



Coccidioidomycosis

STUDY GROUP

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Abstract 1: Susceptibility of *Coccidioides immitis* to putative oxidants of neutrophils

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C. immitis is more resistant to killing by normal human neutrophils than is candida despite the ability of both to stimulate an oxidative burst. Since hypochlorous acid (HOCl) is a potent oxidant produced from Cl⁻ and H₂O₂ with myeloperoxidase, as occurs with degranulation, we studied the effect (as mean ± sem % killing) of 45 minute exposures to 2 - 200 uM OCl⁻ in acetate-buffered medium (pH=5.6) upon 3±1.5 x 10⁵ cfu/ml of arthroconidia (A) from mature growths of mycelia, spherules (S) from 96 hr in Converse medium at 39.5°C, or yeast cells of Candida glabrata:

Fungus	2 uM	10 uM	25 uM	80 uM	200 uM
Canida	21± 9%	100 %	95± 2%		
Arthroconidia	0		96± 4	94± 6%	100 %
Spherules	7± 5		34±16	59± 9	95±6

Killing candida and A by OCl⁻ was similar, but comparable effects on S at these inocula required 4-fold greater concentrations of OCl⁻. However, increasing either S or A inocula reduced % killing (e.g., at 80 uM, 10-fold increase in inocula reduced killing of S to 21 ±5%); adding as little as 0.1% protein such as serum or albumin caused reductions in % killing also, suggesting that OCl⁻ can be significantly depleted at critical concentrations. Thus, the large surface area of S as compared to equal cfu of A or candida may account for their differences in OCl⁻ sensitivity. At pH=7.4, killing of either A or candida required 100-fold increases of OCl⁻; inhibition of incorporation of the chitin precursor, N-acetylglucosamine, into A at physiologic pH also required the higher OCl⁻ concentrations. These studies support the hypothesis that other steps combined with or subsequent to the formation of OCl⁻ may be important correlates of coccidioidal resistance to neutrophil killing.

Abstract 2: IDENTIFICATION AND ISOLATION OF A POTENTIALLY IMMUNODIAGNOSTIC ANTIGEN OF COCCIDIOIDES IMMITIS

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Kaufman and coworkers described a heat stable antigen obtained from saprobic phase culture filtrates of Coccidioides immitis. The antigen is resistant to heating at 60°C for 30 min. The authors determined that the heat stable antigen, designated as IDHS on the basis of its behavior in the immunodiffusion assay, is the most useful coccidioidin (CDN) antigen for specifically immunoidentifying C. immitis cultures. Using our CDN/ anti-CDN reference system and the tandem, two dimensional-immunoelectrophoresis (2D-IEP) technique, we have shown that IDHS is a multicomponent antigen, but that the major component is antigen CS which we had described earlier (CS; Coccidioides-specific). We have isolated and purified antigen CS from the mycelial culture supernatant and determined its protein and carbohydrate composition. The antigen is a glycoprotein and was identified as a polypeptide band of Mr 19,000 by SDS-PAGE. The antigen elicits both cellular immunoreactivity in our immune lymph node proliferation assay, and humoral response demonstrated by ID and ELISA. Preliminary studies of antigen CS in the latter, using Coccidioides positive and negative sera, as well as heterologous sera, suggest that the antigen may be valuable for immunodiagnosis.

Abstract 3: Identification of Antibody-Binding and Lymphocyte Transforming Activity in Toluene Extracted Spherule Lysates of *Coccidioides immitis*

