for soil analyses before disturbance to be implicated in Environmental Impact Reports (EIRs) that should also comprise long-term dust mitigation strategies, such as re-vegetation of the disturbed site, to reduce fugitive dust emissions, so that we can reduce coccidioidomycosis incidence among construction workers and the general public in this area which is characterized by above average population growth, above average poverty, below average education, below average health insurance coverage, and a large population of African Americans, an ethnicity known to be at a higher risk to develop the disseminated form of coccidioidomycosis.

2016 CSG-60 Satellite Meeting: Coccidioidomycosis and Occupational Health
U.C.S.F.-Fresno
The DoubleTree Hotel
Salon A
2233 Ventura St., Fresno, CA 93721
April 8, 2016; 7-9 P.M.

6:45-7:00 P.M. **Registration** (no added cost when registered to attend the CSG 60th Annual Meeting April 9, 2016 at U.C.S.F.-Fresno, Fresno, CA)

7:00-7:05 **Welcome Address: Orion McCotter and Marie de Perio (co-Moderators)**

7:05-7:25
THE IMPORTANCE OF COLLECTING OCCUPATION, INDUSTRY AND WORKPLACE DATA WITHIN COCCIDIOIDOMYCOSIS SURVEILLANCE SYSTEMS
Luckhaupt S

7:25-7:45
SUSPECT COCCIDIOIDOMYCOSIS AMONG WORKERS CONSTRUCTING SOLAR POWER FARMS IN CALIFORNIA: TWICE AS MANY AS LABORATORY-CONFIRMED
Sondermeyer G, McNary J, Gilliss D, Schusterman D, Materna B, Vugia D

7:45-8:15
PANEL DISCUSSION: RISK COMMUNICATION REGARDING COCCIDIOIDOMYCOSIS AND HIGH RISK POPULATIONS; *plus* CALIFORNIA COCCIDIOIDOMYCOSIS COLLABORATIVE
Materna B, Kirt E

8:15-8:30
FARMWORKER CASE CONTROL PILOT UPDATE
McCurdy S

8:30-8:55
PANEL DISCUSSION: EXPLORATION OF THE USE OF THE SPHERULE DERIVED SKIN TEST FOR COCCIDIOIDOMYCOSIS AND ITS APPLICATIONS IN WORKPLACE SETTINGS
De Perio M, Sunenshine R, McCotter O

8:55-9:00 **Closing Remarks: Orion McCotter and Marie de Perio**

The 2016 CSG-60 Satellite Meeeting on Coccidioidomycosis and Occupational Health in general was a forum for state of the art discussion rather than for the presentation of original research. Consistent with these goals, no abstracts from this satellite meeting were submitted for publication in these Proceedings.

COCCI STUDY GROUP 60TH ANNUAL MEETING
AGENDA
Fresno, California
April 9, 2016

7:00-8:00 A.M. **Breakfast, Registration, Poster Set-up**

8:00-5:00 P.M. **Poster Visitation - Hosted in Rooms 136-137**
Moderator: Susan Hoover
List of Posters by Title and Authorship

- **APPROACH TO TUMOR NECROSIS FACTOR-α INHIBITOR RECIPIENTS OR CANDIDATES WITH VARIOUS MANIFESTATIONS OF COCIDIOIDOMYCOSIS**
  Garrett A, Cha S, Wack E, and Blair J

- **INTEGRATIVE MEDICINE PREFERENCES AMONG COCCIDIOIDOMYCOSIS PATIENTS**
  Short J, Bradley C, Millstine D, Stewart T, Burns M, Patron R, Blair J

- **VERTEBRAL COCCIDIOIDOMYCOSIS: A CHALLENGING CASE IN AN IMMUNOCOMPETENT PATIENT**
  Alynbiawi A, Stockamp N

- **THE UTILITY OF USING REAL-TIME PCR IN THE DETECTION OF *COCCIDIOIDES IMMITIS* IN THE CLINICAL SETTING AT THE CENTRAL CALIFORNIA SAN JOAQUIN VALLEY**
  Dizon D, Mitchell M, Peterson M, Libke R, Chin C, Mills P, Oliver D

- **EVIDENCE *COCCIDIOIDES* CAN CAUSE SARCOIDOSIS IN ARIZONA**
  Yourison I, Kuberski T

- **CURE OF COCCIDIOIDAL MENINGITIS: A CASE REPORT**
  Kuberski T

- **ADJUNCTIVE USE Of SERTRALINE IN A PATIENT WITH REFRACTORY COCCIDIOIDAL MENINGITIS**
  Thu Y, Roshan B, Mu A, Nassar N, Libke R, Stockamp N

- **SERTRALINE DEMONSTRATES FUNGICIDAL ACTIVITY AGAINST *COCCIDIOIDES IMMITIS IN VITRO***
  Paul S, Mortimer R, Mitchell M

- **VERTEBRAL COCCIDIOIDOMYCOSIS PRESENTING IN HYPHAL FORM 23 YEARS AFTER AN INITIAL EPISODE OF CUTANEOUS COCCIDIOIDOMYCOSIS.**
  Fernandes I, Stockamp N

- **CLIMATE DRIVERS AND COCCIDIOIDOMYCOSIS INCIDENCE AT THE REGIONAL SCALE**
  Gorris M, Cat L, Randerson J, Treseder K

- **TUBERCULOSIS AND DISSEMINATED COCCIDIOIDOMYCOSIS IN A PATIENT WITH MALNUTRITION**
  Palma Cortés G, Muñoz Torrico M, Valencia Maqueda E, González Valadez H, Pérez Brunet B, Cabello Gutiérrez C

- **CULTURING COCCIDIOIDES: OPTIMIZING IN VITRO CULTURE MEDIA TO REFLECT NUTRIENT AVAILABILITY *IN VIVO***
  Mead H, Barker B

- **COMPARISON OF *COCCIDIOIDES* ANTIBODY DETECTION BY THE MIRA VISTA ENZYME IMMUNOASSAY WITH IMMUNODIFFUSION AND COMPLEMENT FIXATION**
  Holbrook E, Wheat L

- **DISSEMINATED COCCIDIOIDOMYOSIS IN CHILDREN**
  Lee J, McCarty J, Dabrowski L, Tablizo M, Graciano A

- **DIFFERENTIAL DIAGNOSIS BETWEEN COCCIDIOIDOMYCOSIS AND TUBERCULOSIS: CLINICAL AND EPIDEMIOLOGICAL RISK FACTORS IN A HOSPITAL FOR RESPIRATORY DISEASES IN MEXICO CITY**
  Higuera I, Vázquez Manríquez M, González-Valadez J, Palma Cortés G, Cabello Gutiérrez C

- **AN AUTOMATED NODULE CALCULATOR FOR DIFFERENTIATING NODULES CAUSED BY LUNG CANCER FROM THOSE CAUSED BY COCCIDIOIDOMYCOSIS**
  Ronaghi R, Rashidian A, Mills P, Tringali S, Alyafaie N, Kerney W, Lopez T, Monastyrsky D, Tjuanta M, Peterson M

- **MOLECULAR ANALYSIS OF CLINICAL ISOLATES OF *COCCIDIOIDES SP.* FROM MEXICAN PATIENTS**
  Palma Cortés G, Pérez Brunet B, Valencia Maqueda E, González Valadez J, Higuera Iglesias A, Reyes Montes M, Duarte Escalante E, Rivera Becerril F, Cabello Gutiérrez C

- **EPIDEMIOLOGY OF SEVERE COCCIDIOIDOMYCOSIS PNEUMONIA: TWO DECADES IN MEXICO IN THE NATIONAL INSTITUTE OF RESPIRATORY DISEASES "ISMAEL COSIO VILLEGAS"**
  González Valadez J, Higuera I, Anjarath L, Vázquez Manríquez M, Palma Cortés G, Cabello Gutiérrez C

- **PLASMA ELMO3 IN COCCIDIOIDOMYCOSIS**
  Ifeacho V, Almodovar K, Sachdeva M, Ololade J, Risco M, Rubiaco G, Ryazantsev A, Santiago T, Hegde P, Peterson M, Upadhyay D

- **EXPRESSION OF PLASMA CDKN1A INTERACTING ZINC FINGER PROTEIN 1 VARIANT IN COCCIDIOIDOMYCOSIS**
  Ifeacho V, Sachdeva M, Ololade J, Risco M, Rubiaco G, Ryazantsev A, Almodovar K, Hegde P, Peterson M, Upadhyay D

- **IDENTIFICATION BY ELISA OF ANTI-*COCCIDIOIDES* ANTIBODIES IN HUMAN AND DOG POPULATIONS OF ENDEMIC AND NON ENDEMIC AREAS OF COCCIDIOIDOMYCOSIS**
  Suárez-Lozano L, Contreras-Pérez C, Ruiz-González L, Cabello C, Cano-Rangel MA, Cervantes-Olivares R, Durazo M, Gutiérrez-Quiroz M, Luna-Isaac JA, Muñiz-Salazar R, Palma G, Pérez-Mejía A, Ponce-Rosas R, Reyes-Delgado F, Castañón-Olivares LR

- **A QUALITATIVE STUDY OF VALLEY FEVER AMONG HISPANIC/LATINO FARMWORKERS IN CALIFORNIA**
  Portillo-Silva C

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8:00-8:15 A.M. **Convene Meeting/Introductions/PosterLogistics with Susan Hoover/Amenities/D. Stevens *in memorium* for H. Levine Neil Ampel presiding**

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8:15-10:00 A.M. **Clinical Science**
Moderator: Rafael Laniado-Laborin

- **UTILITY OF COMBINED ENDOSONOGRAPHY (EBUS & EUS) IN THE DIAGNOSIS OF COCCIDIOIDOMYCOSIS**
  Sachdeva M, Almovidar K, Upadhyay D, Peterson M, Hegde P

- **IMMUNNE RECONSTITUTION INFLAMMATORY SYNDROME IN PATIENTS WITH AIDS AND DISSEMINATED COCCIDIOIDOMYCOSIS: A CASE SERIES**
  Shein T, Mu A, Paul S

- **THE UTILITY OF SCREENING FOR COCCIDIOIDOMYCOSIS IN RECIPIENTS OF ANTI-TNF-α THERAPY**
  Choi K, Mertz L, Heigh R, Yiannias J, Blair J

- **ALOPECIA ASSOCIATED WITH FLUCONAZOLE: EFFECTS ON THE HAIR CYCLE IN A RAT MODEL**
  Thompson R III, Krois C, Affolter V, Johnson V, Singapuri A, Dennis M, Wiederhold P, Napoli J, Gelli A, White S

- **NOVEL CYP51 INHIBITORS FOR THE TREATMENT OF COCCIDIOIDOMYCOSIS**
  Shubitz L, Trinh H, Roy M, Garvey E, Brand S, Hoekstra W, Schotzinger R

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10:00-10:30 A.M. **Poster Visitation/Break**
Posters 1-12 and 16

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10:30-12:30 A.M. **Laboratory and Basic Science**
Moderator: George Thompson III

- **APX001-A, A NOVEL ANTIFUNGAL DRUG IS ACTIVE AGAINST COCCIDIOIDES *IN VIVO* AND *IN VITRO***
  Fierer J, Viriyakosol S, Kirkland T, Mutz M

- **PERFORMANCE OF COCCIDIOIDOMYCOSIS PCR TESTING IN PATIENTS WITH LUNG NODULES**
  Sachdeva M, Almovidar K, Samuel R, Mills P, Dizon D, Peterson M

- **THE AVIRULENT MUTANT STRAIN ⌒cps1 PROVIDES LONG TERM SURVIVAL FOLLOWING LETHAL COCCIDIOIDES INFECTION IN MICE**
  Shubitz L, Orbach M, Trinh H, Frelinger J, Galgiani J

- ***EX VIVO* CYTOKINE EXPRESSION IN NEWLY DIAGNOSED COCCIDIOIDOMYCOSIS**
  Ampel N, Robey I, Roller B, Chavez S, Nguyen C, Johnson S, Pappagianis D

- **DEVELOPMENT OF AN IMPROVED ANTIBODY DETECTION EIA FOR USE IN IDENTIFICATION OF COCCIDIOIDOMYCOSIS**
  Holbrook E, Malo J, Zangeneh T, Strawter C, Oren E, Robey I, Erickson H, Chahal R, Thompson C, Ampel N, Wheat L, Knox K

- **THE TOTAL AND LECTIN BINDING PROTEOME OF SPHERULIN**
  Lake D, Grys T, Kaushal S, Blair J, Mitchell N, Magee D

- **UNDERSTANDING MECHANISMS OF RECOMBINATION IN *COCCIDIOIDES***
  Teixeira M, Barker B

- **CSF (1,3)-BETA-D-GLUCAN (BG) TESTING IS USEFUL IN DIAGNOSIS OF COCCIDIOIDAL (COCCY) MENINGITIS (CM)**
  Stevens D, Zhang Y, Finkelman M, Pappagianis D, Clemons K, Martinez M

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12:30-1:30 P.M. **Lunch**

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1:30-2:15 P.M. **Business Meeting, Cocci Study Group**
Moderator: Neil Ampel, President, CSG

- ✓ Bylaws amendment discussion and vote
- ✓ CSG #62 (2018) date, host and vote
- ✓ Election for CSG Board Secretary
- ✓ CSG 7th International Conference and Symposium at Stanford University campus (2017)/confirm dates
- ✓ Treasurer's report by Herbert Boro for Royce Johnson
- ✓ **COCCI PNEUMONIA STATUS UPDATE**
  Dixon D
- ✓ **NIKKOMYCIN-Z: STATUS UPDATE AND DEVELOPMENT PLANS**
  Larwood D, Galgiani J

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2:15-3:15 **Ecology and Epidemiology I**
Moderator: Tom Chiller

- **FACTORS ASSOCIATED WITH COCCIDIOIDOMYCOSIS TESTING AMONG COMMUNITY-AQUIRED PNEUMONIA PATIENTS IN SOUTHERN CALIFORNIA, 2011**
  Benedict K, Mody R, Xie F, Rieg G, Yu K, Truong J, Jacobsen S, Tartof S

- **DEMOGRAPHIC CHARACTERISTICS AND INSTITUTIONAL AND COMMUNITY EXPOSURES AMONG CALIFORNIA STATE PRISON INMATES WITH POSITIVE COCCIDIOIDOMYCOSIS (COCCI) SKIN TEST RESULTS**
  Lucas K, Wheeler C, Mohle-Boetani J

- **EPIDIOLOGY OF PEDIATRIC COCCIDIOIDOMYCOSIS IN CALIFORNIA, 2000–2012**
  Sondermeyer G, Lee L, Gilliss D, McCarty J, Vugia D

- **SURVEILLANCE FOR COCCIDIOIDOMYCOSIS IN ARIZONA: 2015 UPDATE**
  Khan M, Rafiq A, Brady S

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3:15-3:45 P.M. **Poster Visitation/Break**
Posters 13-22 (except for 16 that was presented in the morning)

****

3:45-4:45 **Ecology and Epidemiology II**
Moderator: Janis Blair

- **ESTIMATING TRENDS OF COCCIDIODOMYCOSIS IN AN ENDEMIC AREA AFTER LABORATORY REPORTING CHANGES: MARICOPA COUNTY, 2006- 2014.**
  Koski L, Sylvester T, Narang J, Sunenshine R

- **COCCIDIOIDOMYCOSIS AMONG AMERICAN INDIANS AND ALASKA NATIVES, 2001–2013**
  Benedict K, McCotter O, McCollum J, Kennedy J, Bartholomew M, Seaman S, Iralu J, Mody R, McDonald M, Haberling D

- **POPULATION DYNAMICS OF *COCCIDIOIDES* AND THE EMERGENCE OF CLINICAL GENOTYPES**
  Teixeira M; Barker B

- **COCCIDIOIDOMYCOSIS IN RESCUED MARINE MAMMALS ALONG CALIFORNIA'S COAST**
  Muñoz Y, Hannah S, Liwanag H, McDonald G, Mulcahy C, Norris T, Johnson S, Palmer L, Lauer A

5:00 P.M. **Concluding Remarks**
Neil Ampel

7:00 P.M. **Dinner** (by reservation)
Republican Restaurant
2120 Kern St., Fresno, CA 93728

APPROACH TO TUMOR NECROSIS FACTOR-α INHIBITOR RECIPIENTS OR CANDIDATES WITH VARIOUS MANIFESTATIONS OF COCIDIOIDOMYCOSIS

Garrett, Ashley; Cha S; Wack E; Blair J

INTRODUCTION

Inhibitors of Tumor Necrosis Factor-α (TNFI) such as infliximab have become widely used to treat a variety of medical conditions. A few studies within the *Coccidioides*-endemic area have highlighted the potential for severe or disseminated coccidioidomycosis in TNFI recipients, but the optimal approach to TNFI recipients and various coccidioidal manifestations is unknown. We sought to determine the current clinical practices of Infectious Disease (ID) or Pulmonology specialists confronted with this issue.

