ISHAM INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2019, 57, S76–S84
doi: 10.1093/mmy/myy029
Review Article

Review Article

Current Concepts and Future Directions in the Pharmacology and Treatment of Coccidioidomycosis

George R. Thompson III[1,2,*], James S. Lewis II[3], David E. Nix[4] and Thomas F. Patterson[5]

[1]Department of Medical Microbiology and Immunology, University of California, Davis; Davis, California, USA, [2]Department of Internal Medicine, Division of Infectious Diseases, University of California Davis Medical Center; Sacramento, California, USA, [3]Department of Pharmacy, Oregon Health & Science University Hospital and Clinics, Portland, Oregon, USA, [4]Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, Arizona, USA and [5]Division of Infectious Diseases, UT Health San Antonio, and the South Texas Veterans Health Care System; San Antonio, Texas, USA

*To whom correspondence should be addressed. George R. Thompson III, MD, FIDSA, Associate Professor of Medicine, Department of Medical Microbiology and Immunology, Department of Medicine, Division of Infectious Diseases, University of California, Davis, Davis, CA 95616, E-mail: grthompson@ucdavis.edu

Received 2 March 2018; Accepted 19 April 2018; Editorial Decision 13 April 2018

Abstract

Coccidioidomycosis remains a significant clinical problem with substantial morbidity and mortality. The vast majority of infections are asymptomatic and the need for early primary therapy remains controversial. The use of triazole antifungals has improved tolerability of therapy but concerns about acute and long-term toxicities among available agents limit their use. In addition, recent findings of decreased *in vitro* fluconazole susceptibility to as many as 37% of *Coccidioides* spp. isolates raises concerns regarding optimal therapy for these infections as fluconazole is commonly used for therapy including central nervous system disease. Thus, new agents from novel antifungal classes are currently in preclinical and clinical development aimed at reducing toxicity and improving outcomes of these serious infections.

Key words: coccidioidomycosis, *Coccidioides*, antifungal, azoles, fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole, amphotericin.

Introduction

Coccidioidomycosis is a systemic fungal infection caused by *Coccidioides immitis* or *Coccidioides posadasii*.[1] These soil-dwelling dimorphic pathogens reside in the soil of California, Arizona, and parts of Washington, Nevada, New Mexico, and Texas, as well as throughout Mexico, Central and South America.[2,3] Infection occurs following inhalation of arthroconidia (e.g., spores), although the vast majority of infections are thought to be subclinical.[4] Clinically apparent illness typically manifests as a subacute process known as "Valley Fever" (primary pulmonary infection). Symptoms such as cough, fever, chills, dyspnea, and fatigue are common and may last weeks to months.[5]

The decision to treat primary pulmonary infection has not been evaluated in prospective randomized trials. Prior nonrandomized studies have not definitively shown a benefit to antifungal therapy for those with primary pulmonary infection.[5,6] A retrospective study found early therapy may partially abrogate the immune response to treatment,[7] and historical observation prior to the availability of antifungal agents described over 90% of patients recovered without complications.[8] Current guidelines thus recommend an individualized approach to patient management with antifungal therapy offered to those at significant risk for complications or for those with moderate to severe pulmonary disease or disseminated infection.[1] Fluconazole and itraconazole are the agents most frequently prescribed