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Individuals infected with *Coccidioides immitis* (CI) normally develop lasting cellular mediated immunity (CMI). However, during the course of their illness, they also often develop circulating tube precipitin (TP) and complement fixing (CF) antibodies. The fractions of CI responsible for induction of CMI and of TP or CF antibodies are not known. To identify these fractions, we exposed in-vitro produced spherules to 3% toluene for 96 hr and recovered the supernatant, called TSL. At 3.9 *mcg/ml*, TSL produced a line of identity with TP antigen in an agar immunodiffusion assay. However, at concentrations of 125 *mcg/ml*, no CF antigen was found. After gel filtration of TSL, immunoblots using rabbit anti-spherulin antibody demonstrated antigen predominantly in fractions with MW >40 kDa. In vitro lymphocyte transformation (LT) using peripheral blood monocytes from skin-test positive (SK+) and skin-test negative (SK-) donors was measured as a multiplicative stimulation index (SI, $x \pm \text{sem}$). TSL at 50 *mcg* dry wt/ml was equivalent to commercial spherulin in inducing LT with SI = 141 ± 41 among SK+ and 4 ± 1 for SK- donors. On gel filtration, significant LT activity occurred in fractions with MW <40 kDa and between 40-500 kDa. These results show that TSL possesses both CMI and TP antigen activity. Future work should identify which specific fractions of TSL contain these activities.

Abstract 4: Demonstration of endogenous glucanase activity in spherule-endospore phase cultures of *C. immitis*

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To study further the biochemical processes involved in spherule formation and production of endospores, experiments were performed to ascertain if endogenous glucanases were present in the cell-free spherule-endospore cultures filtrates of *C. immitis*. Cell-free fractions were prepared from synchronously grown 28, 36 and 60 hour cultures (corresponding to immature spherule, early endospore release and late post endospore release) Beta-(1,6)-glucanase was not detectable at 28 hours, but was evident at the later time points, with three-fold more activity at 36 hours than at 60 hours. Alpha-(1, 3)-glucanase was detectable at all time points, but the level of activity was highest at the 36 hour period. A disproportionately large amount of beta-(1, 3)glucanase activity was found with activity greatest at 36 hours. The level of activity was 100-fold higher than was shown by the beta-(1, 6) glucanase at 36 hours. Dissolution of the spherule cell wall and release of both endospores and antigen appears to be temporally dependent on glucanase activity, particularly endogenous beta 1, 3)-glucanase. Endospores appear morphologically (light microscope) unaffected by the high levels of beta-(1, 3)-glucanase.

Abstract 5: STUDIES ON COCCIDIOIDOMYCOSIS IN AIDS

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We examined the laboratory aspects of diagnosis of coccidioidomycosis (Cocci) in 11 patients with acquired immunodeficiency syndrome (AIDS) and the qualitative differences between host responses of 6 AIDS and 15 non-AIDS patients with disseminated Cocci at autopsy. Material obtained at bronchoscopy confirmed the diagnosis of pulmonary Cocci in 67% (6/9) of patients, with culture being more sensitive (6/7) than histology (4/8) for diagnosis. At autopsy, AIDS and non-AIDS patients with disseminated disease had similar extent of pulmonary involvement and sites of dissemination. However, AIDS patients had a poorer granulomatous response in lung than non-AIDS patients (semiquantitative grading) and statistically significantly greater numbers of spherules (mean 48.3 ± 29.5 per high-power field for AIDS patients vs. 11.1 ± 10.9 for non-AIDS patients, $p \leq 0.02$). Neither antifungal therapy nor duration of clinical disease influenced the number of organisms present. AIDS patients with disseminated Cocci also had a significantly higher incidence (6/7) of other opportunistic infections at autopsy than non-AIDS patients (4/16), $p \leq 0.007$.

Abstract 6: Serologic studies of Coccidioidomycosis in AIDS patients

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Serologic tests for coccidioidal antibody were performed on specimens from patients with AIDS and coccidioidomycosis (Coccy). The results from these were compiled with those from published papers. Our own tests included immunodiffusion [with serum or CSF concentrated by evaporation under reduced pressure] using heated and unheated coccidioidin to detect precipitin (IgM)(=IDTP) and CF(IgG)(=IDCF) antibodies respectively, and complement fixation (CF). From clinical and serologic data it is evident that some patients had primary coccy while others had exacerbation of old arrested pulmonary coccy under the influence of AIDS.