METHODS

An internet-based survey was constructed to evaluate management recommendations for various common scenarios. We created 5 hypothetical patients, all of whom were treated with (or required institution of) infliximab and had a variety of manifestations of coccidioidomycosis, ranging from asymptomatic seropositivity, to pulmonary or extrapulmonary coccidioidomycosis. Survey questions assessed whether/when infliximab could be started (or re-started) or should be stopped, and details of antifungal treatment (type, dose, duration). After Mayo Clinic Institutional Review Board (IRB) approval, requests for participation were e-mailed to persons on the contact lists of the Arizona Thoracic Society and the Arizona Infectious Diseases Society.

RESULTS

The survey was sent to 392 potential participants with correct addresses. 42/392 (10.7%) responded, of whom 98% were board-certified pulmonary (28/42[67%]) or ID [14/42(33%)] specialists.

When asked about an asymptomatic patient with positive coccidioidal serology and negative chest x-ray, 18(44%) recommended infliximab could be initiated immediately, while 23(56%) did not. Thirty-one (76%) would treat with fluconazole prior to starting infliximab, however there was no consensus regarding antifungal duration . Prior to infliximab initiation, 13(57%) would need to see exclusion of disseminated disease based on history and physical, and 10(43%) would need to see improving serology and exclusion of disseminated disease with diagnostic imaging.

Similar disparities were seen in the 4 other patient scenarios involving the management of a patient with a history of: coccidioidomycosis and a stable pulmonary nodule, non-meningeal disseminated disease, meningitis and a patient on infliximab who developed symptomatic coccidioidomycosis.

CONCLUSIONS

There is no consensus among practicing ID or pulmonary physicians regarding how to best manage patients with coccidioidomycosis who require TNFI. Further research is necessary to identify best clinical practices and determine evidence based guidelines.

INTEGRATIVE MEDICINE PREFERENCES AMONG COCCIDIOIDOMYCOSIS PATIENTS

Short J; Bradley C; Millstine D; Stewart T; Burns M; Patron R; Blair J.
Mayo Clinic Arizona

INTRODUCTION Integrative medicine (complementary and alternative medicine) is used in various forms by coccidioidomycosis patients. Although patients rarely discuss integrative medicine strategies with their physician, adoption is perceived by clinicians to be high, though formal quantification of utilization is lacking. A direct patient survey tool was implemented at Mayo Clinic to determine the prevalence and types of alternative medicine strategies used to cope with coccidioidal symptoms by this population.

METHODS The Division of Infectious Diseases distributed a voluntary, anonymous survey to patients in the Coccidioidomycosis Clinic in 2015. Responses were collected until a goal number of 100 unique surveys were reached. An interim analysis was conducted, with results detailed below. The survey consisted of initial questions regarding patients' duration of diagnosis, overall level of daily fatigue on a 1-10 scale, and a list of 36 integrative medicine modalities to be checked if a patient used, had not used, or was unfamiliar with each modality. Patients were eligible for the study if they had a clinical diagnosis of coccidioidomycosis and provided consent. Participants were not provided compensation or incentive. One completed survey was allowed per patient. Data collection sheets were then analyzed by our biostatistics department with SAS software.

RESULTS Interim analysis of the initial 40 surveys collected revealed a respondent population of 95% carrying a diagnosis of coccidioidomycosis, with 69% stating time from diagnosis greater than 6 months. The top five most utilized integrative medicine modalities are represented below. Other popular alternative therapies included chiropractic care (38%), breathing exercises (37%), acupuncture (32%), and yoga (31%).

Integrative Medicine Modality	Percent of Patients Participating (%)
Nutrition Therapy	48
Massage Therapy	48
Mindful Based Stress Reduction	48
Meditation	42
Exercise Instruction	41

CONCLUSIONS

A substantial proportion of patients with coccidioidomycosis longer than 6 months had incorporated one or more complementary or alternative medicine practices for their coccidioidal illness. Most of our clinicians in the coccidioidomycosis clinic were unaware that patients had incorporated such interventions into their care plan. There are no studies to look at the utility of such a practice, but future studies could assess the efficacy of such interventions. This direct patient survey allows clinicians to gain a better understanding of the prevalence of integrative medicine modalities in this specific population. Awareness of patients' preferences, goals, and approach to wellness are valuable to clinical decision-making and the physician-patient relationship.

VERTEBRAL COCCIDIOIDOMYCOSIS: A CHALLENGING CASE IN AN IMMUNOCOMPETENT PATIENT

Alynbiawi A; Stockamp N

Division of Infectious Diseases, University of California San Francisco - Fresno

INTRODUCTION

Extra pulmonary manifestation of coccidioidomycosis is nearly always the result of hematogenous spread after a primary pulmonary infection. When infection involves the spine, the treatment strategies can be challenging and may require combined medical and surgical management. This case will highlight the challenges in treating complex vertebral coccidioidomycosis in an African American male.

CASE DESCRIPTION

A 22 year old African American man, who recently relocated to central California, was transferred to our hospital with a two month history of productive cough and mid -back pain. Computed tomography showed extensive multi-loculated cystic mass collections throughout mediastinum and lung apices with areas of cavitation (**Figure 1).** Lytic bony lesions involving multiple vertebral bodies with C7 pathological fracture as well as two paravertebral abscesses were observed. Culture of aspirated material from the C7 area revealed *Coccidioides immitis.* Serum coccidioides immunodiffusion testing was positive with a complement fixation (CF) antibody titer of 1:1024. Additionally, the patient underwent cerebrospinal fluid testing that showed evidence of meningitis with a CF titer of 1:2. Despite initial treatment with Liposomal Amphotericin B for 8 weeks, the patient`s condition continued to worsen. Repeated MRI showed worsening of the pathological fracture at the level of C7 with evidence of central spinal stenosis and cord compression and progressive osteomyelitis. Itraconazole (suspension) was then added to amphotericin. Given the progression of the disease as well as spinal instability, the decision was made to proceed with corpectomy and fusion of C3 through T4. Following surgical debulking, the patient's therapy was de-escalated to itraconazole. A follow up MRI showed interval improvement of osteomyelitis at multiple levels.

CONCLUSION

Disseminated coccidioidomycosis can be an extensively morbid event, and there is often great difficulty in controlling the infection. In simple cases, medical management of vertebral coccidioidomycosis can be sufficient. However, this case will illustrate the importance of a combined medical and surgical approach in patients with extensively localized vertebral disease.

THE UTILITY OF USING REAL-TIME PCR IN THE DETECTION OF *COCCIDIOIDES IMMITIS* IN THE CLINICAL SETTING AT THE CENTRAL CALIFORNIA SAN JOAQUIN VALLEY

Dizon D[1], Mitchell M[2], Peterson M[1], Libke R[1], Chin C[1], Mills P[1] and Oliver D[1]
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[2]Microbiology Department, Community Regional Medical Center, Fresno, California, USA

INTRODUCTION Recently, a collaborative study between UCSF Fresno and the Microbiology department of CRMC, validated the development of a real-time PCR assay for *Coccidiodes immitis* using a BD-Max machine. The experience proved that clinically relevant information can be available within 4 h using an RT-PCR method on the BD Max to identify *Coccidiodes immitis* with results congruent with those of culture and histopathology, with 100% sensitivity and 100% specificity, when compared with fungal culture. The results mirror earlier studies in Mayo Clinic by Binnicker and colleagues.

This is the first study to use this machine as the standard test for Cocci-PCR clinically and the first to test it on *Coccidiodes immitis*, as it is endemic to the California Central Valley.

METHODS From March 1, 2014 through Dec 31, 2015, we did a retrospective analysis of 667 specimens of bronchoalveolar lavage fluid, bronchial washings, thoracentesis fluid, cerebrospinal fluid, lung, bone, skin and other body tissue biopsies, sputum and joint fluid aspirations for which Cocci-PCR was ordered.. Depending on the type of sample, we counted as positive those who were identified as proven or probable based on the ATS criteria for diagnosis of Coccidioidomycosis. Simple descriptive statistics were then used to analyze the data.

RESULTS Out of the total 667 patients, 73 (10.9%) were identified as proven or probable coccidioidomycosis. Of these 73, 41 (56.2%) had positive Cocci-PCR. A total of 626 patients had negative Cocci-PCR and out of these, 32 had proven or probable coccidiodomycosis and 594 had a diagnosis other than coccidioidomycosis.
Hence, the Cocci-PCR test demonstrated Sensitivity = 56.2%, Specificity = 100%, Negative Predictive Value = 94.9% Positive Predictive Value = 100%, Precision = 100%, Accuracy = 95.2%.
Out of the 73 that were identified as proven or probable coccidioidomycosis , fungal culture was only positive for 33, giving it a sensitivity of 45.2%.

CONCLUSIONS We were able to demonstrate that the Cocci-PCR test using the BD-Max system is a viable and usable test for coccidioidomycosis in the clinical setting here in Central California. In less than 2 years, clinicians in inpatient and outpatient settings ordered the test when they considered the diagnosis of coccidioidomycosis. When compared with the gold standard of fungal culture, it had a better sensitivity (56.2% vs 45.2%) and was resulted in 4 hours rather than 1-2 weeks.
When comparing this brand new test, different machine and different species of Coccidioides , to the Lightcycler Cocci-PCR used in Arizona, it produced almost the same sensitivity analysis (56.2% vs 56%). The sensitivity for fungal culture in our local laboratory is also the same as that used in Mayo Clinic, AZ (45.2% vs 44%). The specificity and positive predictive value are both at 100%. This means that when we get a positive result within hours, rather than weeks, we can go ahead and treat the patient with confidence and perhaps effect better outcomes.

EVIDENCE *COCCIDIOIDES* CAN CAUSE SARCOIDOSIS IN ARIZONA

Isaac Yourison and Tim Kuberski
University of Arizona College of Medicine, Phoenix

INTRODUCTION

In patients who have both sarcoidosis (sarcoid) and coccidioidomycosis (coccy) there are two potential mechanisms for the fungus to express itself: 1. the patient has sarcoid, receives immunosuppression (i.e., steroids), then experiences an exposure to *Coccidioides* and develops coccy. Alternatively, 2. the patient has an exposure to *Coccidioides* which manifests itself as sarcoid without obvious evidence of coccy. Based on the latter hypothesis we report two patients who confirm a clinical and epidemiologic association between coccy and sarcoid.

METHODS

Two patients who developed both coccy and sarcoid are presented, one is studied prospectively (i.e., a patient with sarcoid was predicted to develop coccy) and the other retrospectively (i.e., a patient with coccy develops sarcoid).

RESULTS

PATIENT ONE (PROSPECTIVE) A 50 year old white male was diagnosed with sarcoidosis in December, 2000, with no evidence of a *Coccidioides* infection. He was started on prednisone for the sarcoid. At an outpatient visit in June, 2001 the patient's *Coccidioides* complement fixation (CF) titer seroconverted from negative to positive at 1:8 with a positive IgM. He was asymptomatic and improving on steroids. The steroids were discontinued in October, 2001 and the patient's CF titers decreased to 1:2. However, in June, 2002 the patient was placed back on steroids because of polyarticular arthritis. While on steroids his CF titers increased to a high of 1:32. Aside from the arthritis, he was asymptomatic for coccy. The steroids were discontinued in December, 2003. His CF titers were elevated at 1:32 for eighteen months. Off the steroids his CF titer went to a low of 1:4 in March, 2006. In June, 2008 he developed swelling of his right sternoclavicular joint. Joint aspiration grew *Coccidioides*. He was placed on oral fluconazole and returned to work. In late 2009 he died because of "cancer of the brain."

PATIENT TWO (RETROSPECTIVE) A 34 year old black male was diagnosed with disseminated coccy in 2009 with myalgias, weight loss, night sweats, pain and swelling in his left elbow. His left elbow was aspirated and cultures grew *Coccidioides*. CF titer was positive at 1:8. In 2012, despite amphotericin B as an outpatient, he became seriously ill with fevers and respiratory failure which required hospitalization and mechanical ventilation. During that hospitalization he underwent a lung biopsy which revealed non-caseating granulomas consistent with sarcoid. There was no histopathologic or culture evidence of *Coccidioides*. His CF titer had become negative. The patient was started on corticosteroids for the sarcoid and also maintained on antifungals. Between 2012 and 2016 he clinically improved and his "sarcoid/coccy" is controlled on low doses of steroids and oral voriconazole.

CONCLUSIONS

Based on literature review, as well as the clinical and epidemiologic observations on these two patients we have hypothesized that sarcoid is the result of a unique cell-mediated immune (CMI) response to *Coccidioides*. Individuals that have a "strong" CMI response are immunologically able to develop a "sarcoid" response to *Coccidioides* with no organisms being present.