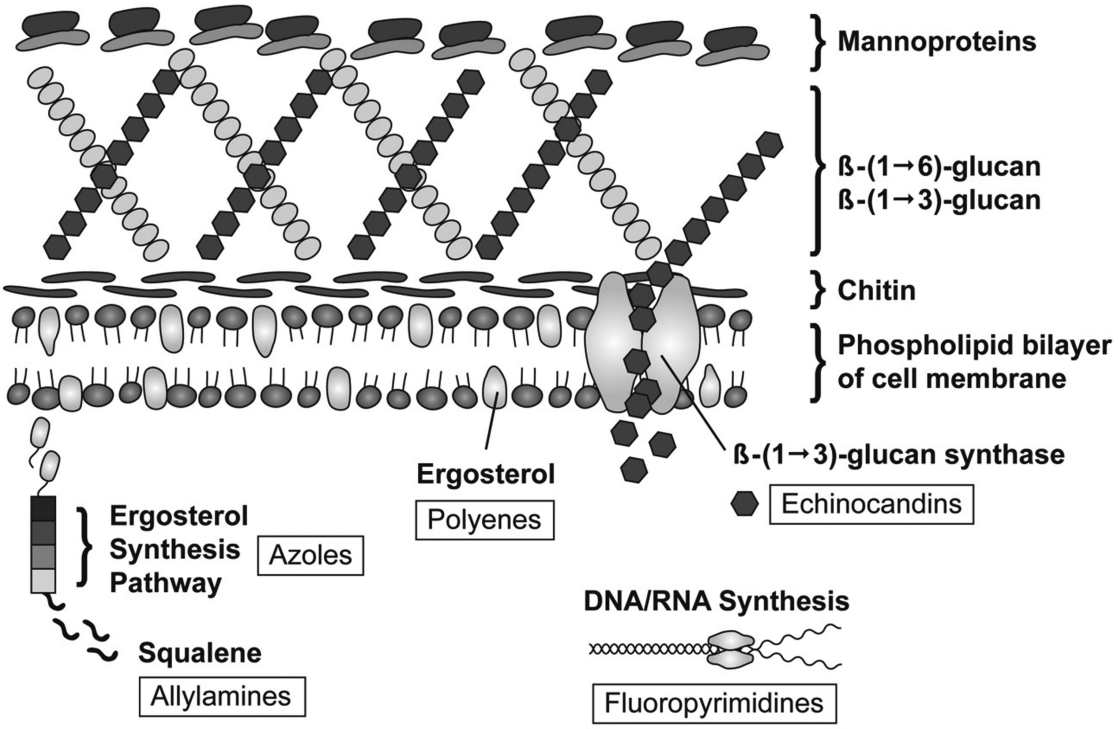

Figure 1. Targets of systemic antifungal agents.

for the various manifestations of coccidioidomycosis; however, the last decade has seen renewed interested in the development of new antifungal compounds. An understanding of the differences in each agent in their pharmacokinetic/pharmacodynamic interactions, oral bioavailability, toxicity, and drug-drug interaction profile is of paramount importance during the care of patients with this disease.

Triazoles

The triazoles exert their effects within ergosterol synthesis by inhibition of cytochrome P450 (CYP)-dependent 14-α-demethylase preventing the conversion of lanosterol to ergosterol (Fig. 1).[9] This inhibition leads to an increase in toxic methylsterols causing a disruption of the packed acyl chains of fungal phospholipid cell membranes. Following this destabilization of membrane-associated enzymes, including those in the electron transport chain, fungal growth is inhibited.

The triazoles exhibit significant differences in their affinity for the 14-α-demethylase enzyme, and these differences are largely responsible for their varying antifungal potency and spectrum of activity. Cross-inhibition of several human CYP-dependent enzymes (3A4, 2C9, and 2C19) is responsible for the majority of the clinical side effects and drug-drug interactions within this class.[10]

Fluconazole

Fluconazole remains the most frequently prescribed antifungal for coccidioidomycosis due to its low cost, excellent oral bioavailability, relatively dose-dependent adverse-effect profile, and tolerability. Available in both an intravenous and oral preparation, fluconazole has excellent oral absorption (>90%) that is unaltered by food or gastric pH. Fluconazole is widely distributed into body fluids and tissues and is not significantly protein bound (~10%).[11] Fluconazole penetrates most sites, and high concentrations can be measured in the majority of tissues. Importantly in the care of coccidioidomycosis, fluconazole achieves clinically useful concentrations within the cerebrospinal (CSF) fluid with levels approximately 50–70% of those found in the serum.[12] The relatively long half-life (~30 hours) allows for once daily dosing of fluconazole (Table 1). The majority of the drug is eliminated unchanged in the urine (~80%). Pharmacokinetic/pharmacodynamic studies have not established optimal parameters for antifungals used in the treatment of coccidioidomycosis, although fluconazole *in vitro* mean inhibitory concentrations (MICs) are significantly higher than those seen with other triazoles. In one study, increased fluconazole MICs were seen in a significant number of *Coccidioides* spp. isolates tested (MIC $\geq$ 16 μg/ml, 37.3%; $\geq$32 μg/ml, 7.9%) as compared to MICs of mould-active triazoles (itraconazole, voriconazole, and posaconazole).[13] It should be noted that this *in vitro* finding has not been correlated with patient outcomes, yet these results raise significant concerns about optimal therapy in serious infection. Although higher fluconazole doses are typically recommended during treatment—which may overcome decreased fluconazole susceptiblity,[1] murine models have demonstrated a dose-dependent response to fluconazole,[14] and itraconazole

TABLE 1. Pharmacokinetics of antifungals useful in the treatment of coccidioidomycosis.