Of 22 patients, 4 were seronegative (one additional Patient1s serum yielded a questionable reaction). Of the seropositive patients, several yield IDTP and/or IDCF Plus CF. The titer of the latter ranged upward to 2^{11} (1:2048) and reflected the severity of coccy as is observed also in non AIDS patients. While some of the seronegative patients may have died before they had sufficient time to develop detectable coccidioidal antibody, one should be alert to the possibility that AIDS patients may not yield the expected humoral response to infection with *f. immitis*.

Abstract 7: Coccidioidomycosis during Pregnancy

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Although previous literature suggests that coccidioidomycosis (coccy) during pregnancy is devastating and associated with a high maternal mortality, this view has recently been challenged. Because of this, we elected to identify cases of coccy during pregnancy in Tucson, Arizona from the years 1980 through 1985. We reviewed cases at 3 major health facilities: the University of Arizona Medical Center; Tucson Medical Center, a community hospital where the majority of deliveries were performed; and the University of Arizona Student Health Center. Overall, 10 cases of coccy occurred in 47,120 pregnancies. The mean age of the women was 26 yr and the majority were white. Only 1 had an underlying disease, JODM. Six were diagnosed during the 1st or 2nd trimester and 1 prior to pregnancy. Three were diagnosed in the immediate post-partum. Two of these three went on to develop disseminated coccy with meningitis. Only one other woman developed disseminated infection. All others resolved. There were no maternal deaths and of the six who delivered, all infants were healthy. No pregnancies were terminated because of coccy. In conclusion, coccy during pregnancy is uncommon. Although there were no maternal deaths, its occurrence in the immediate postpartum appears to be associated with severe disseminated infection.

Abstract 8: Coccidioidal Peritonitis Associated With Continuous Ambulatory Peritoneal Dialysis

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Infectious peritonitis is a common complication of continuous ambulatory peritoneal dialysis (CAPD). However, most cases are due to external contamination by bacteria and, less commonly, by fungi. We report the first 3 cases of peritonitis due to Coccidioides immitis (CI) diagnosed during CAPD. In one case, pulmonary coccidioidomycosis occurred 10 yr prior to the onset of coccidioidal peritonitis. However, in the other two, peritonitis occurred within 6 mos of pulmonary infection. Clues suggesting the diagnosis of coccidioidal peritonitis were a previous history of pulmonary coccidioidomycosis, peritoneal fluid eosinophilia, and failure to respond to anti-bacterial therapy, and positive coccidioidal complement-fixation serologies. CI was readily isolated on both routine bacterial media and on specific fungal media. However, KOH preparations were uniformly negative. No patient had evidence of CI at any site other than the peritoneum. In two of the cases, the course was protracted until the peritoneal catheter was removed. All three patients received systemic antifungal therapy but, in each instance, its effect was unclear. In conclusion, coccidioidal peritonitis associated with CAPD appears to be a rare, relatively benign manifestation of CI infection that improves with removal of the peritoneal catheter.

Abstract 9: First Case of Primary Coccidioidomycosis in Guatemala

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On 12/5/86 3 teenagers explored an archeological site in El Progreso, Motagua Valley, Guatemala.

Three days later A.Q., a 17 year old Hispanic male with prior history of asthma, developed fever and exacerbation of asthma. A chest x-ray was normal. During the next 10 days he developed fevers to

400C, right pleuritic chest pain, sore throat, shortness of breath, and a macular erythematous rash on upper extremities and chest that disappeared over 5 days.

Examination 12/18 showed mild dullness right lung base, bilateral wheezing, few rales.

Chest x-ray showed diffuse bilateral broncho-alveolar infiltrate and small right pleural effusion. On 1/4/87 left pleuritic pain developed and left effusion was seen on x-ray.

Fungal cultures from sputum, broncho-alveolar lavage, and pleural fluid were negative.

Patient	Date	Immunodiffusion		Complement fixation titer	Skin test
		IgM	IgG		
A.Q.	12/13/86	0	0	0	
	1/07/87	+	0	0	
	2/02/87	+	+	1:16	+
	3/19/87	+	+	1:8	
M. F.	2/02/87	0	+	1:2	
H. P.	2/02/87	0	0	0	0

Because of persisting symptoms, ketoconazole 200 mg q.d. was given to A.Q., with resolution of illness in 2 weeks. The Motagua Valley is endemic for coccidioidomycosis; except for higher relative humidity, it resembles the Lower Sonoran Life Zone. The first case of disseminated coccidioidomycosis in Guatemala was described in 1960 and >10 have been reported. This is the first reported case of primary coccidioidomycosis in Guatemala.

Abstract 10: Comparison of Conventional Broth and Radiometric Methods for the Detection of *Coccidioides immitis* in the Blood

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In a previous study, we examined the incidence of fungemia due to *Coccidioides immitis* (CI) and found that while CI grew readily in vented trypticase soy broth (TSB), we encountered no instances of CI fungemia using a radiometric blood culture system (BACTEC). In the present study, we inoculated coccidioidal spherules into the following blood culture media: aerobic BACTEC TSB (A), anaerobic BACTEC TSB (AN), vented BACTEC TSB, biphasic brain heart infusion, TSB and thioglycollate broth (TG). All bottles were incubated at 35° C and examined daily. Bottles A and AN were incubated and handled according to the recommended radiometric routine. Visible growth occurred within 2 days in all media except AN and TG. Growth occurred as a characteristic mycelial ball. Despite visible growth, radiometric indices for A and AN did not reach significance. Inoculation of blood with the spherules did not allow visualization of the mycelial balls if the bottle was agitated prior to visual examination. In conclusion, CI grows in a variety of standard blood culture media. However, its growth is not detected radiometrically, presumably because it does not produce enough $^{14}\text{CO}_2$. In order to use the radiometric blood culture system to detect CI, we recommend additionally inoculating a sample of blood into a vented aerobic BACTEC bottle, incubate it without shaking and examine it daily for visible growth; or examine the radiometric blood culture bottles for visible growth after allowing blood to settle.

Abstract 11: Indirect Enzyme Immunosorbent Assay of Coccidioidal IgM Antibody in Serum

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Enzyme Linked Immunosorbent Assay (ELISA) can quantitatively detect the presence of coccidioidal IgM antibody. Heated coccidioidin antigen, diluted 1:500, was absorbed on the surface of polystyrene wells. Serum diluted 1:2000 was added. The attachment of coccidioidal IgM antibody was then detected by alkaline phosphatase labeled anti-human globulin. The substrate P-nitrophenyl phosphate was acted upon by the alkaline phosphatase. This produces a yellow color, the intensity of which was measured spectrophotometrically.

Routine testing, including EIA-IgM, complement fixation, tube precipitin, immunodiffusion, and latex agglutination was performed on 792 sera.

Testing procedures did not detect IgM in any serum with an EIA-IgM optical density (O.D.) of less than 0.30. Sera with O.D. of 0.30 or greater were all confirmed as reactive when concurrent, previous, or subsequent sera were available. EIA-IgM had 89% agreement with the tube precipitin test. The 11% disagreement appears to be EIA's increased sensitivity and specificity.

The latex agglutination test was only used when weak tube precipitin or foggy immunodiffusion results needed confirmation. There was a 97% agreement between EIA and latex results. There was 100% agreement between detectable IgM lines on ID plates and O.D. readings greater than 0.60.

The use of an EIA-IgM test for the detection of coccidioidal IgM in sera diluted 1:2000 appears to be as sensitive as the latex test and more specific than the other tests.

Abstract 12: Extraction and detection of coccidioidal Antigens

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Serum antibodies may interfere with antigen detection by inhibition immunoassays if they bind antigen in the fluid phase ("lowers" concentration) or if they block binding sites on the solid phase ("raises" concentration). Because acid and heat (AH, pH= 3 and temp= 96°C for 20 min) are used to disrupt immune complexes and denature antibodies in other antigen assays, we assessed the effect of AH on detection of heat-stable spherule antigens (SA) from Coccidioides immitis by inhibition ELISA. Prior to assay, SA was added to 1:10 dilutions of IgM-containing sera from 19 patients who had symptoms of primary coccidioidal pneumonia. When a high concentration (10 ug/ml) of SA was added, patient antibody obscured antigen detection and this interference was eliminated by AH. When SA was not added, patient antibody raised apparent antigen concentration. This effect was reduced but not completely eliminated by AH. However, the magnitude of the residual effect from patient sera was independent of patient anti-SA IgM activity, and in separate measurements of undiluted sera, SA was detected in 8 of 15 of these sera (range: 0.3- 1.7 ug/ml). In related studies, we also found that AH reduced rabbit antibody activity ≥ 640 -fold. AH facilitates the interpretation of inhibition ELISA antigen tests. Our findings confirm the presence of coccidioidal antigens in sera from infected patients.

Abstract 13: COCCIDIOIDOMYCOSIS, AMPHOTERIN B AND THE KIDNEY

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Coccidioidomycosis usually affects the kidney on a microscopic level and not functionally. Amphotericin B has both reversible and irreversible effects on the kidney. Reversible effects include reduced creatinine clearance, distal R.T.A., renal potassium and magnesium wasting. Irreversible effects include acute renal failure without recovery, CRF accompanied by hypertension leading eventually to ESRD (End Stage Renal Disease).

Five cases are presented. All had ESRD, 2 were transplanted, 2 died, 1 remains chronic hemodialysis. Two patients had IV Amphotericin B prior to starting chronic hemodialysis and developed ESRD. One had a bilateral nephrectomy 3 years post starting chronic hemodialysis which showed acquired cystic renal disease. Two patients had both tuberculosis and Coccidioidomycosis. Both transplants are doing well. Mechanisms of renal damage by Amphotericin B included vasoconstriction, damage to distal tubular cells and indirectly by electrolyte depletive effects. Factors that decrease nephrotoxicity have not withstood controlled clinical trials in humans. Calcium channel blockers and angiotensin converting enzyme inhibitors have not been tried. IV Amphotericin B should be stopped at a serum creatinine of 2.5mg. These patients should have careful follow-up of both kidney function and blood pressure, as some of these patients go on to develop ESRD.

Abstract 14: Current status of clinical trials of the Mycoses Study Group

Galgiani, JN, and others of the NIH-NIAID Mycoses Study Group

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Itraconazole has been administered to 48 patients with progressive skeletal (11), soft tissue (13), or pulmonary (24) lesions. Overall, 56% had failed or relapsed from prior therapy. 36 patients had their therapy begun at 400 mg/day (200 mg BID) and of the other 12 started at 100 (6 patients) or 200 (6 patients) mg/day, 9 had their dosage increased. Subsequent evaluations every three months expressed response as the percentage of composite improvement of initial abnormalities. Most patients appeared to respond to treatment: by six months, abnormalities for the three different types of progressive infection ranged on average from 40% to 60% of baseline. Culture results are as follows:

	<u>Skeletal</u>	<u>Pulmonary</u>	<u>Soft tissue</u>	<u>Total</u>
# enrolled	11	24	13	48
# flu cult.	5	19	8	32
#negative	3	14	3	20

23 patients have discontinued therapy because of successful response (14), unsatisfactory efficacy (3), prohibitive drug toxicity (1), unrelated deaths (2), or poor compliance/enrollment error (3). To date one responder has experienced recurrence at a prior site one month after stopping treatment.

Fluconazole has been administered to 19 patients with progressive skeletal (4), soft tissue (2), or pulmonary (13) lesions. Overall, 58% had failed or relapsed from prior therapy. Patients had therapy begun with 50 mg/day and 12 have been increased to 100 mg/day. Subsequent evaluations utilized the same methods as for itraconazole. Current status (% of baseline/# evaluated) is as follows:

	<u>Skeletal</u>	<u>Pulmonary</u>	<u>Soft Tissue</u>	<u>Total</u>
3 months	89% / 3	61% / 9	34% / 2	61%/14
6 months	75% / 2	73% / 6	-	74%/ 8

Of 7 who have discontinued therapy. 1 each had responded and failed; the other 5 were not evaluable.