CURE OF COCCIDIOIDAL MENINGITIS: A CASE REPORT

Tim Kuberski
University of Arizona College of Medicine, Phoenix

INTRODUCTION

There is evidence in experimental animals that coccidioidal meningitis (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.

CASE REPORT

The patient is a white 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; cerebrospinal fluid (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 doses 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 returned negative for eighteen months and he was doing well. This case report details the clinical findings, treatment and outcome of a patient with CM treated with LAB as the primary agent of therapy.

RESULTS

Fifteen years later, the patient is functioning normally, asymptomatic with respect to CM and without recurrence.

CONCLUSIONS

This patient was presented previously in 2011, but the case was not published because of the concern by Coccy Study Group experts that the patient had not been followed long enough to be deemed cured. Review of the literature has revealed the longest interval documented for a coccy relapse was 12 years. After 15 years this patient suggests that CM can be cured. This case is important because the inclination of clinicians is to not use LAB aggressively for a CM cure because of the management issues. The early use of fluconazole in CM ultimately only controls the infection and can be associated with relapses related to compliance.

ADJUNCTIVE USE Of SERTRALINE IN A PATIENT WITH REFRACTORY COCCIDIOIDAL MENINGITIS

Thu, Ye; Roshan, Bahkt; Mu, Anandit; Nassar, Naiel; Libke, Robert; Stockamp, Nathan
Division of Infectious Diseases, University of California San Francisco - Fresno

INTRODUCTION

Most patients with coccidioidal meningitis are treated with oral fluconazole, although this is only effective in 70% of cases and disease progression remains a significant problem. We describe a case of refractory coccidioidal meningitis where sertraline (a selective serotonin reuptake inhibitor) was added to voriconazole. Data on use of sertraline in fungal infections is emerging and has not been reported in a clinical case of coccidioidal meningitis.

CLINICAL PRESENTATION

A 30 year old Hispanic male with a history of depression on paroxetine was diagnosed with coccidioidal meningitis requiring a ventriculoperitoneal shunt. After five months of fluconazole 800 mg PO daily, he developed new onset back pain and upper extremity weakness. Imaging revealed an Arnold Chiari malformation and syringomyelia throughout thoracic spine (**Figure 1**). He underwent surgical decompression of the malformation and fluconazole was switched to voriconazole 200 mg TID. However, two months later, he developed nystagmus, double vision, neck pain, and worsening hydrocephalus on MRI. His cerebrospinal fluid (CSF) quantitative immunodiffusion titer was 1:32. Sertraline was added to voriconazole in escalating doses to the FDA approved maximum dose of 200mg PO daily. No significant change in QTc or liver enzyme changes were noted after sertraline was started. Currently patient is tolerating both sertraline and voriconazole. Long term follow up for clinical improvement is planned.

DISCUSSION

Sertraline is an intriguing possibility for adjunct therapy in patients with refractory disease. This abstract highlights the novel use of an antidepressant class compound in a case of coccidioidal meningitis. Sertraline was noted to aid CSF clearance in a study of patients with cryptococcal meningitis from Uganda. Recent data from our institution has shown in vitro activity of sertraline against *Coccidioides immitis*. After several months, there have been no demonstrable adverse effects on this regimen. The effective therapeutic dose of sertraline in coccidioidal meningitis needs to be defined, but is anticipated to be up to 400mg. Further investigations are underway to understand the role of sertraline in coccidioidal meningitis.

SERTRALINE DEMONSTRATES FUNGICIDAL ACTIVITY AGAINST *COCCIDIOIDES IMMITIS IN VITRO*

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[1]Department of Internal Medicine/[2]Department of Family and Community Medicine, UCSF Fresno Medical Education Program, Fresno, CA, 93701, [3]Department of Microbiology, Community Regional Medical Center, Fresno, CA, 93701.

BACKGROUND

Coccidioidomycosis causes substantial morbidity in endemic areas, and treatment of disseminated infections may require lifelong antifungal therapy. The anti-depressant serotonin-reuptake inhibitor sertraline has been reported to have activity against other fungi in vitro, possibly inhibition of protein synthesis. As improved treatment options are needed for coccidioidomycosis, the fungicidal activity of sertraline against *C. immitis* was investigated *in vitro*.

METHODS

C. immitis was identified in fungal cultures from clinical specimens using the Hologic Gen-Probe nucleic acid based assay. *C. immitis* colonies were isolated from cultures on Sabouraud-dextrose agar slants in the biosafety level 3 laboratory of Community Regional Medical Center. Stock solutions of sertraline and fluconazole were made at 5 mg/mL in DMSO. Following reference protocol Clinical and Laboratory Standards Institute M27-S4 and M38-A2, Minimum Inhibitory Concentration (MIC) was determined after a 5 day incubation in RPMI culture medium. The Minimum Fungicidal Concentration (MFC) was determined after this incubation by plating 0.25 ml of each culture on Saboraud-dextrose agar plates.

RESULTS

For four clinical isolates of *C. immitis* the MIC and MFC were determined for fluconazole, sertraline and for the two drugs combined at equal concentration as seen in this table:

Drug	MIC (mcg/mL)			
fluconazole	4	8	16	32
sertraline	4	4	8	8
fluc + sert	4	2	4	4
	MFC (mcg/mL)			
fluconazole	4	16	16	32
sertraline	4	8	8	8
fluc + sert	2	4	4	4

CONCLUSIONS

For four clinical isolates of *C. immitis*, sertraline had an equal or lower MIC than the standard of care treatment fluconazole. The sertraline MFC was also equal to or lower than that of fluconazole. In combination the two drugs had at least additive effectiveness. The MIC of sertraline for *C. immitis* is higher than sertraline therapeutic blood concentrations, however, sertraline concentrations in the central nervous system (CNS) can approach these levels. These results indicate that sertraline may have potential as an additional agent for the treatment of *C. immitis* infection.

VERTEBRAL COCCIDIOIDOMYCOSIS PRESENTING IN HYPHAL FORM 23 YEARS AFTER AN INITIAL EPISODE OF CUTANEOUS COCCIDIOIDOMYCOSIS.

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INTRODUCTION

In most pathologic specimens, *Coccidioides immitis* is identified in spherule form. Reactivation events have been reported. In this case, we report on a woman who developed vertebral coccidioidomycosis approximately 23 years after an initial presentation of cutaneous coccidioidomycosis. We also review the uncommon occurrence of identifying hyphae from a vertebral lesion.

CASE DESCRIPTION

A 56-year-old East Asian female was hospitalized after four months of progressively worsening back pain, beginning after a fall. She had a history of amphotericin treated cutaneous coccidioidomycosis in 1992, and a history of poorly controlled insulin dependent type 2 diabetes mellitus. She reported fevers, night sweats, and weight loss but no skin abrasions, lesions, nor pulmonary symptoms. An MRI of the lumbar spine showed L2/3 osteomyelitis associated with discitis and psoas abscess. A vertebral bone biopsy was performed, and histopathology revealed the unique occurrence of fungal hyphae within the biopsied fibrocartilage adjacent to the bone (**Figure 1)**. Subsequent cultures grew *C. immitis,* and her serum complement fixation titer was 1:128 at diagnosis.

CONCLUSION

This case has two important points. First, identification of *C. immitis* hyphae from bone or fibrocartilage without a draining sinus tract is uncommon for a pathogen that traditionally exists as a yeast form in vivo. However, there are case reports of hyphae and arthroconidia isolated from cutaneous lesions, the cerebrospinal fluid -where a reservoir such as a shunt device was present, and pulmonary cavities.[1, 2] Arthroconidia have also been isolated from gastric washings.[3] Diagnosis depends on a combination of culture of tissue, serology and histopathology. The presence of hyphae when culture is unavailable should not negate the possibility of *C. immitis* in a differential. Second, clinicians should continue to be vigilant about the possibility of recurrence of coccidioidomycosis.[4] As our case demonstrates, reactivation can occur up to three decades after the original infection during an immunosuppressive state.

CLIMATE DRIVERS AND COCCIDIOIDOMYCOSIS INCIDENCE AT THE REGIONAL SCALE

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INTRODUCTION

Studies analyzing climate drivers on coccidioidomycosis incidence as well as methods to predict future outbreaks have been largely limited to the county level. Furthermore, the relationships between climate conditions, the environmental niche in which *Coccidioides spp.* lives, and increases in coccidioidomycosis cases has yet to be established. Previous studies have recognized precipitation to be a significant driver in coccidioidomycosis incidence [*Comrie* 2005, *Park, Sigel, Vaz et al.*, 2005] and mean annual precipitation in the Southwest is projected to decrease by 20% and shift to less frequent, but more intense storms by 2100 [*Karl et al.*, 2009; *Schoof et al.*, 2010]. This shift is likely to intensify periods of drought and may increase the amount of viable *Coccidioides spp.* spores. Regional climate change impacts on soil composition and precipitation regimes could cause a shift in the climate envelope of *Coccidioides sp*. This study looks at regional-scale coccidioidomycosis incidence and its relationship to climate drivers by compiling the first robust coccidioidomycosis incidence database, incorporating county-level case totals at its finest temporal resolution.

METHODS

We inquired county and state health agencies throughout Arizona, California, New Mexico, Nevada, and Utah for coccidioidomycosis case totals on the finest temporal resolution possible, and for the longest duration possible. Climate datasets analyzed against the coccidioidomycosis incidence database include precipitation, Palmer drought index, soil moisture, and normalized difference vegetation index.

RESULTS

The coccidioidomycosis incidence database is non-uniform and consists of weekly, monthly, quarterly, and annual time scales by the county and state level. Monthly incidence data is currently available for 85 out of 140 counties/Nevada Health Districts. Monthly data is available for all counties in Arizona since 1990 (pending), New Mexico from 2006, Utah from 1995, and most high-incidence counties in California (e.g., Kern, Kings). Annual data is available on the county-level for Arizona, California, New Mexico, and the Nevada Health Districts from 2001, and Utah from 1995. Defining relationships between climate drivers and coccidioidomycosis incidence is ongoing.

CONCLUSIONS

We will create a statistical-based, regional climate envelope model of *Coccidioides sp.* that combines the dominant climate drivers, regional soil samples analyzed by PCR methods (see "Regional Environmental Soil and Air Sampling of *Coccidioides spp.* and Airborne Fungal Spore Distribution Patterns" by Cat, LA) that further define the local environmental conditions (e.g., soil moisture) in which *Coccidioides sp.* lives, and the robust coccidioidomycosis incidence database. This model will be used to forecast the current risk of exposure, and where *Coccidioides spp.* may spread under future climate change scenarios.

TUBERCULOSIS AND DISSEMINATED COCCIDIOIDOMYCOSIS IN A PATIENT WITH MALNUTRITION

Palma Cortés Gabriel[1], Muñoz Torrico Marcela V.[1], Valencia Maqueda Elba L.[1], González Valadez Jalil[2], Higuera Iglesias Anjarath L.[2], Pérez Brunet Belem[1], Cabello Gutiérrez Carlos[1]

NOT PUBLISHED PER FIRST AUTHOR REQUEST

CULTURING *COCCIDIOIDES*: OPTIMIZING *IN VITRO* CULTURE MEDIA TO REFLECT NUTRIENT AVAILABILITY *IN VIVO*

H.L. Mead[1, 2], B.M. Barker[1, 2]

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[2]Pathogen Genomics Division, Translation Genomics Research Institute-North, Flagstaff, AZ

INTRODUCTION

The pathogenic soil dwelling fungi, Coccidioides immitis and C. posadasii can be found in arid desert regions and cause an estimated 150,000 cases of coccidioidomycosis, also known as valley fever, in the United States each year. The current media for culturing spherules is not nutritionally representative of a mammalian respiratory system or conducive to *in vitro* immunology experiments. Supplemented RPMI media was used to produce the spherule form in a previous study. RPMI media is routinely used in cell culture applications making it useful for *in vitro* immunology experiments.

METHODS

Using the supplemented media and an attenuated biosafety level two (BSL2) *Coccidioides*, preliminary trials were conducted to determine which factors, such as cell density, temperature, time, CO_2 and O_2 concentration, would affect spherule development. Potential conditions were identified, reproduced in triplicate, and compared to determine the most successful method of growth.

RESULTS

The BSL2 strain cultured in the supplemented RPMI media successfully grew spherules at several conditions similar to the host environment. Temperature ranged between 37-39°C and CO_2 concentration between 5-15%. The supplemented RPMI media produced both spherule and mycelial morphology under normoxic conditions. Spherule development between the two media types was relativity equivalent, and the highest percentage of parasitic morphology occurred at 15 % CO_2. Hypoxia impaired the growth of mycelial structures while allowing for growth of spherules. Additionally, hypoxic conditions nearly inhibited growth in Converse media, while only slowing growth in the supplemented RPMI.

DISCUSSION

The supplemented RPMI media is an excellent candidate for culturing Coccidioides spherules and can be applied to future research in the BSL3 laboratory. The components of the media provide the organism with nutrients that are similar to those found in a host respiratory system, and the conditions of growth are favorable for mammalian immune cells allowing *in vitro* immunology experiments.

COMPARISON OF COCCIDIOIDES ANTIBODY DETECTION BY THE MIRA VISTA ENZYME IMMUNOASSAY WITH IMMUNODIFFUSION AND COMPLEMENT FIXATION

Holbrook, Eric, Wheat, Lawrence J.
MiraVista Diagnostics, Indianapolis, Indiana U.S.A.

INTRODUCTION

Enzyme immunoassays are more sensitive than immunodiffusion (ID) or complement fixation (CF) for the detection of antibodies. The sensitivity of the two commercial antibody detection assays was estimated to be between 68% and 72%, as determined by testing 150 specimens from patients with confirmed coccidioidomycosis (Sunenshine, R ICAAC 2014). Specificity was between 93% and 95% in an evaluation of healthy blood donors from Phoenix, Arizona. The purpose of this study is to evaluate a semi-quantitative method for measurement of IgM and IgG anti-Coccidioides antibodies in an assay developed at MiraVista Diagnostics, which has been validated for clinical testing according to CLSI guidelines.

METHODS

Specimens: A total of 100 serum specimens that were submitted for anti-Coccidioides antibody testing by ID and CF to the Kern County public health service laboratory. Specimens were concentrated 8 fold before ID testing and reported as positive, weakly positive, very weakly positive or negative. The clinical diagnosis of these individuals was unknown, but 51 of the specimens were positive for Coccidioides antibody by ID and/or CF.

MVista anti-Coccidioides antibody EIA: The assay uses microplates coated with a proprietary Coccidioides antigen. Specimens were diluted 1000 fold and 100 µLs was added to wells of the coated microplate and incubated for one hour. Antibody is detected using biotinylated anti-human IgM or anti-human IgG. Results are expressed as units determined by extrapolation from a standard curve. Results of ≥10 units were classified as positive, 7.0-9.9 units as indeterminate, and 0 to 6.9 units as negative.