	Antifungal agent								
Pharmacokinetic parameter	AmB-d	ABCD	ABLC	L-AMB	FLU	ITRA	VORI	POSA	ISAV
Oral bioavailability (%)	NA	NA	NA	NA	90%	55%[a]	96%	54%[b]	98
Food effect (Cmax)	NA	NA	NA	NA	NA	See footnote[c]	↓by 34%	↑16%	↓by 9%
Distribution									
V_d (l)	0.3–4.0	3–4	131	0.1	0.6	796	4.6	260	450
Total C_{max}	2–4 mcg/ml	2.6 μg/ml	1.7	57–83[d] mcg/ml	6.7	2.3		3.3 ng/ml	7.5
Protein binding	>90%	>90%	>90%	>90%	10%	99%	58%	>98%	>99%
CSF penetration	0–4%	<5%	<5%	<5%	60%	~0%	~50%	~0%	~10%
Metabolism	Minor hepatic	Unknown	Unknown	Unknown	Hepatic	Hepatic	Hepatic	Minor hepatic	Hepatic[e]
Elimination	Unk	Unknown	Unknown	Unknown	Urine	Feces	Hepatic	Feces and urine	Feces and urine
Half-life (hours)	15–48	28	173	7–10	20–50	16–28	Dose-dependent	26–31	130

Amb-d, amphotericin B deoxycholate; ABCD, amphotericin B collodoidal despersion; ABLC, amphotericin B lipid complex, L-AMB, liposomal amphotericin B; FLU, fluconazole; ITRA, itraconazole; VORI, voriconazole; POSA, posaconazole; ISAV, isavuconazole; Vd, volume of distribution; Cmax, maximum concentration; AUC, area under the curve; CSF, cerebrospinal fluid.

[a]Using oral solution formulation.

[b]Absorpion using tablet formulation.

[c]Absorption of itraconazole capsules is enhanced by food and gastric acidity. Itraconazole solution bioavailability is decreased with concurrent food intake.

[d]Using a dose of 5 mg/kg/day.

[e]Metabolism of the isavuconazonium prodrug is via plasma esterases.

has been found superior in the treatment of some extrapulmonary forms of coccidioidomycosis in a prospective randomized study.[15]

Adverse effects from fluconazole are generally benign; however, hepatotoxicity and cardiac toxicity due to prolongation of the QTc interval can occur with any of the triazoles and neither is clearly dose- or time-dependent. Alopecia, xerosis, and cheilitis are the most frequent side effects of fluconazole and are reversible following discontinuation of therapy.[16]

Fluconazole is a strong inhibitor of CYP2C19 and 2C9, and moderate inhibitor of CYP3A4 and significant drug-drug interactions can thus occur (Table 2).

Therapeutic drug monitoring (TDM) of fluconazole therapy is not generally recommended due to its high bioavailability and a lack of defined target serum concentrations.[17] However, at high doses, such as those frequently used in coccidioidomycosis[1] or in patients with renal dysfunction or morbid obesity, fluconazole exposure may be profoundly altered and difficult to predict. Monitoring fluconazole serum drug levels may theoretically be useful in these settings or in those during treatment of an isolate with decreased *in vitro* antifungal susceptibility.

Table 2. Summary of triazole mediated cytochrome P450 drug-drug interactions.

	Drug				
Drug mechanism	FLU	ITRA	VORI	POSA	ISAV
Inhibitor 2C19	++		+++		+
2C9	++	+	++		+
3A4	+	+++	++	+++	++
Substrate 2C19			+++		
2C9			+		
3A4		+++	+		+

Itraconazole

Itraconazole is also frequently prescribed during the treatment of coccidioidomycosis, and extensive experience with this agent has been garnered since its approval.[15,18] Itraconazole is available in both capsule and oral solution formulations with an intravenous formulation available in some countries (not within the USA). The bioavailability of itraconazole is highly variable; the capsule formulation has a bioavailability of ~55%, and absorption is improved when given with food and an acidic gastric pH for solubilization. The solution formulation has 30–37% greater bioavailability than that of the capsule, and absorption is not altered by gastric pH.[19] The solution, however, does have more gastrointestinal intolerance than the capsule.