Abstract 15: Pharmacokinetics of Fluconazole (FCZ) in Cerebrospinal Fluid (CSF) and Serum in Human Coccidioidal Meningitis (CM)

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CM untreated is 100% lethal; the only proven Rx is intra-CSF amphotericin (AmB), which is difficult, toxic, commonly unsuccessful. FCZ, a triazole, unlike other systemic azoles has low protein binding (11%); serum $t_{1/2}$ = 22 h. Twenty-four paired serum and CSF samples were obtained 0.5-27 h after oral FCZ 50-100 mg doses QD over 17 wk. Rx in 3 patients, also receiving intermittent intrathecal AmB. Samples were bioassayed excluding AmB. Peak serum and CSF levels occurred 2-6 and 4-8 h post-dose; were 3.5 and 2.3 mcg/ml after 50 mg, 4.5 and 3.4 after 100. Trough levels were 0.4 and 0.3, and 2.2 and 2.1, respectively. Pharmacokinetic curves in CSF were similar to serum, with initial dip at 1-2 h; accumulation in neither fluid was apparent during Rx. Mean CSF levels were 70-81% of serum after 50 mg in 3 patients, 79% after 100. This CSF penetration is unique for azoles. One patient had been given \leq 1600 mg ketoconazole QD with serum levels to 38.2 mcg/ml; CSF levels ranged 0.12-1.08 and max., penetration only 3%. FCZ was well-tolerated by all. These kinetics are promising re possible FCZ utility as adjunct or sole Rx in fungal meningitis.

Abstract 16: UNUSUAL SOLUTIONS IN the MANAGEHENT of COCCIDODALMENINGITIS

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We have reported the use of high-dose intrathecal (I.T.) Amphotericin B in the treatment of coccidioidal meningitis, thereby achieving improved, long term survival (1). In some complicated cases however, conventional administration of I.T. AMB has to be modified. CASE REPORT: A 21 year old Navajo man with hydrocephalus of unknown origin received a V.P., shunt elsewhere in Arizona. Nine months later he came to us with weight loss, gross ataxia, and diplopia. CSF revealed 5000 mgs of protein, 35 mgs of glucose, 259 WBCs, coccidioidal titer > 1:32 and CSF would "gel" spontaneously due to very high IgG level of 1800 mgs. Head CT scan verified hydrocephalus and his V.P. shunt revised, but required the insertion of a dual ventricular shunt. A lumbar radionuclide CSF study showed very rapid leakage of CSF within 6 hours from the subarachnoid space into the paravertebral venous plexus with almost complete block at T1. With this valuable information of altered CSF dynamics, he was begun on daily lumbar I.T. AMB in 10 ml of Lactated Ringers at 0.25 mgs and raised rapidly to 0.75 mgs (every dose included 25 mgs of hydrocortisone (1)). After 12 lumbar doses, CSF would no longer "gel" and cisternal injections were begun with dose increased to 1.25 mgs every other day. Oral ketoconazole at 1200 mgs a day was added and I.V. AMB at 50 mgs on alternate days. Within a time span of 3 months he received a total of 43.3 mgs of I.T. AMB, 900 mgs of I.V. AMB. He continues on oral ketoconazole, has totally recovered from ataxia and diplopia and returned to work.

1. Labadie, E.L., Hamilton, R.H., *Arch. Int. Med.*, 146:2013-2018, 1986

Other presentations Abstracts not Published:

- Pathological features of fungal infection in AIDS patients - The USC experience: *Gaw, A*
- Isolation frequency of *C. immitis* from rodent burrows in Arizona as compared to non-specific sites: *Leathers, C.R*
- Diagnostic considerations in coccidioidal meningitis - Criteria for starting IT Therapy: *Einstein, H*
- Vasculitic complications associated with coccidioidal meningitis: *Williams, Einstein, H. Pappagianis, D., Morrison, J*