RESULTS

IgG antibodies were detected by EIA in 31 of 36 (86.1%) specimens tested positive for antibody by CF. False-negative results occurred in 5 of 12 specimens that were positive using undiluted serum. IgG antibodies were also detected in 8 of 64 (12.5%) specimens that were negative by CF. IgG antibodies were detected by EIA in 32 of 45 (71.1% %) specimens that were positive for antibody by IDCF. Negative results occurred in 13 (28.9%) specimens that were weakly (3) or very weakly (10) positive by IDCF, four of which had indeterminate results by EIA. IgG antibodies were detected in 7 of 55 (12.7%) specimens that were negative by IDCF. IgM antibodies by EIA were detected in 18 of 28 (64.3%) of specimens that were positive by ID TP. IgM negative specimens were weakly or very weakly positive by IDTP. IgM antibodies were detected by EIA in 6 of 72 (8.3%) specimens that were negative by ID TP.

CONCLUSIONS

IgG and IgM antibody detection by EIA demonstrated good agreement with ID and CF. Disagreement occurred in specimens that were weakly positive by ID, CF or EIA. Additional studies are required to determine sensitivity and specificity in known cases and controls.

DISSEMINATED COCCIDIOIDOMYOSIS IN CHILDREN

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INTRODUCTION

Coccidioidomycosis is a soil fungus native to the San Joaquin Valley of California. Initial symptoms are non-specific leading to delayed diagnosis. Disseminated disease although rare in children can be devastating.

OBJECTIVE

To describe the clinical presentation, treatment and outcome of coccidioidomycosis in children admitted to a tertiary Pediatric Intensive Care Unit (PICU) located in the San Joaquin Central Valley.

METHODS

Retrospective review of charts, laboratory and imaging records of all coccidioidomycosis patients admitted to the PICU between Jan 1st 2009- Dec 31st 2014.

RESULTS

Seven patients (4 males, 3 females) were admitted to the PICU, mean age 6 years (.5-18 years). All patients had at least one previous medical visit, four previously hospitalized for pneumonia and one for "viral meningitis". Disseminated disease (central nervous system, cardiac, mediastinal, and/or bone disease) was present in all cases. Diagnosis was made by enzyme linked immunoassay, immunodiffusion, complement fixation, fungal culture and/or histopathology. All patients received intravenous amphotericin. Six patients received both amphotericin and an azole antifungal. Three patients, refractory to amphothericin, received intravenous caspofungin and voriconazole. One patient had fungal meningoencephalitis and also received intrathecal amphothericin and interferon gamma. Treatment continued until the normalization of titers and clinical and radiologic resolution of the disease. Mean length of treatment was 16 months (3- 29 months).Patients underwent surgical debridement and excision of fungal lesions. Mean PICU length of stay was 19 days (2-78 days) and mean hospital length of stay was 94 days (7-196 days). Two patients died.

CONCLUSIONS

Despite being in an endemic area, coccidioidomycosis diagnosis and subsequent treatment is delayed due to lack of recognition. Risk factors for disseminated disease in previously healthy children are not known. Further studies elucidating immune factors and effectiveness of combination antifungals are needed.

DIFFERENTIAL DIAGNOSIS BETWEEN COCCIDIOIDOMYCOSIS AND TUBERCULOSIS: CLINICAL AND EPIDEMIOLOGICAL RISK FACTORS IN A HOSPITAL IN RESPIRATORY DISEASES IN MEXICO CITY

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INTRODUCTION

Coccidioidomycosis is an endemic systemic mycosis is also known as Valley Fever, Fever San Joaquin disease Posadas and Wernicke's disease. Cases of Pneumocystis fungus share similar clinical features with Tuberculosis, and both infections coexist in the same patient, complicating the diagnosis and treatment.

OBJECTIVES

To describe the clinical and epidemiological factors of coccidioidomycosis and pulmonary tuberculosis and highlight the factors that differ in clinical diagnosis.

MATERIAL AND METHODS

Case (Ca) and controls (Co), hospitalized patients were included with a confirmed diagnosis of coccidioidomycosis and tuberculosis, they were matched by age and sex. Variables included: place of birth, occupation, education, laboratory and imaging studies, signs and symptoms, comorbidities, body mass index, duration and hospitalization, mortality, evaluation of respiratory failure, APACHE II. Analysis with SPSS 13.0, measures of frequency and association corresponding calculated.

RESULTS

110 cases (Ca) of coccidioidomycosis and 110 controls (Co) of all hospitalized tuberculosis and confirmed by microbiology and cabinet were included; $\overline{X}$ age 41 years in both groups, the occupational hazard Ca 54.5% vs 14.5% Co X2 164 and P <0.000, there was no difference in the level of schooling. There were differences in the number of comorbidities were not significant P> 0.05. Symptoms with significant differences were: hemoptysis, chills, sweating, pleural pain and dyspnea P <0.05. The Ca APACHEII $\overline{X}$ 5.82 σ 39, vs APACHEII Co $\overline{X}$ 7.26 σ 3.7, P 0.044. The evolution of Ca $\overline{X}$ 29 months σ 35.6, vs Co $\overline{X}$ six months σ 9.5, P <0.000, Ca $\overline{X}$ hospital days 38 days 73 vs σ Co $\overline{X}$ 16 days σ 12, P = 0.000.

CONCLUSIONS

Coccidioidomycosis and tuberculosis lung share similar clinical and epidemiological features, however, there are important findings during hospitalization that can support the differential diagnosis. In cases of coccidioidomycosis was significantly higher symptoms such as hemoptysis, chills, sweating, pleural pain, dyspnea and epidemiological risk as work activity (mason and farmer), more than 6 months late diagnosis and prolonged hospital stay greater than 38 days.

AN AUTOMATED NODULE CALCULATOR FOR DIFFERENTIATING NODULES CAUSED BY LUNG CANCER FROM THOSE CAUSED BY COCCIDIOIDOMYCOSIS

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INTRODUCTION

Differentiating lung nodules caused by lung cancer from those caused by Coccidioidomycosis poses a significant challenge to clinicians. Calculators have been developed to predict the probability of malignancy in lung nodules, but we have found these calculators to perform poorly in a Coccidioidomycosis endemic area (1). We have developed a model which may improve our ability to differentiate the cause of nodules using clinical and radiographic features. We have tested this model on retrospective patients, but we have not yet tested the model prospectively or in other geographic areas outside the Fresno region. In order to test the model, we have developed an electronic application to use with cell phones and electronic devices.

MATERIALS AND METHODS

As previously described, we have analyzed clinical and radiographic parameters among over 300 patients seen at UCSF Fresno with lung nodules. Using these patients, we completed a linear regression and identified 12 clinical and radiographic variables that differentiate the two groups. Using the resulting odds ratio we assigned a pointe to each characteristic. We have subsequently retrospectively tested the model in a separate group of 143 patients seen at UCSF Fresno. In order to test the model in a broader patient population that includes other areas that are endemic for Coccidioidomycosis, we have developed an application for the cell phone and other electronic devices that will allow us to test the model.

RESULTS

By entering the data on patients into the calculator, the application will calculate a numerical score with a probability of high, intermediate or low for lung cancer. In the background, these data will be sent in encrypted format to a central database at UCSF-Fresno. We will subsequently follow up on these patients to learn the actual diagnosis and test the utility of the model across many geographic sites.

DISCUSSION

We have developed an electronically available risk calculator using clinical and radiographic characteristics to better differentiate nodules caused by lung cancer from those caused by Coccidioidomycosis lung infection. With this app we will collect data from other geographical areas endemic to Cocci and test the accuracy of the calculator prospectively. We hope to enroll several interested clinicians at the Cocci Study Group meeting.

MOLECULAR ANALYSIS OF CLINICAL ISOLATES OF *COCCIDIOIDES SPP.* FROM MEXICAN PATIENTS

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INTRODUCTION

Coccidioidomycosis (CM) is a fungal disease that primarily affects the respiratory system. It is reported that in the United States of America (US) 150 000 new cases each year and it is likely that the situation in Mexico is similar. The CM is caused by two species, *Coccidioides immitis* and *Coccidioides posadasii* both etiologic agents have similar phenotypic characteristics, so it is difficult to differentiate. Currently there are molecular markers that identify separately. We analyze microsatellite sequences from different strains of Coccidioides, isolated from Mexican patients from different geographic origins, were located within existing phylogenetic groups.

METHODS

61 isolates were analyzed which were cultured, inactivated and processed for DNA extraction. It was conducted nine microsatellite amplification and It was subjected to sequencing reaction according to the method of Sanger. For analysis of the number of microsatellite repeats, it obtained and was assigned genotype as reference genomes obtained from Gene Bank. The phylogenetic trees were performed using the program MEGA 6.0 and the strains were grouped according to their geographical origin obtained from medical records.

RESULTS

The predominant species in Mexico was *C. posadasii* and in northwestern *C. immitis*. Molecular markers are 621.2 and GAC both markers with greater reliability for identifying Coccidioides species, because the number of repetitions usually very marked between the two species. With the construction of phylogenetic trees, you can say that about 80% of the isolates were identified as C. posadasii and 20% to C. immitis. The geographical location of the isolates showed that *Coccidioides spp*. is not only limited to E.U and northern Mexico, but also has spread to central and southern Mexico.

CONCLUSIONS

Molecular markers proved to be a tool with high resolving power to identify the species of Coccidioides and therefore, prompt and appropriate treatment of the patient, which is very important as Coccidioides is occurring in places where there is no knowledge of the disease.

EPIDEMIOLOGY OF SEVERE COCCIDIOIDOMYCOSIS PNEUMONIA: TWO DECADES IN MEXICO IN THE NATIONAL INSTITUTE OF RESPIRATORY DISEASES "ISMAEL COSIO VILLEGAS"

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INTRODUCTION

Coccidioidomycosis is caused by a biphasic-dimorphic fungal pathogen divided by two different species, Coccidioides immitis and Coccidioides posadasii (not CA) present in the rest of the US, Mexico, Central and South America. This fungus grows in semi-desert areas. In Mexico the majority of cases are in the north and the true incidence is unknown since 1995.

OBJECTIVE

To describe the transition and epidemiological factors of coccidioidomycosis in the last two decades in patients INER.

METHODS

Transversal study. 159 patients diagnosed with coccidioidomycosis captured the period 1994-2015 secondary information from medical records was used. Variables: age, gender, residence, origin, occupation, education, comorbidities, weight, height, days duration, hospital stay, discharge, years lost to disability and APACHE II. Analysis with SPSS 13.0, measures of frequency and association corresponding calculated.

RESULTS

The analysis compared the two decades, the rate of 2-24 per thousand expenses increased pneumonia; the average age 39 years (σ 17.2) vs 42 years (σ 16.2). The sex ratio 1:9 vs 4:6 predominantly men, occupational hazard for both sexes 71% vs 52% with significant risk for men X^2= 5.059, p= 0.025, p = 0.029. Comorbidities in both periods: Diabetes Mellitus (31%), hypertension (10%) and Tuberculosis (8%) (X^2= 5.098, p= 0.078). The maximum number of readmissions 4 vs 11 (X^2= 19.09, p= <0.001). APACHEII mild (56%) vs APACHEII severe (78%) (X^2= 38.28, p= 0.004). The evolution of 32 months (σ 28.4) vs 25 months (σ 35.13) (X^2= 58.11, p= 0.230). The length of hospital stay 26.2 days (σ 27.7) vs 3.4 (σ 79.9) (X^2= 63.34, p= 0.429), the years lost to disability 34 years of healthy life (σ 16.6) vs 31 (16.9) (X^2= 78.5, p= 0.33).

CONCLUSIONS

Coccidioidomycosis increased 13 times compared to the previous decade. The average time for diagnosis is high increasing costs and days of hospitalization, complications and mortality. It is a disease with a good impact by incorporating labor education and prevention, diagnosis and treatment as well as quality of life.

PLASMA ELMO3 IN COCCIDIOIDOMYCOSIS

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INTRODUCTION

In Central California, endemic Coccidioidomycosis (Cocci) infection is a major confounding diagnosis for lung nodules in smokers who are at high risk for cancer. Serological studies have limited role in endemic area since these patient may have had prior subclinical exposure. Neither the Malignancy Risk Calculators, nor the ATS Guidelines which recommend surgical resection of sizable lung nodule without a biopsy are applicable in our patients. Therefore, differentiating lung nodules of Cocci etiology from cancer is important in order to prevent unnecessary lung resection surgeries. We studied the role of plasma engulfment and cell motility 3 gene (ELMO3) in differentiating cocci from cancer in patients with lung nodules that are at high risk for cancer.

METHODS

We performed RNA, miRNA extraction, cDNA synthesis and Quantitative RT-PCR to detect the expression of engulfment and cell motility 3 gene in human plasma samples collected from patients with biopsy proven lung cancer and Cocci.

RESULTS

Our data showed that the expression of plasma ELMO3 was significantly reduced in biopsy proven Cocci patients. While, there was significant upregulation of Plasma ELMO3 expression in patients with biopsy proven lung cancer as compared to controls.

CONCLUSION

Our findings suggest that plasma ELMO3 expression can be valuable in ruling out cocci and ruling in lung cancer in high risk individuals with lung nodules. Further validation studies are required to determine the clinical utility of these markers. If validated, our finding may open up a possibility of utilizing a new diagnostic test to differentiate cocci from cancer in patients with lung nodules.

Funded by CCFMG Research Grant (PI: DU)

EXPRESSION OF PLASMA CDKN1A INTERACTING ZINC FINGER PROTEIN 1 VARIANT IN COCCIDIOIDOMYCOSIS

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INTRODUCTION

Endemic Coccidioidomycosis (Cocci) is a major confounding diagnosis for lung nodules in smokers who are at high risk for cancer. Serological studies have limited role in endemic area since these patient may have had prior subclinical exposure. None of the Lung Cancer Risk Assessment calculators nor the AATS and ATS Guidelines which recommend surgical resection of sizable lung nodule without biopsy are applicable in our patients. It is critically important to differentiate lung nodules of Cocci etiology from cancer to prevent unnecessary lung resection surgeries. In this study, we examined if CDKN1A interacting zinc finger protein 1 can help in ruling out Cocci in patients with lung nodules that are at high risk for cancer.

METHODS

We performed RNA, miRNA extraction, cDNA synthesis and Quantitative RT-PCR for CDKN1A interacting zinc finger protein 1 variant on human plasma samples collected from patients with biopsy proven lung cancer and Cocci.

RESULTS

In high risk smokers with lung nodules, the plasma CDKN1A interacting zinc finger protein 1 variant expression were significantly reduced in biopsy proven Cocci patients as compared to controls, while Ciz1b variant expressions were statistically significantly upregulated ($p<0.005$) in patients with biopsy proven lung cancer.

CONCLUSION

Our finding suggest that plasma CDKN1A interacting zinc finger protein 1 variant expression can be valuable in ruling out cocci and ruling in lung cancer in high risk individuals with lung nodules. Further validation studies are necessary to assess clinical utility of these markers in high risk patients with lung nodules residing in the region of endemic mycosis.

Funded by CCFMG Research Grant (PI: DU)

IDENTIFICATION BY ELISA OF ANTI-*COCCIDIOIDES* ANTIBODIES IN HUMAN AND DOGS POPULATIONS OF ENDEMIC AND NON ENDEMIC AREAS OF COCCIDIOIDOMYCOSIS

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INTRODUCTION In adaptive immunity we know that the production of antibodies is generated by the penetration of an initial dose of antigen. On this argument is based the assumption that people and animals living in endemic areas of coccidioidomycosis have developed titers of anti-*Coccidioides* antibodies by asymptomatic, recent or past, infections; consequently, the presence of low titers of such antibodies, it is normal in these populations. To date, there is no study to approve or dismiss that claim. The aim of this study was to compare the prevalence of anti-*Coccidioides* antibodies by ELISA, between human and canine population; in an endemic area for coccidioidomycosis *vs.* an area not endemic.

METHODS A local coccidioidin was used for standardization of ELISA. Human sera from eight patients previously diagnosed with coccidioidomicosis (positive control) with Capillary Tube Agglutination and positive culture, and 50 sera from persons with no signs or symptoms of this disease, healthy, living in Mexico City (negative control) were used. Also we studied sera from 24 patients with histoplasmosis and 12 with aspergillosis, both previously diagnosed just by Capillary Tube Agglutination. In the case of canine sera, we only had one sera with antibodies anti-*Coccidioides* previously analyzed with Double Immuno-Diffusion Test and 50 sera from dogs with no signs of disease and residents in Mexico City. Dilutions of sera, antigen and conjugate were probed and the cutoff points were established. Two hundred fifty-three human sera from endemic area and 120 from non-endemic area were studied. Regarding dogs, the study was made in 74 sera from endemic area and 110 from not endemic.

RESULTS From 253 human sera collected of endemic area, only 48 (23%) were positive and 205 (77%) negative. Regarding the 120 sera from no endemic area, we had 12 positive (10%) and 108 (90%) negative sera. All dog sera tested were negative for anti-*Coccidioides* antibodies.

CONCLUSIONS The statistical tests shows that in Mexico, in coccidioidomycosis endemic areas humans and dogs are susceptible animals to infection by *Coccidioides* spp, but not with so high prevalence as has been reported in the traditional literature.

A QUALITATIVE STUDY OF VALLEY FEVER AMONG HISPANIC/LATINO FARMWORKERS IN CALIFORNIA

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INTRODUCTION

The San Joaquin Valley is known to be one of the most robust agricultural areas in he U.S., but it is also one of the most endemic areas for valley fever. The majority of agricultural workers in this region are Hispanic/Latino. It is important to consider the occupational exposure to coccidioidomycosis in light of existing health inequalities this population faces, routinely shaped by migration that is in many cases complicated by unauthorized status. Very little is known about how Hispanic/Latino farmworkers experience these underlying processes in direct relation to valley fever.

METHODS

In-depth semi-structured interviews will be conducted with a purposeful sample of Hispanic/Latino outdoor agricultural workers in the San Joaquin Valley, with a self-reported diagnosis of valley fever (n=15). This study is guided by the concept of structural vulnerability (Quesada, Hart, Bourgois 2011) and will focus on socio-economic and politically contextualized understanding of valley fever in relation to ethnicity, race, gender, and class; work practices, perceptions of risk and disease causality; access and barriers to healthcare. Interviews will last about 2 hours, using probes and leaving room for the participant to respond openly. All interviews will be audio-recorded, translated (if originally in Spanish), transcribed verbatim, and qualitatively analyzed. Grounded theory will be applied in developing an inductive analysis, progressively refining emergent themes and generating codes for the categories and processes studied.

RESULTS

The results are pending until the conclusion of this study. The aim is to provide contextualized understanding that can be used to inform valley fever prevention and treatment strategies, and ameliorate the health of Hispanic/Latino agricultural workers.

CONCLUSION

Coccidioidomycosis prevention and treatment strategies targeted at Hispanic/Latino farmworkers should take into account the economic and socio-political context in which it is produced.

UTILITY OF COMBINED ENDOSONOGRAPHY (EBUS & EUS) IN THE DIAGNOSIS OF COCCIDIOIDOMYCOSIS

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INTRODUCTION

Coccidioidomycosis is a fungal infection endemic to the southwestern United States identified at times when patients present with mediastinal lymphadenopathy. Combined endobronchial ultrasound/endoscopic ultrasound (EBUS & EUS) allows for robust sampling of lymph node stations. This study is the first to assess the utility of combined EBUS & EUS in the diagnosis of coccidioidomycosis with mediastinal lymphadenopathy in an endemic coccidioidomycosis area.

METHODS

We retrospectively reviewed charts of patients with mediastinal lymphadenopathy who underwent combined endosonographic lymph node biopsy (EBUS & EUS – Fine Needle Aspiration) between between September 2015 and January 2016. Simple descriptive statistics were used to analyze the data obtained in the study.

RESULTS

We identified 43 patients with mediastinal lymphadenopathy who underwent combined EBUS & EUS. Twenty of the 43 (47%) were identified as cancer, 20 (47%) had other diagnoses with benign lymph node tissue present in the specimen, and 3 of the 43 (6%) were identified as proven or probable coccidioidomycosis. All 3 patients who were were identified as proven or probable coccidioidomycosis had positive fungal cultures and positive cytology for coccidioidomycosis. 1 of the 3 had positive PCR tests. When evaluating lymphadenopathy secondary to coccidioidomycosis combined EBUS & EUS demonstrated sensitivity and specificity of 100%.

CONCLUSIONS

Combined endosonographic procedure done in the same setting is a relatively new technique. It allows for greater evaluation of lymph nodes compared to a single technique alone. Combined EBUS & EUS has a high sensitivity and specificity when evaluating lymphadenopathy secondary to coccidioidomycosis. Further investigation with a sample size should be undertaken to better define the sensitivity, and ultimately the utility of this method.

IMMUNNE RECONSTITUTION INFLAMMATORY SYNDROME IN PATIENTS WITH AIDS AND DISSEMINATED COCCIDIOIDOMYCOSIS: A CASE SERIES

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INTRODUCTION

Coccidioidomycosis frequently disseminates in patients with AIDS and causes substantial morbidity and mortality. After starting antiretroviral therapy (ART), a paradoxical clinical worsening may occur in the form of Immune Reconstitution Inflammatory Syndrome (IRIS). To date, only two cases of IRIS due to coccidioidomycosis have been reported. We report four cases of IRIS in HIV-infected patients with coccidioidomycosis. All four patients died of worsening inflammation from IRIS after initiating ART. The optimal timing of ART in patients with AIDS and coccidioidomycosis remains to be elucidated.

METHODS

Review of medical records of patients with AIDS co-infected with coccidioidomycosis.

RESULTS

Four patients were identified with AIDS and disseminated coccidioidomycosis. All four patients showed initial clinical improvement with antifungal therapy. Antiretroviral therapy was begun from six days to thirty days after initiation of antifungal therapy. All four patients developed worsening clinical and radiologic findings from three days to twenty eight days after initiating of ART. Despite ongoing supportive care, antifungal and antiretroviral therapy, all four patients died from their disease.

CONCLUSIONS

Early initiation of ART in coccidioidomycosis led to IRIS with fatal outcomes in the four patients reported here. From these cases we cannot determine the optimal timing for initiation of ART, however, it is possible that delaying ART for a minimum of five weeks as is done with cryptococcal infection may lower the risk of IRIS.

THE UTILITY OF SCREENING FOR COCCIDIOIDOMYCOSIS IN RECIPIENTS OF ANTI-TNF-α THERAPY.

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INTRODUCTION

TNF-α inhibitors (TNF-I) are commonly used today to treat a wide variety of immune-mediated disorders. These medications are linked with an increased risk of mycobacterial, viral, and fungal infections, and some society guidelines recommend screening for tuberculosis, hepatitis B and C, human immunodeficiency virus, and active life-threatening fungal infections. Patients are also commonly screened for coccidioidomycosis (cocci) in Arizona.

Available information regarding cocci infection in the setting of TNF-I is limited to case reports and small-scale retrospective studies. The aim of our study was to determine the number of cocci seropositive patients identified on screening; and to describe what evaluation, treatment, and follow-up transpired for these individuals.

METHODS

We electronically searched for all patients receiving TNF-I from 9/4/2010 to 4/22/2015. The records for seropositive patients were then reviewed in detail.

RESULTS

2218 individuals received TNF-I, 994 of whom had screening labs, and 837/994 (84%) had screening coccidioidal serologies performed. Of these, 67/837 (8.0%) were seropositive, 24/67 (35.8%) were found on initial (pre-TNF-I) screening, 11/67 (16.4%) on annual screening, and 32/67 (48%) were identified when symptoms were evaluated. Of the 35 cases identified via screening, 1 (2.9%) case was diagnosed with cocci infection after the discontinuation of the TNF-I, and 5 (11.4%) cases had pre-existing diagnoses of cocci, leaving 29 new diagnoses of cocci. Among these 29, 4 (13.8%) were diagnosed with active pulmonary cocci, 6 (20.7%) with asymptomatic seropositivity, and 19 (34.4%) with EIA IgM-only positivity, suggestive of possible falsely positive serology. There were no cases of disseminated cocci. Of the 29 newly-diagnosed cocci, 7 (24.1%) had their TNF-I discontinued, 12 (41.3%) were started on fluconazole, and 20 (69%) were referred for Infectious Disease evaluation. None of the cases, including the 5 excluded cases with pre-existing diagnoses of cocci, experienced reactivation or worsening of their disease while on TNF-I.

CONCLUSIONS

Significant resources are used to screen asymptomatic patients prior to and during TNF-I therapy, but infrequently identify active coccidioidal infections that might not have otherwise been identified.

ALOPECIA ASSOCIATED WITH FLUCONAZOLE: EFFECTS ON THE HAIR CYCLE IN A RAT MODEL

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BACKGROUND

The association of alopecia with fluconazole was first noted by Pappas et al, and it was speculated by others these effects were possibly related to an unidentified P450 interaction between fluconazole and retinoic acid derivatives given the "retinoid-like" toxicity profile of hair loss, dry skin, mucus membranes, and nail changes observed in some patients on fluconazole. We sought to evaluate the hair-cycle specific changes of fluconazole in a rat model and to determine if any association with retinoic acid levels was notable.

METHODS

Male Wistar rats weighing 200-220 gm (Charles River Laboratories) were fed a standard diet. Rats were randomized 1:1 to fluconazole (35 mg/kg/day) or no fluconazole and sacrificed on days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70. Fifty hair samples from the caudal and 50 from the cranial aspect were obtained for microscopic examination at each time point. Plasma, skin, liver, and brain samples were obtained at each time point for microscopic examination and retinoic acid quantification by HPLC (UC-Berkley Napoli Lab). Plucked and intact hair tissue samples were staged in blinded fashion by UC-Davis veterinary dermatopathology. Human patients complaining of alopecia while on fluconazole also underwent plasma retinoic acid determination.

RESULTS

Fluconazole precipitated follicles into a state of premature rest (telogen effluvium) compared to the untreated group by day 21 in a rat model. Despite the inhibition of CYP26B1 by fluconazole administration, plasma and tissue levels of retinoic acid were no different between groups in either rats or human patients.

CONCLUSION

Fluconazole promotes the development of telogen effluvium. Although retinoic acid levels were not elevated in the plasma or tissues of either the rat model or human patients, subcellular effects cannot be ruled out. Future work examining the mechanism of fluconazole induced alopecia (direct or indirect mechanism) should be undertaken.

NOVEL CYP51 INHIBITORS FOR THE TREATMENT OF COCCIDIOIDOMYCOSIS

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BACKGROUND
Highly selective fungal CYP51 inhibitors have the potential to improve treatment of coccidioidomycosis due to improved therapeutic indices. The investigational oral agent VT-1161, currently in Phase 2 studies for mucosal and superficial fungal infections, has previously been shown to reduce fungal burden and improve survival in murine coccidioidomycosis models. In addition, there is an ongoing search for more potent compounds that retain the hallmark low toxicity of these next-generation CYP51 inhibitors. The objectives of these studies were to (1) assess VT-1161 treatment of dogs with naturally occurring coccidioidal pneumonia to define initial PK/PD relationships; (2) discover a candidate molecule with greater potency in a murine model of CNS coccidioidomycosis.
METHODS
Client-owned dogs that were serologically or cytologically positive for coccidioidomycosis and had radiographic findings consistent with coccidioidal pneumonia received 60-day treatment with VT-1161. Plasma was collected on days 14, 28, and 60-67, and drug levels were determined by LC/MS-MS. Clinical pathology, serology, and radiology were determined at enrollment and exit; clinical responses were scored on a scale modified from the Mycoses Study Group. For the murine studies, 8-week old female Swiss-Webster mice were infected intracerebrally with spores of C. posadasii, strain Silveira, and test compounds were administered by oral gavage for 7 days, starting 48 hours post-infection. Mice were sacrificed 24 hours after the last dose and brain fungal burden measured. In a survival model, test compounds were administered orally for 14 days, followed by a 4-week observation period.
RESULTS
Dogs responded equally well to high and low doses of VT-1161. The mean reduction in disease score was 8.3 for the high dose and 9.6 for the low dose. The reduction in clinical score was significant ($P<0.001$) between study start and completion for all dogs combined and was not different for the two doses. The mean plasma concentration for the high-dose group (36 ± 14 mg/ml) was approximately twice that of the low-dose group (19 ± 8 mg/ml). Although these levels of VT-1161 are near the highest levels studied in Phase 2 trials in humans, a more potent molecule is preferred. In murine studies, the novel compound VT-1598 was ~10-fold more potent than VT-1161 at reducing fungal burden in the CNS model of coccidioidomycosis. A dose of 4 mg/kg VT-1598 reduced brain fungal burden to a significantly greater extent than 20 mg/kg VT-1161. In a mouse survival study, VT-1598 prolonged survival in a dose-dependent manner, but did not exceed survival with VT-1161 treatment at 20 mg/kg, and residual brain fungal burden was similar for the high-dose VT-1598 and VT-1161 groups.
CONCLUSIONS
VT-1161 was efficacious in treating naturally occurring coccidioidomycosis in privately-owned dogs at plasma levels that are near those achieved in on-going clinical studies. However, VT-1598 was more potent than VT-1161 in reducing fungal burden in a mouse model of CNS coccidioidomycosis. Given these and other data, clinically efficacious plasma levels of VT-1598 are predicted to be in the range of 1-5 mg/ml, which should be safely achieved in humans.

APX001-A, A NOVEL ANTIFUNGAL DRUG, IS ACTIVE AGAINST COCCIDIOIDES *IN VIVO* AND *IN VITRO*

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Introduction

Coccidioidomycosis is a difficult to treat fungal infection. Current therapy relies heavily on azole drugs, amphotericin derivatives, and rarely echinocandins, but in many cases of disseminated infection, these drugs are only partially effective and do not eradicate the fungus from the body. Nikkomycin Z, an inhibitor of chitin synthase, is a promising new drug for the treatment of coccidioidomycosis. APX001-A is a new class of antifungal under development by Amplyx Pharmaceuticals in La Jolla, CA. It is an inhibitor of a protein required for inositol acylation, an early step in the formation of glycosylphosphatidylinositol (GPI). As a result, GPI anchored glycoproteins, major constituents of eukaryotic cell walls, cannot be synthesized. This gene is highly expressed in hyphae and spherules of *Coccidioides.*

Methods

We tested the activity of APX-001A against the *C. immitis* RS strain and against *C. posadasii* C735 by agar dilution using 50 arthroconidia/dilution. C57BL/6 mice were given APX001-A, 50 mg/kg in 0.1 mL of acidic glucose vehicle BID, starting day 4 after infection and continuing for 10.5 days. Controls received only vehicle. We sacrificed the mice one day after finishing treatment and did quantitative mycology of lungs and spleens.

Results

The MIC was 0.019 for RS and 0.16 mcg/mL for C735. There was nearly a 1,000 fold decrease in lung CFU in treated mice compared to controls. The treated mice had no dissemination to their spleens compared to 8/10 controls with dissemination (geometric mean of 3.7 $\log_{10}$).

Conclusion

This orally absorbed drug with a unique mechanism of action is active against Coccidioides *in vitro* and *in vivo*. Our results in mice are very encouraging as BID dosing is sub-optimal given the pharmacokinetics of the drug in mice.

PERFORMANCE OF COCCIDIOIDOMYCOSIS PCR TESTING IN PATIENTS WITH LUNG NODULES

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INTRODUCTION

Coccidioidomycosis is a fungal infection endemic to the southwestern United States commonly identified when patients present with lung nodules. Currently, the laboratory methods most frequently used to diagnose coccidioidomycosis include serology, histopathology, and culture. Due to limitations of these methods, in recent years a real-time polymerase chain reaction (PCR) assay was developed and validated using the BD Max extraction kit and a master mix prepared by BioGx Inc.This study is the first to investigate the performance characteristics of coccidioidomycosis PCR testing in patients with lung nodules who underwent biopsy.

METHODS

Nine hundred fifty-nine patients underwent coccidioidomycosis PCR testing at our institution between March 2014 and January 2016. Of the 959, we retrospectively reviewed 138 patients who presented with lung nodules and underwent biopsy and PCR testing. Simple descriptive statistics were used to analyze the data obtained in the study.

RESULTS

Of the 138, 15 (11%) were identified as proven or probable coccidioidomycosis, 65 (47%) were identified as cancer, and 58 (42%) had other or nonspecific diagnoses. Three of 138 had positive PCR tests: 3 of 15 (20%) with proven or probable coccidioidomycosis and 0 of 123 without diagnostic criteria for coccidioidomycosis. Two of 15 (13%) had positive culture test. Organisms consistent with coccidioidomycosis were seen on histology of each of the patients with positive PCR and cultures were positive in 1 of 3 patients with positive PCR tests. PCR thus demonstrated a sensitivity, specificity, positive predictive value, and negative predictive value of 20, 100, 100, and 84%, respectively.

CONCLUSIONS

The sensitivity of the PCR test in this clinical setting was similar to the sensitivity of histology or fungal culture. In its current form, PCR offers little additional information to culture and histology in diagnosing nodules due to coccidioidomycosis. This suggests the potential need to revisit the technique to improve its sensitivity.

THE AVIRULENT MUTANT STRAIN ⌢cps1 PROVIDES LONG TERM SURVIVAL FOLLOWING LETHAL COCCIDIOIDES INFECTION IN MICE

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INTRODUCTION Coccidioidomycosis is an endemic fungal disease that causes significant morbidity and has a high cost of treatment in both humans and animals, such that a preventive vaccine would be highly beneficial. Since this is an orphan disease, any preventative vaccine candidate to become clinically available must be relatively inexpensive to develop and manufacture. The vaccine candidate, ⌢cps1, a strain of Coccidioides posadasii with a large gene deleted (6K base pairs), demonstrates only slight reduction in arthroconidial production in vitro and appears completely avirulent in normal and immunocompromised mice. The goal of these studies was to ascertain the level of protection afforded by vaccinating BALB/c and C57BL/6 (B6) mice and assess total lung fungal burden or survival following lethal infection with virulent Coccidioides spp.

METHODS Six to 8 wk old B6 or BALB/c mice were vaccinated IN, IP, or SC with live ⌢cps1 spores (range, 100 spores -500,000 spores); mice were vaccinated with 10,000 spores unless otherwise specified. Control vaccinations included saline, recombinant Ag2/PRA_{1-106}-CSA with adjuvant, or adjuvant alone. Mice were either vaccinated once or twice 2 weeks apart, followed by challenge with virulent spores IN 4 weeks later. Infectious doses of wild type Coccidioides were lethal, ranging from 50-100 spores. For survival studies, mice were kept 4 weeks or 6 months after challenge with virulent spores; for lung fungal burden studies, mice were sacrificed at 2 weeks.

RESULTS B6 mice vaccinated either IP or SC with ⌢cps1 experienced residual lung fungal burdens less than 1000 colony-forming units (cfu) (combined IP and SC, Log 2.3), significantly less than rAg2/PRA_{1-106}-CSA (Log 4.6, $P=0.001$) or saline (Log 6.7, $P<0.001$). Nineteen of 20 BALB/c mice vaccinated IN or SC survived 4 weeks, and 7 (35%) had no fungal growth from lungs at sacrifice, while both recombinant Ag and saline control groups died on days 13-16. One ⌢cps1-vaccinated mouse had Log 4.66 cfu at sacrifice and the remaining mice had ≤1000 cfu. All B6 mice vaccinated SC and challenged with 100 spores of either C. posadasii (10 mice) or C. immitis (10 mice) survived 180 days in good clinical condition, while saline controls were moribund by day 18 post-infection. At doses ranging from 100 spores to 500,000 spores SC, fungal burden was significantly lower in all ⌢cps1-vaccinated groups than in saline control mice. There was a dose response that plateaued between 100,000 and 500,000 spores. A single dose of 500,000 spores resulted in fungal burdens similar to two doses of 100,000 spores, showing that a single dose of live spores was highly protective.

CONCLUSIONS The ⌢cps1 mutant vaccine candidate provides excellent reduction in fungal burden against either species of Coccidioides, and affords long term survival in two highly susceptible strains of mice. Furthermore, its growth characteristics in vitro lend itself to a feasible and inexpensive formulation. These findings support the ⌢cps1vaccine candidate for further clinical development.

EX VIVO CYTOKINE EXPRESSION IN NEWLY DIAGNOSED COCCIDIOIDOMYCOSIS

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BACKGROUND

The cellular immune response plays an important role in the control of human coccidioidomycosis. We have shown that *ex vivo* incubation of whole blood with the coccidioidal antigen preparation T27K elicits a Th1 cellular immune response in supernatant from individuals who are coccidioidal immune and asymptomatic. We have later found that levels of IL-17 and IL-6 are higher in those with non-meningeal disseminated coccidioidomycosis compared to those with pulmonary disease. We are now performing a prospective study of subjects with newly diagnosed coccidioidomycosis and have expanded the range of cytokines/chemokines (CK/CC) studied.

METHODS

Subjects seen for the first time were eligible for enrollment if they did not have a diagnosis of coccidioidal meningitis. After informed consent, 5 mL of blood was collected into sodium heparin and incubated with 20 μg/mL T27K or nothing (control) for 18 hr at 37°C in 5% CO_2. The supernatant was collected and frozen at -80°C until assayed using the Luminex magnetic bead multiplex system for 30 (CK/CC).

RESULTS

To date, 14 patients have had CK/CC analysis completed. The median time from diagnosis to assay was 15.5 days. All had pulmonary disease. CK/CC data were available for 12 subjects. For 11 CK/CC, median concentrations were at least 10-fold higher than control. These are shown below as median pg/mL, with minimum and maximum below:

Th1 cytokines			Inflammatory cytokines					Chemokines		
IFN-γ	IL-2	TNF-α	GM-CSF	IL-1β	IL-5	IL-6	IL-13	MIG	MIP-1α	MIP-1β
446	1003	1554	162	169	13	4950	38	565	18100	5598
50	97	32	15	11	4	142	14	35	411	1671
1739	2017	6700	333	725	87	4950	179	4979	18100	24292

Nineteen CK/CC were not elicited by T27K, including IL-4, IL-10, IL-12, and IL-17.

CONCLUSIONS

These results demonstrate that certain CK/CC are robustly expressed by *ex vivo* antigen stimulation in early coccidioidomycosis. Many of these have never previously been assayed. Following the clinical course of these subjects and repeating these assays at a later date could allow for a CC/CK biosignature that might predict clinical outcome.

DEVELOPMENT OF AN IMPROVED ANTIBODY DETECTION EIA FOR USE IN IDENTIFICATION OF COCCIDIOIDOMYCOSIS

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INTRODUCTION

Coccidioidomycosis is a mycoses of varying severity ranging from subclinical to life-threatening disease. Detection of anti-*Coccidioides* IgG and/or IgM antibodies by immunodiffusion (ID) or enzyme immunoassay (EIA) are the two most common methods used to support a diagnosis. Here, we present the characteristics of a new antibody detection assay for the diagnosis of coccidioidomycosis, the MVista® *Coccidioides* antibody detection EIA (MVD EIA).

METHODS

Serum samples from patients with a coccidioidomycosis diagnosis (n=103), as determined by serology and/or culture followed by confirmatory case review (JM, TZ, CT), and controls (n=220). Samples were diluted and added to microtiter plate wells coated with *Coccidioides* antigen. Standards and controls containing anti-*Coccidioides* antibodies were utilized to translate results into EIA units (EU). McNemar's test was used to compare matched pair test data.

RESULTS

The MVD EIA detected IgG, IgM or either antibody to *Coccidioides* in 87.4%, 61.2% and 88.3%, respectively, in sera from subjects with coccidioidomycosis. Antibody was detected in 85.3% of samples collected <3 months after diagnosis and 91.8% of samples collected >3 months after diagnosis. Specificity was determined to be 92.3% for IgG, 96.4% for IgM and 91.4% for both using human control sera. The MVD EIA demonstrated improved sensitivity compared to ID, as both ID and EIA detected 61 cases (59.8%), the EIA detected 29 cases (28.4%), ID detected 2 cases (2.0%) and neither detected 10 cases (9.8%) [McNemar χ^2: 21.8, $p<0.0001$]. Compared to complement fixation (CF), both methods detected 38 cases (61.3%), the EIA detected 20 cases (32.3%), CF detected 2 cases (3.2%) and neither detected 2 cases (3.2%) [$p=0.0001$]. The MVD EIA also demonstrated improved sensitivity compared to a commercially available EIA, with both assays detecting 61 cases (59.2%), the MVD EIA alone detecting 30 cases (29.1%), the commercial EIA alone detecting 1 case (1.00%) and neither detecting 11 cases (10.6%) [McNemar χ^2: 26.3, $p<0.0001$].

CONCLUSIONS

The MVD EIA is sensitive and specific for use with patient sera. The MVD EIA demonstrates improved sensitivity compared to commercial EIAs and traditional serology. The use of this assay has the potential to aid in the diagnosis of coccidioidomycosis by providing increased sensitivity compared to currently available assays, and improved throughput and turnaround time compared to classical serology methods.

THE TOTAL AND LECTIN BINDING PROTEOME OF SPHERULIN

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BACKGROUND

Although the genomes of Coccidioides sp. have been sequenced, a publically available proteome from the fungus does not exist. To address this gap in knowledge, we generated the proteome of Spherulin (a well-studied lysate of fungal spherules).

METHODS

Spherule-phase Coccidioides posadasii (strain Silveira) was maintained in continuous culture in Converse medium. Arthrospores (spherules and endospores) were collected by centrifugation, washed in water and fixed with 0.5% formalin. Spent medium was concentrated using 10kDa ultrafiltration and is called Spherulin-filtrate (Sph-F). Spherulin lysate (Sph-L) was prepared from pelleted spherules and endospores and lysed using a Beadbeater. Since we desired as many proteins as possible, Sph-F and Sph-L were combined and are referred to as "Spherulin" in this report. Spherulin was subjected to SDS-PAGE followed by in-gel trypsin digest. Tryptic peptides were processed and run on a QExactive Plus mass spectrometer. Mass spectra were searched with the Broad Institute's Coccidioides Genomes project, Swissprot and RefSeq databases using Myrimatch software (version 2.1.38). Spherulin was also run through sWGA and GSL-II lectin affinity columns followed by mass spectrometry analysis to identify a lectin-binding glycoproteome of Spherulin.

RESULTS

1390 proteins were identified in our Spherulin preparation. After sWGA and GSL-II lectin affinity purification of Spherulin, 224 and 195 Coccidioidal glycoproteins were identified respectively. 434 hypothetical proteins were identified, constituting 31% of the 1390 proteins identified from Spherulin. The sWGA and GSL-II glycoproteome fractions were completely contained within the total Spherulin proteome.

CONCLUSIONS

This study provides proof that predicted "hypothetical proteins" listed in the Broad Institute database are indeed expressed. Since sWGA and GSL-II both bind to N-acetylglucosamine (GlcNAc), it was expected that the glycoproteins bound by each would completely overlap. However, only 145 Coccidioidal glycoproteins in Spherulin bound to both lectins suggesting that there may be some affinity or structural difference in glycoprotein binding between the lectins. This report of the proteome of Spherulin is intended to be available to enhance the study of Coccidioides sp. and to lead to better diagnostics, treatments and eventual cure.

UNDERSTANDING MECHANISMS OF RECOMBINATION IN *COCCIDIOIDES*

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INTRODUCTION

Coccidioidomycosis manifestations vary from a mild flu-like disease to severe disseminated infections in both healthy and immunocompromised individuals. In addition, Coccidioides species are capable of infecting a wide array of mammals, such as wild rodents and dogs. Evolutionary analysis using a series of genetic markers has revealed high levels of genetic diversity and admixture within this genus, which could be linked to phenotypic plasticity and broad host range. Importantly, these studies have provided strong evidence that recombination and introgression are the main sources of genetic variation within and between *Coccidioides* species. Molecular analysis of *Coccidioides* genomes reveled the presence of functional Mating Type (MAT) loci and other mating regulators in both species. Moreover, the balanced 1:1 idiomorphic distributions of MAT1-1 and MAT1-2 genes in both *Coccidioides* species in the environment are compatible with sexually recombining fungi. To date, the main route of transmission of the disease is thought to be the inhalation of dust containing infectious arthroconidia derived from mitosis, which is a recombination independent process. At this time, only an asexual life cycle of both *Coccidioides* species has been characterized.

METHODS

Liquid monosporic cultures of each isolate were grown in glucose yeast extract for 5 days under agitation at 30ºC to produce inoculum. Each mating cross consisted of two isolates of known mating type inoculated at ~1 cm apart on soil extract agar and V8 juice agar plates with and without human or horsehair incubated at room temperature and normal atmospheric gas conditions for six months. Mating crosses were examined for sexual related structures using both macroscopic and microscopic techniques. Colony intersections with confluent grow were fixed using 37% formaldehyde vapor killing method. Fixed mycelial fragments were stained using lactophenol blue for phase contrast microscopy, or fixed for scanning electron microscopy.

RESULTS

Because sexual structures have not been observed in *Coccidioides* species, the signs of sexual mating were compared to other Eurotiomycetes. Macroscopic signs of mating among Coccidioides isolates on agar plates included confluence of mycelia of both mating types in the contact zone and peripheral edges. This is an indication of compatible mating strains. We noticed the presence of tiny white/dark grains containing highly coiled and interlocked hyphae only on specific media and conditions. Most Onygenalean species produce spherical (cleistothecia) or pear-shaped (gymnothecia) ascomata harboring uncinate, curved, or helical appendages, which were observed in our crosses.

CONCLUSIONS

Microscopic sexual structures that have been characterized in other Onygenales include tightly interwoven hyphae, which may contain multiple asci, each containing four to eight globose ascospores. We are yet to observe ascospores directly; however, all other structures have now been observed.

CSF (1,3)-BETA-D-GLUCAN (BG) TESTING IS USEFUL IN THE DIAGNOSIS OF COCCIDIOIDAL (COCCY) MENINGITIS (CM)

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INTRODUCTION

Diagnosing CM can be problematic owing to infrequency/delay of positivity of CSF culture and/or of CSF antigen, particularly if primary coccy infection is unrecognized.

METHODS

We tested 37 CSF specimens, 26 from confirmed (CSF culture and/or antigen) CM and 11 from patients with suspected microbial meningitis without fungal diagnosis, for BG titers (Fungitell®, ACC).

RESULTS

Coccy CSF specimens ranged from 18-3300 pg/ml, controls <3.9-103. Diagnostic performance was determined using 31 pg/ml cutoff (bottom of serum range per directions for commercial kit, though further serial dilutions of the standard indicated linearity to 3.9). Sensitivity was 96%, specificity 82%, positive & negative predictive value 93% & 90%, area under receiver-operator curve 0.937. Fifteen/15 samples >103 pg/ml were coccy. The one false negative specimen was from patient near death with syrinx, without inflammatory evidence of meningitis activity. Serial samples from some patients were positive up to 8 yrs., indicating no loss of positivity with chronicity. Samples stored frozen since 2000 included 2 of 3 highest values, indicating fresh samples not required. 3/3 positive samples were negative in coccy PCR [DMID 79:214]. We did not find correlation CSF BG with CSF coccy Ab titer (no Ab correlation also reported with coccy CSF antigen, CID 61:1521). In our rabbit CM model, testing CSF, no correlation with CNS CFU or response to Rx noted.

DISCUSSION

Previous study [JCM 50:3060] using 31 pg/ml cutoff indicated serum sensitivity 53% in acute, 50% in resolved, 83% in disseminated and meningeal coccy. Three published studies of other fungal meningitides ranged 86-1524 pg/ml CSF, with 37 controls <4-115; CSF>serum; correlation with response. A rabbit candida meningitis study (AAC 52:1421) also found CSF BG>serum, and more sensitive than CSF culture, correlation with tissue burden and disease course, slower CSF than serum BG clearance.

CONCLUSION

CSF BG titer analysis had good diagnostic performance. CSF BG testing can be useful in CM, and a commercial kit is available. It will be of interest to correlate with course, treatment, outcome, inflammation, antigen. The only mycoses with common CNS involvement are cryptococcal and coccy, so CSF BG testing can be generally useful in meningitis diagnosis.

NIKKOMYCION-Z – STATUS UPDATE AND DEVELOPMENT PLANS

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INTRODUCTION

Nikkomycin-Z (NikZ) has been discussed many times at the Coccidioidomycosis Study Group: in 2005, the FDA IND was transferred to the University of Arizona, and in 2007, Valley Fever Solutions (VFS) was formed to assist in NikZ's development. We have used previously manufactured NikZ to conduct a Phase I multidose clinical trial and a preclinical PK/PD study in mice to identify plausible drug dosing for future efficacy trials in humans. We present here the status of recent development work and our plans to move NikZ into Phase IIa clinical trials.

METHODS

NikZ is a secondary metabolite of a strain of *Streptomyces tendae*. Vahe Bandarian at the University of Arizona reengineered the strain to eliminate the production of Nikkomycin X, a major contaminant interfering with the purification of NikZ. Mutagenized progeny were used to modify the past manufacturing process.

RESULTS

Using our revised manufacturing process we have made 500 g with an analytic profile compellingly similar to that of the NikZ used in past clinical trials. We are currently scaling this process to multiple kilogram production, which will require 1,000 to 25,000 Liter fermentation. We plan to use newly produced NikZ in two phase IIa studies. One, supported by an NIH cooperative agreement, is to treat patients with early coccidioidal pneumonia to explore whether NikZ reduces the duration of illness. A second, if investment is forthcoming, is to treat patients with chronic pulmonary or disseminated coccidioidal infection using an adaptive design and a modified Mycoses Study Group scoring assessment of response.

CONCLUSION

Despite the protracted time of development to date, NikZ continues to be in active development. Because NikZ is designated both an orphan drug and a "Qualifying Infectious Diseases Product" by the FDA, it would enjoy 12 years of marketing protection beginning with its approval as a treatment for coccidioidomycosis. The pace of NikZ development at this stage is limited only by the availability of investment funds to accomplish the necessary studies.

FACTORS ASSOCIATED WITH COCCIDIOIDOMYCOSIS TESTING AMONG COMMUNITY-AQUIRED PNEUMONIA PATIENTS IN SOUTHERN CALIFORNIA, 2011

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INTRODUCTION

In highly-endemic areas of Arizona, coccidioidomycosis causes an estimated 15–29% of community-acquired pneumonia (CAP). Similar data are not available from California. We conducted a retrospective study of CAP outpatients diagnosed at Kaiser Permanente Southern California facilities to determine the percentage of patients tested for coccidioidomycosis, the percentage who subsequently tested positive, and factors associated with testing and testing positive.

METHODS

CAP was defined as a CAP International Classification of Diseases, Ninth Revision (ICD-9) code used during an outpatient visit during 2011 and a chest x-ray and a systemic antibacterial prescription two weeks before to four weeks after the first CAP ICD-9 code in a patient with no documented coccidioidomycosis before 2011. Records of CAP patients were searched to identify those tested for coccidioidomycosis within one year after CAP diagnosis. Coccidioidomycosis was defined as a positive enzyme immunoassay, complement fixation, or immunodiffusion test, or *Coccidioides* identified in a clinical sample by culture or histology. Multivariable logistic regression was used to identify demographic and clinical factors associated with being tested for coccidioidomycosis and with testing positive. The reference age group was ≥65 years old and the reference race/ethnicity was non-Hispanic whites.

RESULTS

A total of 2,061 (6.1%) of 33,756 CAP patients were tested for coccidioidomycosis; of those, 377 (18%) tested positive. Females (adjusted odds ratio [aOR] 0.86, 95% confidence interval [CI] 0.77–0.95), patients <15 years old (aOR 0.29, CI 0.22–0.24), and Hispanics (aOR 0.82, CI 0.72–0.93) were less likely to be tested. Testing was most common in Kern County and in pulmonary clinics. Inpatient visits, chest x-ray orders, and repeat antibiotic prescriptions (aOR ranged from 1.36 [1.15–1.60] for one additional prescription to 2.05 [1.29–3.25] for three additional prescriptions) in the year after CAP diagnosis were associated with increased odds of coccidioidomycosis testing. Characteristics associated with testing positive for coccidioidomycosis included age 15–64 years (aOR 1.84, CI 1.33–2.59), Black race (aOR 1.98, CI 1.25–3.08), Hispanic ethnicity (aOR 1.34, CI 1.01–1.78), and residence in Kern County (aOR 2.59, CI 1.89–3.59, compared with Los Angeles County).

CONCLUSIONS

Healthcare providers should consider testing for coccidioidomycosis among CAP patients in Southern California who have failed antibacterial therapy, especially those who live in counties with high numbers of cases. Although Blacks are known to have greater risk of disseminated disease, our findings suggest they may also be at increased risk of primary pulmonary disease. Further investigation is needed to assess why Hispanics were less likely to be tested but were more likely to test positive than non-Hispanic whites.

DEMOGRAPHIC CHARACTERISTICS AND INSTITUTIONAL AND COMMUNITY EXPOSURES AMONG CALIFORNIA STATE PRISON INMATES WITH POSITIVE COCCIDIOIDOMYCOSIS (COCCI) SKIN TEST RESULTS

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INTRODUCTION

California state prison inmates with medical conditions with increased risk of coccidioidomycosis (cocci) are restricted from endemic area institutions. In 2015, we offered inmates statewide the Spherusol® cocci skin test. We medically restricted those with negative results from prisons A and B, which have extremely high cocci rates. We describe inmate demographic characteristics and prison and community exposures associated with a positive test.

METHODS

We matched inmate skin test results with demographic data, incarceration history, and admission from an endemic county. We created mutually exclusive incarceration categories based on cocci exposure risk: 1) ever at prison A or B in 2010–2011 (highest rate years); 2) ever at prison A or B in other years; 3) ever in another endemic prison; or 4) never in an endemic prison. Based on univariable and stratified analyses, we developed a logistic regression model to assess the association between test positivity and age, race/ethnicity, and prison and community exposures.

RESULTS

Of 36,789 inmates who completed the skin test, 3,169 (8.6%) had a positive result. Independent predictors of test positivity are presented in the table below. We found no association between skin test positivity and race/ethnicity.

Independent predictors of a cocci skin test positive result among California state prison inmates, January 2015.

Risk Factor	Positive N (%)	Adjusted OR	95% CI
Prison A in 2010 or 2011	462 (32.9)	10.6	8.6 - 13.2
Prison B in 2010 or 2011	179 (22.3)	6.0	4.7 - 7.7
Prison A other years	644 (16.6)	4.3	3.5 - 5.3
Prison B other years	398 (10.2)	2.5	2.0 - 3.1
Other endemic prison	1,363 (5.9)	1.6	1.3 - 1.9
Non-endemic prison	123 (3.2)	*Ref*	
High Risk County	656 (19.2)	2.6	2.3 - 2.8
Medium Risk County	184 (15.0)	2.1	1.7 - 2.4
Low Risk County	2,329 (7.2)	*Ref*	
Age > 45	1,305 (11.1)	1.9	1.7 - 2.1
Age 31-45	1,405 (9.0)	1.6	1.4 - 1.8
Age ≤30	459 (4.9)	*Ref*	

CONCLUSIONS

Given the very high rates of cocci at prisons A and B and statewide in 2010–2011, the strong association between test positivity and incarceration at prisons A and B in these years is explained by a high exposure to cocci. The association with age is likely due to a greater chance of being exposed to cocci rather than a greater likelihood of cocci infection after exposure.

EPIDIOLOGY OF PEDIATRIC COCCIDIOIDOMYCOSIS IN CALIFORNIA, 2000–2012

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INTRODUCTION

Reported coccidioidomycosis cases have increased in the southwestern United States since 2000. However, there are few publications on pediatric coccidioidomycosis. We sought to describe the epidemiology of coccidioidomycosis in the California pediatric population during 2000–2012.

METHODS

We reviewed surveillance and hospitalization datasets for years 2000–2012 and death datasets for years 2000–2010 to identify coccidioidomycosis-associated cases, hospitalizations, and deaths in pediatric (≤17 years old) California residents. We calculated rates and described demographic characteristics of cases and hospitalized patients and, using Poisson regression, calculated bivariate relative risks (RR) to identify potential demographic risk factors. We identified immunocompromising conditions associated with hospitalization and death and calculated hospitalization charges.

RESULTS

We identified 3453 cases, 1301 hospitalizations, and 11 deaths associated with coccidioidomycosis in the California pediatric population. During 2000–2012, annual case and hospitalized patient rates increased and were highest in males, those in the 12–17 age group, and residents of the California endemic region. Compared with White children, African-American children were significantly more likely to be hospitalized (RR = 1.4, $P = 0.01$). Approximately 12.0% of those hospitalized and 27% of those who died had an immunocompromising condition. Hospitalized patients accrued $149 million in total hospital charges.

CONCLUSIONS

Similar to recent increases among adults, reported pediatric coccidioidomycosis cases and hospitalizations have increased in California since 2000, disproportionately affecting certain demographic groups. The burden of coccidioidomycosis among California children emphasizes the need for more awareness and research into this reemerging fungal disease in endemic and non-endemic areas.

SURVEILLANCE FOR COCCIDIOIDOMYCOSIS IN ARIZONA: 2015 UPDATE

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INTRODUCTION

Two-thirds of all coccidioidomycosis cases reported nationally reside in Arizona. Coccidioidomycosis is reportable to the Arizona Department of Health Services (ADHS). Typically, monthly counts of reported cases peak in December or early January. However, in September, 2015, 964 cases were reported, the highest since July, 2012. We describe the seasonality of reported coccidioidomycosis between 1998 and 2015, assess whether seasonality changed over time, and identify periods of excess incidence.

METHODS

Data on confirmed coccidioidomycosis cases reported between 1998 and 2015 was extracted from the ADHS surveillance system. Wavelet analysis was performed to assess changes in periodicity. Periodic regression was used to estimate seasonal baseline incidence. Data were detrended using cubic polynomials. Data from 2009-2012 were excluded due to surveillance changes. Analyses were conducted using EPIPOI and SAS 9.3.