Itraconazole is a lipophilic antifungal, has a long plasma half-life (~30–40 hours), is highly protein bound (99.8%), and undergoes extensive hepatic metabolism with over 30 metabolites. One of these, hydroxy-itraconazole, has *in vitro* antifungal activity as well. Despite poor bone penetration,[20] prior studies have shown an enhanced response rate in itraconazole treated patients compared to those receiving fluconazole during the treatment of osseous coccidioidomycosis (70% vs 37% response rate, $P = .03$).[15] Relapse rates following discontinuation of study drug were also lower in the itraconazole treated group compared to fluconazole (18% vs 28%). This study builds on *in vitro*[13] and murine models of infection showing favorable PK/PD determinants for itraconazole compared to fluconazole, yet additional

comparative studies are needed to determine superiority.[21] Itraconazole also exhibits poor CSF penetration, however, in both animal and clinical studies has proven highly efficacious in the treatment of coccidioidal meningitis.[21–23]

Adverse effects from itraconazole may occur including hepatotoxicity and QTc prolongation as mentioned above. Gastrointestinal distress is common with the oral solution and is thought secondary to the cyclodextrin vehicle used to solubilize itraconazole with this formulation. More severe side effects include the development of hypertension, hypokalemia, and peripheral edema.[24] This effect was recently determined to be caused by inhibition of human 11β-hydroxysteroid dehydrogenase (11β-HSD) causing the syndrome of apparent mineralocorticoid excess (AME). Although guidance in these circumstances is limited, this syndrome has resolved with a reduction in the dose or a change to another, structurally unrelated triazole (e.g., fluconazole or voriconazole). Heart failure has also been described secondary to the negative inotropic effects of itraconazole, and it should be avoided in patients with a history of ventricular dysfunction of congestive heart failure.[25]

Itraconazole, a strong inhibitor of CYP3A4 as well as P-glycoprotein, is also a substrate for CYP3A4. Significant drug-drug interactions may occur with co-administration of other agents that are metabolized by CYP3A4 or that use P-glycoprotein transporters.[26] In addition, drugs that induce CYP3A4 isozymes may lead to profound increases in itraconazole clearance and sub-therapeutic plasma concentrations.[27]

Therapeutic drug monitoring of itraconazole is generally recommended due to the erratic absorption and limited bioavailability of current formulations.[17] Target serum levels for itraconazole in the treatment of coccidioidomycosis have not been definitively demonstrated; however, a concentration-effect has been shown in the treatment of most other mycoses.[17] Toxicity has similarly been correlated with serum drug levels.[28] It is important to consider the technique used for itraconazole TDM as bioassay results are typically 2–10-fold higher than those obtained by high-performance liquid chromatography (HPLC). HPLC procedures used for TDM quantify both itraconazole and hydroxyitraconazole separately.[29] To make the HPLC assay more reflective of bioassay results, it is common practice to add the concentrations of itraconazole and hydroxyitraconazole together and report a total drug concentration. However, hydroxyitraconazole has more potent activity against the bioassay test organism than itraconazole, a finding that is not necessarily true in patient samples.[30]

Voriconazole

Voriconazole is often reserved for patients with coccidioidomycosis who are intolerant or refractory to fluconazole or itraconazole. However, compared to other agents, voriconazole exhibits more drug-drug interactions, variable metabolism, and significant long-term toxicity concerns.[31,32] Also available in both intravenous and oral formulations, voriconazole has moderate lipophilicity and excellent oral bioavailability; however, absorption is decreased with food by ~30%, and administration on an empty stomach is preferable.[10] The intravenous form contains a sulfobutyl-β-cyclodextrin for solubility that is known to accumulate in patients with renal dysfunction; however, the clinical implications of this remain unclear.[33] Voriconazole is widely distributed throughout the body and is able to penetrate the CSF and has demonstrated efficacy in cases of coccidioidal meningitis.[31,34] The half-life of voriconazole is variable and patient dependent.

Adverse effects from voriconazole include hepatotoxicity and QTc prolongation as mentioned above for other triazoles. In addition, there are several unique side effects of voriconazole compared to other triazoles in clinical use. Visual disturbance including photopsia (the perception of flashing lights), photophobia, and color changes have all been observed and are thought secondary to selective and reversible dysfunction of retinal ON-bipolar cells.[35] These effects are usually associated with peak serum concentrations and occur 30–60 minutes following oral or IV administration.[36] These effects are reversible and typically abate after 30–60 minutes, and no irreversible ocular toxicity has been described.

Visual hallucinations have also been reported and are distinct from the aforementioned complaint of photopsia. This effect is more common with serum voriconazole concentrations >5.5 μg/ml.[37] Neurologic toxicity including confusion, agitation, and myoclonus may also occur and are similarly associated with serum levels exceeding 5.5 μg/ml.

Cutaneous adverse events including rashes have been seen in ~7% of patients, and these are typically photosensitivity reactions.[36] These effects may additionally lead to skin carcinoma following long-term therapy.[38] Although this was initially presumed secondary to a disruption in normal retinol metabolism by voriconazole, this has not been demonstrated.[39] Alopecia, xerosis, and nail changes are also common with prolonged voriconazole administration.[40]

Voriconazole is the only trifluorinated antifungal in clinical use, and long-term administration in patients with impaired renal function has been associated with the development of fluoride excess and periostitis/exostoses.[41,42] Patients with this manifestation exhibit bone pain, and elevations of serum alkaline phosphatase levels; periosteal elevation is observed on radiographic imaging of the affected site. Cessation of voriconazole is required for resolution of this manifestation.[43]

Therapeutic drug monitoring of voriconazole is recommended given the dose-response relationship that has been demonstrated in the treatment of other mycoses[37] and the variability of patient serum drug levels in patients receiving standard dosing regimens.[44] Recent work has shown voriconazole TDM does not impact the incidence of adverse events but does have

a significant effect on the likelihood of voriconazole discontinuation and a therapeutic response is more frequent in patients undergoing TDM.[45] In contrast, a meta-analysis reported that patients with therapeutic concentrations were twice as likely to respond to treatment, and those with supratherapeutic concentrations were four times as likely to experience toxicity.[46]

Posaconazole

Posaconazole was initially available only as an oral suspension and although effective in both the prophylactic and treatment setting for other mycoses,[47] adequate absorption was a significant problem.[48] An intravenous formulation and a delayed release oral tablet formulation have since been developed, and these offer substantial improvements with significantly higher serum levels observed in patients following a transition from the suspension to the tablet formulation.[49] Bioavailability of the new tablet is not affected by food or gastric acid, but the oral suspension requires a fed state to maximize bioavailability. Posaconazole penetrates most sites well, although similar to itraconazole CSF levels are generally not observed. Clinical experience with posaconazole in the treatment of CNS coccidioidomycosis is limited, although success has been reported.[31] The half-life of posaconazole is ~27 hours and allows for once daily dosing with the intravenous or tablet formulation. The suspension formulation requires more frequent dosing due to decreased bioavailability. The difference in dosing between the oral suspension formulation, and the tablet formulation has led to significant medication errors and has prompted warning letters from both US and European regulatory agencies. The majority of the drug is eliminated via the fecal route unchanged (77%). Urine concentrations are negligible.

Adverse effects from posaconazole are primarily gastrointestinal with nausea, vomiting, and diarrhea relatively common. Hypokalemia, hypertension, and peripheral edema have also been described, and the mechanism of 11β-hydroxysteroid dehydrogenase inhibition by posaconazole has been demonstrated, although in select cases 11β-hydroxlase may also be involved.[50] Hepatotoxicity and cardiac toxicity due to prolongation of the QTc interval have also been described. The IV formulation of posaconazole contains a cyclodextrin vehicle, and in the setting of renal dysfunction this solubilizing agent may accumulate. Posaconazole undergoes hepatic metabolism via glucuronidation and also has the capacity for drug-drug interactions through inhibition of cytochrome P450 (CYP450) 3A4 isoenzymes.[51]

Therapeutic drug monitoring of posaconazole concentrations is recommended in most current IDSA guidelines. The tablet formulation has significantly improved drug exposure and in other mycoses this has correlated with efficacy; however, toxicity may also be associated with high drug concentrations and additionally serves as a means to ensure patient compliance.[52]

Posaconazole has consistently been found to be the most active azole in animal models of infection.[53,54] The ability to sterilize tissues in these models has been shown to be superior to itraconazole and has not been duplicated with any of the other currently available azole compounds. While posaconazole has been shown to be effective in refractory cases of coccidioidomycosis, no consistent clinical benefit over other triazoles has been demonstrated.[55–58] Unfortunately, there are currently no plans to for the large clinical trial that would be required to prove the advantage of posaconazole seen in animal models is clinically relevant when compared to the more widely accepted and considerably less expensive fluconazole and itraconazole.

Isavuconazole

Isavuconazonium sulfate (referred to in this paper as isavuconazole) is a prodrug cleaved by plasma esterases into the active isavuconazole moiety. Available in both an oral and IV formulation, the intravenous formulation does not contain cyclodextrin. Loading doses are required over the initial 48 hours of therapy. Isavuconazole has a prolonged half-life (~130 hours), which allows once-daily dosing when the drug reaches steady state and has a large volume of distribution (450 L). Oral capsules are well absorbed with a bioavailability of ~98% that is unchanged by food intake. Isavuconazole is widely distributed though body tissues and has demonstrated efficacy against a number of mycoses in severely immunocompromised patient populations.[59–61] Data in coccidioidomycosis are limited to a case series of patients with primary disease[62]; however, animal and human studies have demonstrated efficacy for CNS infections caused by other mycoses,[63] and a single patient receiving isavuconazole salvage therapy for coccidioidal meningitis did exhibit a successful response.

The most commonly observed adverse effects are nausea, vomiting, diarrhea, headache elevated transaminases, and hypokalemia, although overall drug-related side effects with isavuconazole are less frequent than in those receiving voriconazole.[64] In contrast to the other triazoles, isavuconazole is associated with QTc shortening although the clinical significance of this remains unclear, it may be useful in patients receiving multiple other QTc prolonging medications.

Significant interactions with drugs metabolized by cytochrome P450 occur, especially with substrates and inducers of the CYP3A4 enzyme although preclinical studies and limited clinical data suggest these drug interactions are less severe than with other triazole agents.

Further studies are needed to clarify whether elevated isavuconazole levels are associated with toxicity and whether TDM is helpful with either the oral or IV formulation. No definitive recommendation has been for or against isavuconazole TDM and clinical experience continues to accumulate.

Polyenes

The primary antifungal mechanism of amphotericin B has historically been considered due to the formation of ion channels in the

fungal cell membrane. Recent evidence suggests amphotericin B actually forms large extramembranous aggregates that extract ergosterol from lipid bilayers resulting in cell death.[65] Similarly, (off-target) binding to cholesterol in mammalian cell membranes results in end-organ dysfunction and the high rate of adverse events observed with polyene administration.

Amphotericin B is not absorbed orally and is currently available in multiple IV formulations each with different pharmacokinetics and different but overlapping toxicity profiles: amphotericin B deoxycholate (AmBd), liposomal amphotericin B (L-AMB), amphotericin B colloidal dispersion (ABCD), and amphotericin B lipid complex (ABLC).

Amphotericin B is highly protein bound (95%) before distribution primarily into the reticuloendothelial tissue and kidney. Drug elimination is biphasic with a terminal half-life for AmB deoxycholate of up to 15 days, and the primary route of elimination is not known. Serum levels are not influenced by hepatic or renal dysfunction and it is poorly dialyzed

Nephrotoxicity is common and occurs with all formulations; however, the lipid formulations exhibit a much lower frequency of nephrotoxicity than AmBd. Direct vasoconstriction of the renal afferent arterioles has been demonstrated and is the primary mechanism of AmB induced nephrotoxicity.[66] Hypokalemia due to urinary potassium wasting, hypomagnesemia, metabolic acidosis secondary to renal tubular acidosis (type 1), and polyuria due to nephrogenic diabetes insipidus have each been described with amphotericin B administration and are presumed secondary to the membrane altering properties of AmB formulations.[67,68] Infusion reactions of phlebitis, fever and chills have been described with each formulation. The infusion related reaction of dyspnea, chest and back pain, and hypoxia is primarily seen with L-AMB.[69] Hepatotoxicity has been observed with AmB formulations as well with mild bilirubin and/or alkaline phosphatase elevation those most frequently observed. Anemia also can be seen and is secondary to AmB-mediated suppression of erythropoietin production.[70]

Prior to the development of triazole antifungals, amphotericin B deoxycholate was the primary agent in the treatment of severe or disseminated coccidioidomycosis.[71] Following the availability of the less toxic triazoles, amphotericin B formulations have been largely relegated to patients intolerant or refractory to other agents. For those with severe infections the lipid-based formulations are likely a superior option to amphotericin B deoxycholate given their lower incidence of nephrotoxicity.[72] The lipid formulations have demonstrated efficacy in numerous animal models of coccidioidal infection,[73–76] and although clinical reports are limited, over a decade of experience has demonstrated efficacy against most forms of coccidioidomycosis.

Despite its utility in other fungal meningitides, amphotericin B deoxycholate has no role in the treatment of coccidioidal meningitis when given intravenously[77] but has been a useful agent when given via the intrathecal route. Intrathecal therapy requires significant provider expertise to both mitigate and recognize the complications of therapy.[78,79] Reports of successful use of L-AMB have been presented and found efficacious in the treatment of coccidioidal meningitis refractory to triazoles[77]; however, this remains a salvage option until further data is presented.

Combination therapy

The rationale for combination therapy is to maximize treatment by targeting multiple targets or metabolic pathways, or different points in the same pathway, to improve efficacy by an additive or synergistic effect. Antifungal drug combinations have been evaluated *in vitro* and in animal models in a number of prior studies for other mycoses with variable results. Combination therapy is the current standard of care for cryptococcal meningitis,[80] a benefit has been suggested in subgroups treated for invasive aspergillosis[81] and candidemia.[82] There are no comparative trials evaluating combination treatment to guide therapeutic decision making in the care of human coccidioidomycosis, however animal models have suggested a potential benefit for combination therapy.[83] Although echinocandins have highly variable in vitro activity and should not be used as monotherapy in the treatment of coccidioidomycosis, a murine model of infection evaluating mice treated with caspofungin plus amphotericin B deoxycholate was found to have lower colony forming units (cfu) per gram of tissue than groups receiving either agent as monotherapy. Clinical reports describing the utility of combination therapy are limited and consist of retrospective studies.[77,84–86] No evidence of antagonism was described in these publications, and a potential benefit was described in the majority of the patients studied.

Novel agents in preclinical development

The morbidity of coccidioidomycosis remains significant and even in patients with uncomplicated primary pulmonary infection symptoms last for weeks to months.[5] It is unclear if symptoms are secondary to ongoing and uncontrolled subclinical fungal infection or if these phenomenon are immunologic in nature. The development of effective and potentially nontoxic fungicidal therapy would be a welcome advance in the treatment of coccidioidomycosis, and fortunately numerous agents are in development with novel mechanisms of action, reduced toxicity, and/or a low likelihood of significant drug-drug interactions. New formulations of amphotericin B, including orally administered nanoparticle and cochleate formulations, are currently under development and hold promise for further reductions in nephrotoxicity and other adverse effects.[87] A new itraconazole formulation (SUBA-itraconazole) is also under development and has enhanced oral absorption compared to the liquid or capsule forms.[88] Novel glucan synthase inhibitors that may be used in combination (rezafungin and SCY-078) are also in preclinical development.[89] Nikkomycin Z, a chitinase inhibitor, has demonstrated potent activity in animal models of

coccidioidomycosis and is nearing phase 2 clinical trials. Agents in early development include: APX001 (a GPI-anchor inhibitor), T2307 (a fungal mitochondrial inhibitor), MGCD290 (a histone deacetylase inhibitor), geldanamycin (heat shock protein 90 inhibitor), F901318 (dihydroorotate inhibitor), and ASP2397 (unknown mechanism).[90] Other agents with existing indications for noninfectious conditions have been identified in screening assays to have activity against fungal pathogens (sertraline, auranofin, etc.) and are currently under investigation for potential activity against *Coccidioides* spp.,[91,92] and it is likely agents with ability to manipulate the immunologic response, repurposed from current cancer immunotherapy, will also be proven to have a role in the treatment of severe fungal infections.

Significant developments in antifungal therapy have been brought forth over the past decade. The majority of these new agents have offered pharmacokinetic/pharmacodynamic improvements over prior agents, have reduced toxicity or have fewer predicted drug-drug interactions. Despite these improvements, further advancements are urgently needed, and cost considerations for what is in many cases a chronic disease must be considered. A number of new agents are currently in clinical trials and are likely to have a future role in the treatment of coccidioidomycosis. These agents will need to be evaluated in comparative trials to properly identify their role in treatment and to definitively ascertain the benefits of each agent.

Acknowledgments

We wish to recognize the Burden Family Valley Fever Fund in support of this manuscript.

Declaration of interest

G.R.T. has received research support from Astellas, Cidara, Mayne, Merck, Scynexis, and served as a consultant for Amplyx, Astellas, Mayne, Merck, and Vical. J.S.L. has served as a consultant for Astellas and Merck. D.N. has no conflicts of interest. T.F.P. has served as a consultant for Astellas, Basilea, Gilead, Merck, Pfizer, Scynexis, and Toyama. The authors alone are responsible for the content and the writing of the paper.

References

1. Galgiani JN, Ampel NM, Blair JE et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016; 63: e112–146.
2. Brown J, Benedict K, Park BJ, Thompson GR, 3rd. Coccidioidomycosis: epidemiology. *Clin Epidemiol*. 2013; 5: 185–197.
3. Engelthaler DM, Roe CC, Hepp CM et al. Local population structure and patterns of Western hemisphere dispersal for *Coccidioides* spp., the fungal cause of Valley fever. *MBio*. 2016; 7: e00550–16.
4. Stockamp NW, Thompson GR, 3rd. Coccidioidomycosis. *Infect Dis Clin North Am*. 2016; 30: 229–246.
5. Blair JE, Chang YH, Cheng MR et al. Characteristics of patients with mild to moderate primary pulmonary coccidioidomycosis. *Emerg Infect Dis*. 2014; 20: 983–990.
6. Ampel NM, Giblin A, Mourani JP, Galgiani JN. Factors and outcomes associated with the decision to treat primary pulmonary coccidioidomycosis. *Clin Infect Dis*. 2009; 48: 172–178.
7. Thompson GR, 3rd, Lunetta JM, Johnson SM et al. Early treatment with fluconazole may abrogate the development of IgG antibodies in coccidioidomycosis. *Clin Infect Dis*. 2011; 53: e20–24.
8. Dickson EC, Gifford MA. Coccidioides infection (coccidioidomycosis). ii. the primary type of infection. *Arch Intern Med*. 1938; 62: 853–871.
9. van den Bossche H, Willemsens G, Cools W, Lauwers WF, Le Jeune L. Biochemical effects of miconazole on fungi. II. inhibition of ergosterol biosynthesis in *Candida albicans*. *Chem Biol Interact*. 1978; 21: 59–78.
10. Thompson GR, 3rd, Cadena J, Patterson TF. Overview of antifungal agents. *Clin Chest Med*. 2009; 30: 203–215, v.
11. Dodds Ashley ES LR, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. *Clin Infect Dis*. 2006; 43: S28–39.
12. Arndt CA, Walsh TJ, McCully CL et al. Fluconazole penetration into cerebrospinal fluid: implications for treating fungal infections of the central nervous system. *J Infect Dis*. 1988; 157: 178–180.
13. Thompson GR, 3rd, Barker BM, Wiederhold NP. Large-scale evaluation of in vitro amphotericin B, triazole, and echinocandin activity against *Coccidioides* species from US institutions. *Antimicrob Agents Chemother*. 2017; 61: e02634–16.
14. Clemons KV, Hanson LH, Perlman AM, Stevens DA. Efficacy of SCH39304 and fluconazole in a murine model of disseminated coccidioidomycosis. *Antimicrob Agents Chemother*. 1990; 34: 928–930.
15. Galgiani JN, Catanzaro A, Cloud GA 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: 676–686.
16. Pappas PG, Kauffman CA, Perfect J et al. Alopecia associated with fluconazole therapy. *Ann Intern Med*. 1995; 123: 354–357.
17. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. *Antimicrob Agents Chemother*. 2009; 53: 24–34.
18. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NAIAD Mycoses Study Group. *Am J Med*. 1990; 89: 282–290.
19. Barone JA, Moskovitz BL, Guarnieri J et al. Enhanced bioavailability of itraconazole in hydroxypropyl-beta-cyclodextrin solution versus capsules in healthy volunteers. *Antimicrob Agents Chemother*. 1998; 42: 1862–1865.
20. Zhu ES, Thompson GR, Kreulen C, Giza E. Amphotericin B-impregnated bone cement to treat refractory coccidioidal osteomyelitis. *Antimicrob Agents Chemother*. 2013; 57: 6341–6343.
21. Kamberi P, Sobel RA, Clemons KV et al. Comparison of itraconazole and fluconazole treatments in a murine model of coccidioidal meningitis. *Antimicrob Agents Chemother*. 2007; 51: 998–1003.
22. Sorensen KN, Sobel RA, Clemons KV et al. Comparison of fluconazole and itraconazole in a rabbit model of coccidioidal meningitis. *Antimicrob Agents Chemother*. 2000; 44: 1512–1517.
23. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med*. 1990; 112: 108–112.
24. Sharkey PK, Rinaldi MG, Dunn JF et al. High-dose itraconazole in the treatment of severe mycoses. *Antimicrob Agents Chemother*. 1991; 35: 707–713.
25. Itraconazole [package insert]. (Sempera) product monograph. Janssen-Cilag GmbH N, Germany, 2003.
26. Backman JT, Kivisto KT, Olkkola KT, Neuvonen PJ. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol*. 1998; 54: 53–58.
27. Moon SM, Park HY, Jeong BH et al. Effect of rifampin and rifabutin on serum itraconazole levels in patients with chronic pulmonary aspergillosis and coexisting nontuberculous mycobacterial infection. *Antimicrob Agents Chemother*. 2015; 59: 663–665.
28. Lestner JM, Roberts SA, