

Treatment studies for coccidioidomycosis: past, present and future

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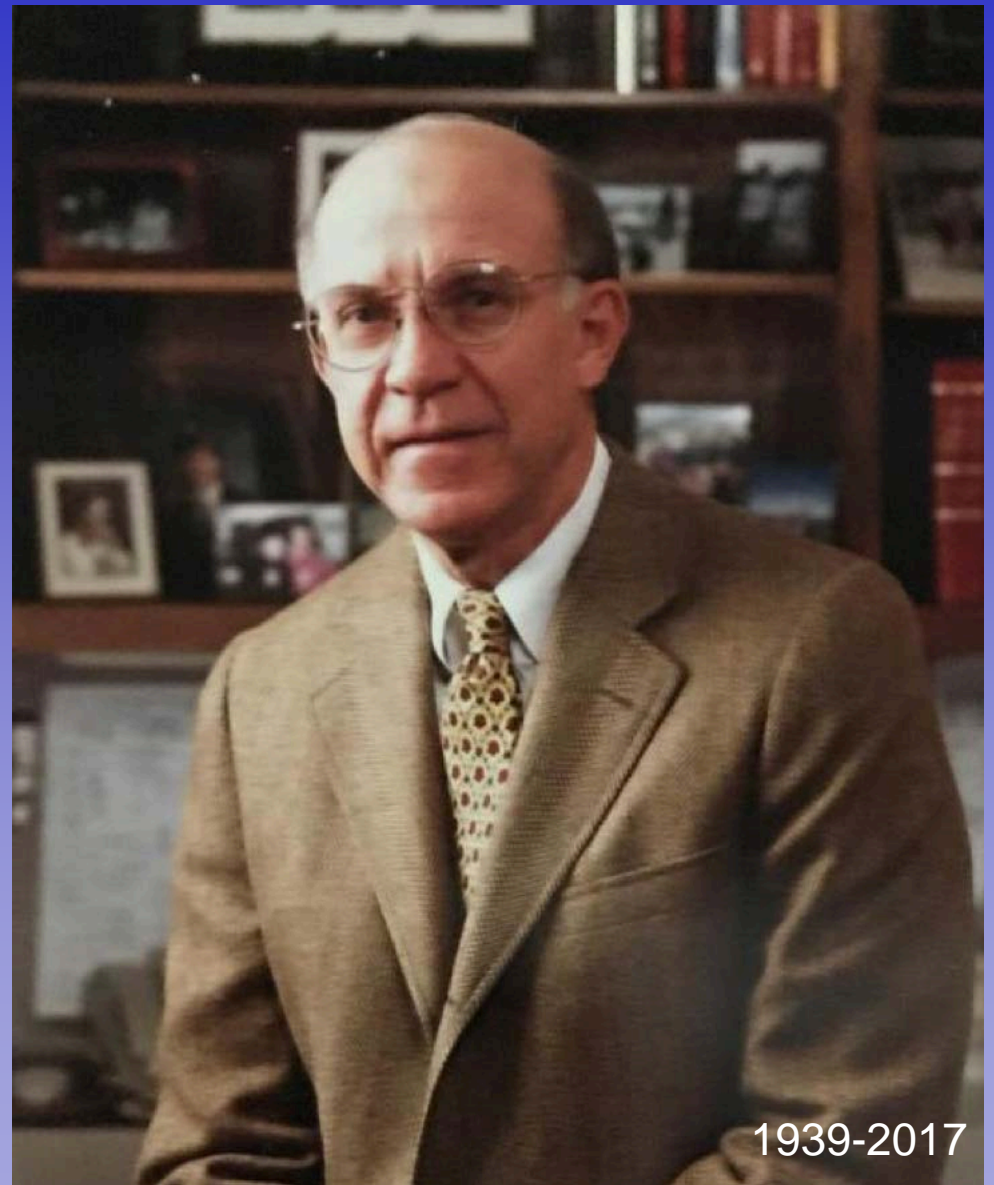
The Past

Mycoses Study Group

- The Mycoses Study Group (MSG) started in 1978 as a contract through NIAID
- It was awarded to the University of Alabama at Birmingham (UAB)
 - William E. Dismukes, M.D. (PI)
- Its goal was to perform multicenter collaborative clinical trials for prevention and treatment of invasive fungal infections.
- In 2005, NIAID elected to terminate the contract, effective April 2007.

Bill Dismukes was the original principal investigator of the NIAID Mycoses Study Group (MSG), and led it from 1978-2006. Under his leadership, the MSG was involved in the publication of over 130 manuscripts, book chapters, reviews, and editorials.