RESULTS

The rate of reported coccidioidomycosis in 2015 was 114.4 (n=7,630) reported cases per 100,000 person-years. Case counts began increasing in April and peaked in September of 2015, earlier than prior years. Wavelet analysis identified annual and semi-annual peaks in incidence increased. No significant changes in periodicity were noted. Baseline monthly incidence was 332 cases; primary and secondary peaks were observed every 12.9 months and 7.1 months, respectively. Case counts in late 2015 exceeded the epidemic threshold defined by the baseline model.

CONCLUSIONS

The incidence of reported coccidioidomycosis increased substantially in late 2015. Factors affecting fungal growth and/or dispersal may explain the unusual temporal distribution of case reports. Though unlikely to explain the magnitude of the overall increase and altered seasonality, surveillance artifacts and changes in careseeking or testing practices cannot be ruled out.

ESTIMATING TRENDS OF COCCIDIODOMYCOSIS IN AN ENDEMIC AREA AFTER LABORATORY REPORTING CHANGES: MARICOPA COUNTY, 2006- 2014

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INTRODUCTION

Approximately 70% of reported Arizona coccidioidomycosis cases occur in Maricopa County. In 2009, a major laboratory began reporting all enzyme immunoassay (EIA)-positive results to public health, leading to increased reported cases until 2011. However, this laboratory began using a more reliable EIA test, reducing false-positive EIA reports, contributing to decreased reported cases during 2012. These laboratory reporting changes have made interpreting Arizona coccidioidomycosis surveillance trends challenging.

METHODS

Three data sources were compared: state laboratory surveillance, hospital discharge (HDD), and death certificate data. Cases were identified in HDD and death data using coccidioidomycosis ICD codes.

RESULTS

From 2006-2011, the reported coccidioidomycosis case rate increased substantially, from 116.4 to 351.2 cases/100,000 persons, respectively. This same trend was seen in hospitalizations from 2006-2011, increasing from 42.4 to 66.9 hospitalizations/100,000 persons. Notably, from 2010 – 2011, the reported case rates and hospitalizations increased by 41% and 13% respectively, during which no laboratory reporting changes occurred.
Since 2011, reported case and hospitalization rates decreased from 351.2 to 97.5 cases/100,000 persons and 66.9 to 41.5 hospitalizations/100,000 persons, respectively. Emergency department visits increased steadily between 2006 and 2013, rising from 4.5 to 16.7 visits per 100,000 persons. However in 2014, the rate decreased to 13.4 visits per 100,000 persons. Also in 2014, coccidioidomycosis death rates decreased slightly from 2013 (1.07 from 1.45 deaths/100,000 persons, respectively), after having remained relatively constant during from 2006 to 2013.

CONCLUSIONS

Reported Arizona coccidioidomycosis cases and hospitalizations follow a similar trend between 2006 and 2014, despite changes in laboratory reporting. This suggests a true peak in incidence in 2011 and an actual decline in 2012, although both were likely exaggerated by laboratory reporting changes. Increasing trends in emergency department visits despite declining disease rates could reflect changes in insurance coverage of Maricopa County residents during those years. Lastly, stable and then declining death rates might reflect advances in the management of medical complications of disseminated disease.

COCCIDIOIDOMYCOSIS AMONG AMERICAN INDIANS AND ALASKA NATIVES, 2001–2013

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[1] Centers for Disease Control and Prevention
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INTRODUCTION

Although American Indians and Alaska Natives (AI/AN) have been found to have particularly high infectious disease-related hospitalization and mortality rates, few studies have looked specifically at the epidemiology of coccidioidomycosis among AI/AN. Improved understanding of the epidemiology is needed given the number of AI residing in endemic areas of the United States. We describe coccidioidomycosis-associated hospitalizations and outpatient visits during 2001–2013 in the Indian Health Service (IHS) system and compare hospitalizations with data from the Agency for Healthcare Research and Quality's National (Nationwide) Inpatient Sample (NIS).

METHODS

IHS National Patient Information Reporting System (NPIRS) data were examined to identify coccidioidomycosis-associated hospitalizations and outpatient visits using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 114.0–114.9. NPIRS contains hospital discharge and outpatient visit records from IHS, tribally-operated, and IHS-contracted health care facilities. Age adjusted rates were calculated as visits per 1,000,000 user population (eligible AI/AN who received IHS care within the most recent three years). Poisson regression was used to calculate rate ratios (RR) and 95% confidence intervals (CIs). Estimates of coccidioidomycosis-associated hospitalizations among the U.S. general population were obtained using the NIS, a nationally-representative sample of discharges from community hospitals. NIS hospitalization rates per 1,000,000 persons were calculated using the National Center for Health Statistics annual bridged-race population denominators.

RESULTS

AI/AN had the highest average annual coccidioidomycosis-associated hospitalization rate (44/1,000,000; CI 36-51) of any racial/ethnic group in the NIS compared with 9.6/1,000,000 (CI 8.9-10) for Non-Hispanic whites. NPIRS data showed a total of 461 coccidioidomycosis-associated hospitalizations (average annual rate 35/1,000,000) in the IHS population; the rate among AI/AN males (45/1,000,000) was higher than that among AI/AN females (27/1,000,000). The median length of stay for coccidioidomycosis-associated hospitalizations among AI/AN was 6 days (Interquartile range 3, 10). The average annual outpatient visit rate was 757/1,000,000; rates were highest in the Southwest (2,085/1,000,000) followed by the West (219/1,000,000) and increased most years from 530/1,000,000 in 2001 to 1,096/1,000,000 in 2013. The median number of coccidioidomycosis-associated outpatient visits per person was 3 (Interquartile range 1, 8).

CONCLUSIONS

AI/AN experience high coccidioidomycosis-associated hospitalization rates. Yearly trends in coccidioidomycosis-associated outpatient visits in the IHS population were similar to the general increase in hospitalizations and reported cases nationwide in the last decade. Future work is needed to better understand risk factors for coccidioidomycosis among AI/AN.

POPULATION DYNAMICS OF *COCCIDIOIDES* AND THE EMERGENCE OF CLINICAL GENOTYPES

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INTRODUCTION

Over the past 20 years, a general picture of the genetic diversity and population structure of *Coccidioides* has been reported. The genus is composed of two genetically diverse species: *C. immitis* and *C. posadasii*. Genotypic data suggest two subpopulations within *C. immitis*, divided into central and southern California populations; and three populations of *C. posadasii*, divided into Arizona, Mexico and Texas/South America populations. However, admixture within and among these populations, and the current paucity of environmental isolates, limit our understanding of the population genetics of Coccidioides.

METHODS

We accessed the population structure of 619 *Coccidioides* isolates (495 from Arizona) via STUCTURE 2.3.1 software on 9 unlinked microsatellite loci. *Coccidioides* population splits and mixtures trees were also inferred using a statistical model related to common ancestors through a graph of ancestral populations via TreeMix software. Nei's unbiased estimate was inferred using GENALEX 6.501, to complete a principal coordinate analysis (PCoA) and population genetics parameters.

RESULTS

STRUCTURE analysis based on 619 isolates revealed three strongly supported *Coccidioides ssp*. populations: *C. immitis* (n=61), *C. posadasii* Mexico/Texas/South America (n=63) and *C. posadasii* Arizona (n=495). There is an indication of additional population structure within *C. immitis*, separating San Joaquin Valley from San Diego and Mexico isolates. For *C. posadasii* Mexico/Texas/South America population, two optimal clusters were detected: one including Texas/South America isolates and a second constituted by Mexican isolates. The Mexican isolates display a high level of hybridization between two different populations as well with *C. immitis*. Finer scale population structure analysis of 495 individuals within the Arizona population suggests at least 3 different *C. posadasii* sub-populations: Clinical samples from PHOENIX and TUCSON fall in two different populations according to STRUCTURE. Interestingly, all soil-derived and some veterinary/clinical samples constitute a third population (AZ_SOIL) apart from the clinical TUCSON and PHOENIX populations. The population tree presented supports a migration event from AZSOIL population to TUCSON population. In addition a low number of clinical isolates clustered with AZSOIL population leading us to consider variable pathogenicity and/or host specificity.

CONCLUSIONS

Previously described *Coccidioides* population structure is upheld, and finer scale population structure within Arizona is indicated. Environmental isolates have a higher diversity than human patient isolates. The SOIL sub-population is basically placed within the Arizona clade. The migration event from the SOIL to TUCSON may reflect selection of more pathogenic genotypes, as only 40% of infections are thought to be symptomatic. Even fewer of these would result in severe disease.

COCCIDIOIDOMYHCOSIS IN RESCUED MARINE MAMMALS ALONG CALIFORNIA'S COAST

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[5]Marine Mammal Care Center at Fort McArthur, 3601 S Gaffey St, San Pedro, CA 90731

INTRODUCTION

Coccidioidomycosis is suspected to be the number one fungal infection among stranded marine mammals in California. However, nothing is known about differences in prevalence of the disease in pinnipeds along California's coast, how the disease affects rehabilitation of stranded animals, or if some age groups are more vulnerable than others. Arthroconidia from the soil-dwelling fungal pathogen *Coccidioides* spp. can become airborne when soil is disturbed in endemic areas and subsequently transported by the wind to non-endemic areas, including California's coast, e.g. by strong Santa Ana winds in the fall. It cannot be excluded though that soils on the Channel Islands where sea mammal rookeries exist could also support the growth of the pathogen.

METHODS AND RESULTS

In our ongoing project, we examined 151 serum samples from predominantly California sea lions (*Zalophus californianus*) (n= 135) and from some rare northern fur seals (*Callorhinus ursinus*) (n=16) with apparent respiratory problems, so far. We included animals of all age groups, and both sexes, which were rescued at several Marine Mammal Centers (MMC) along California's coast between 2012 and 2015 and which were treated at the MMC in Sausalito and the MMC in San Pedro. By performing immunodiffusion assays in collaboration with the laboratory of the Kern Medical Center in Bakersfield, CA, to detect IgG and IgM antibodies, we found IgM antibodies against the pathogen in (n=19) 12.6% of all blood sera samples which indicates acute coccidioidomycosis. Only few animals were positive for IgG only. We also found that among the 16 northern fur seals that were included in this study and which were rescued in 2015, 3 individuals clearly suffered from coccidioidomycosis (IgM positive). This is of major concern because the northern fur seals are a rare species in California with one small rookery on one of the Channel Islands. Animals of all age groups and both sexes were affected, but our data set is too small to detect if a particular age group is at a higher risk of contracting coccidioidomycosis.

CONCLUSION

Our work indicates that coccidioidomycosis should be considered as a major reason of sea mammal strandings along California's coast.

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2016 Cocci Study Group 60th Annual Meeting Hosts

Michael Peterson, Robert Libke and Paul Mills
Monica Sozinho and Virginia Coningsby, event coordinators
U.C.S.F.-Fresno, Community Regional Medical Center, Fresno, CA

2016 Cocci Study Group 60th Annual Meeting Moderators

Poster Presentations	Susan Hoover
Clinical Science: Oral Presentations	Rafael Laniado-Laborin
Laboratory and Basic Science: Oral Presentations	George Thompson III
Ecology and Epidemiology: Oral Presentations	Tom Chiller and Janis Blair
Satellite: Cocci and the Environment	Bridget Barker
Satellite: Cocci and Occupational Health	Orion McCotter and Marie de Perio

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Annual Meetings of the Coccidioidomycosis Study Group

No.	Date	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	November 30-December 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	CA Thoracic Society
10	December 7, 1965	Phoenix, AZ	2nd Cocci Centennial Conference
11	April 19, 1967	Palm Springs, CA	CA Thoracic Society
12	May 1, 1968	Fresno, CA	CA Thoracic Society
13	April 15, 1969	San Diego, CA	CA Thoracic Society
14	April 1, 1970	San Francisco, CA	CA Thoracic Society
15	April 6, 1973	Newport Beach, CA	CA Thoracic Society
16	April 5, 1974	Sacramento, CA	CA Thoracic Society
17	September 30, 1974	San Francisco, CA	Cocci Cooperative Treatment Group
18	April 2, 1975	San Diego, CA	CA Thoracic Society
19	July 31, 1975	San Diego, CA	Cocci Cooperative Treatment Group
20	January 14-15, 1976	San Diego, CA	Cocci Cooperative Treatment Group
21	April 7, 1976	Palo Alto, CA	CA Thoracic Society
22	May 18, 1977	San Francisco, CA	Am Lung Association
23	April 5, 1978	Beverly Hills, CA	CA Thoracic Society
24	May 15, 1979	Las Vegas, NV	Am Lung Association

No.	Date	Location	Held in Conjunction with
25	April 11, 1980	Sacramento, CA	CA Thoracic Society
26	March 28, 1981	San Francisco, CA	CA Thoracic Society
27	May 15, 1982	Los Angeles, CA	AM Lung Association
28	March 20, 1983	La Jolla, CA	CA Thoracic Society
29	March 14-17, 1984	San Diego, CA	4th Cocci Centennial Conference
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 Cocci 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	April 23-26, 2006	Stanford, CA	6th International Symposium on Cocci
51	March 29, 2007	Tempe, AZ	-

No.	Date	Location	Held in Conjunction with
52	April 5, 2008	San Diego, CA	-
53	April 4, 2009	Bakersfield, CA	-
54	March 27, 2010	Surprise, AZ	-
55	April 2, 2011	Davis, CA	-
56	March 24, 2012	Tucson, AZ	-
57	April 6, 2013	Pasadena, CA	-
58	April 5, 2014	Phoenix, AZ	-
59	April 11, 2015	San Diego, CA	-
60	April 8-9, 2016	Fresno, CA	-

Important Internet Web Sites

- **The Cocci Study Group – sponsor of the annual valley fever scientific meeting - site of archived CSG Proceedings**

The Coccidioidomycosis Study Group was created in San Francisco, California on July 18, 1956. This group oversees conferences, annual meetings and research studies. Much of the documented knowledge of the pathogenesis, mycology and clinical aspects of Coccidioidomycosis originated from studies performed by this research group.

www.coccistudygroup.com

- **The Valley Fever Center for Excellence – site of archived CSG Proceedings**

The Valley Fever Center for Excellence, located at the University of Arizona in Tucson, was established to address the problems caused by the fungus, *Coccidioides*, the cause of coccidioidomycosis (Valley Fever). Two-thirds of all *coccidioides* infections in the United States occur in Arizona, mostly in the urban areas surrounding Phoenix and Tucson. The Center's mission is to mobilize resources for the eradication of Valley Fever (Coccidioidomycosis) through: 1) the development of public awareness and education about Valley Fever, 2) the promotion of high quality care for patients with Valley Fever, and 3) the pursuit and encouragement of research into all aspects of *Coccidioides sp*. and the diseases that it causes.

www.vfce.arizona.edu

- **Valley Fever Americas Foundation**

The Valley Fever Americas Foundation (VFAF) was founded by Rotary Clubs in 1995 to promote research for the cure for Valley Fever.

www.valleyfever.com