Coccidioidomycosis: Clinical, Diagnostic, and Therapeutic Challenges

F. Donovan[I]

[I]Division of Infectious Diseases, Department of Medicine, The University of Arizona, Tucson, United States of America

Coccidioidomycosis (CM) caused by *Coccidioides* spp. is a health threat in endemic Southwest US and worldwide, due to expanding range and increased international travel. 60% of those exposed to the fungus are asymptomatic, 30% have pulmonary infection mimicking flu-like illness/pneumonia. 5-10% develop disseminated CM. 1-3% disseminate to the central nervous system and can be fatal. Culture is the gold standard for CM diagnosis, it takes days to grow, and it has significant safety concerns for the personnel. Most of coccidioidal testing is done via serology. The enzyme immunoassay test has marginal sensitivity and specificity. The lateral flow assay sensitivity is only 31%, with specificity of 92%. The polymerase chain reaction (PCR) has acceptable sensitivity and specificity but is limited to samples obtained from invasive procedures. The cell-free DNA PCR is an alternative noninvasive rapid diagnostic option for circulating fungal cell-free DNA detection, with sensitivity of 33% in pulmonary disease, 52% in disseminated CM. Available CM treatments are limited to Amphotericin B and triazole antifungal agents. Amphotericin B causes nephrotoxicity/electrolyte imbalance. Triazoles may cause poor tolerability/adverse reactions. Novel antifungals with better tolerability /effectiveness are urgently needed. Olorofim, the first orotomide antifungal agent, active in vitro against filamentous/dimorphic fungi, including *Coccidioides* spp. It inhibits fungal dihydroorotate dehydrogenase, blocking pyrimidine biosynthesis, causing fungal cell death. Another novel antifungal is fosmanogepix, prodrug of manogepix, an inhibitor of the fungal enzyme Gwt1, with broad spectrum in-vitro activity against yeasts and molds. Turletricin is the latest antifungal agent for treating invasive molds, selective to fungal ergosterol and exhibits enhanced ergosterol extraction. This study is to heighten global CM awareness, and spark interest in improved diagnosis, treatment, and CM prevention.