<http://www.msgerc.org/>



1939-2017

NIAID



MSG

UAB



Coccidioidomycosis Subgroup

Design
Statistical support
Gretchen Cloud†

Industry
(funding)



John Galgiani*
David Stevens
Tony Catanzaro
Royce Johnson
Dick Graybill

MSG coccidioidomycosis publications

- Dismukes WE, et al. Treatment of systemic mycoses with ketoconazole: emphasis on toxicity and clinical response in 52 patients. National Institute of Allergy and Infectious Diseases collaborative antifungal study. *Ann Intern Med.* 1983;98(1):13-20.
- Graybill JR, et al. Itraconazole treatment of coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med.* 1990;89(3):282-90.
- Galgiani JN, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med.* 1993;119(1):28-35.
- Catanzaro A, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med.* 1995;98(3):249-56.
- Galgiani JN, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. *Ann Intern Med.* 2000;133(9):676-86.
- Catanzaro A, et al. Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. *Clin Infect Dis.* 2007;45(5):562-8. doi:CID50452 [pii] 10.1086/519937.

Present

- Since 2007, there have been no controlled trials of therapy for coccidioidomycosis
- The only comparative trial of azole therapy in coccidioidomycosis was in 2000
 - Galgiani JN, Catanzaro A, Cloud GA, Johnson RH, Williams PL, Mirels LF et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. Ann Intern Med. 2000;133(9):676-86.
- Since then, there have been case series and reports
- However, case series and reports are **flawed** by inherent biases
 - results in **reduced strength of recommendations**
 - forces **dependence on “expert opinion”**

Why the present model that relies on industry support does not support treatment studies in coccidioidomycosis

- Pharmaceutical companies currently operate under much stricter profit margins than in the past
- The cost of developing pharmaceuticals is currently prohibitive
- There must be a large market to support new drug development

Coccidioidomycosis is a small market

- **179,106** cases of IA and mucormycosis hospitalizations 2000-2013
 - Vallabhaneni S, et al. Open Forum Infect Dis. 2017;4(1)
- **~32,000** coccidioidomycosis-associated hospitalizations over a decade
 - **25,217** coccidioidomycosis-associated hospitalizations 2000-2011 in California
 - Sondermeyer G, et al. Emerg Infect Dis. 2013;19(10)
 - **725** hospitalizations in Arizona in 2017
 - ADHS
- **Market for preventive therapy**
 - Invasive molds: **HUGE**
 - Coccidioidomycosis: **VERY SMALL**

Coccidioidomycosis is a small market

- Coccidioidomycosis is not an attractive target to develop new antifungals
- Support beyond industry is required

Future

Some present unanswered questions

- Management of primary pulmonary disease
- Best antifungal for non-meningeal disease
 - pulmonary
 - disseminated
- Management of coccidioidal meningitis
 - best antifungal
 - currently available triazoles
 - newer antifungals
 - can therapy be stopped?
 - role of IT amphotericin B
 - role of IV liposomal amphotericin B
- Management of patients on biologics and with transplants

Coccidioidomycosis Study Group (CSG)


“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.”

Coccidioidomycosis Study Group

- A non-affiliated organization whose primary goal is to host an annual meeting dedicated to presenting new information and research on coccidioidomycosis
- It has a Board and by-laws
- It is not legally or financially organized
- Funds are donated by members* and held by a separate 501c(3) entity
- CSG has never previously **overseen** a **research study**
- But its members have enormous expertise in the management and treatment of coccidioidomycosis and many have been involved in research studies

*anyone who attends the annual meeting

Proposal

- GR Thompson has proposed to use CSG members and the board as an advisory panel for treatment studies
 - He has created a clinical consortium
 - UC Davis
 - Kern Medical Center
 - Mayo Clinic in Arizona
 - University of Arizona - Tucson
 - Mayne Pharmaceuticals indicated support for a study of suba-itraconazole through this consortium
- 
- The logo for the CSG Consortium, featuring a yellow chevron shape pointing left, followed by the text "CSG Consortium" in yellow.

Proposal

- This mechanism could increase the number of coccidioidomycosis-related treatment studies
- But
 - It does not provide independent design and statistical support
 - It is unlikely to lead to studies of
 - best management practices
 - newer drugs or targets that are coccidioidal specific
- **Collaboration with NIAID and/or FDA through the MSGERG with the CSG consortium**
 - to design and implement treatment trials for coccidioidomycosis
 - most productive and effective way to achieve goals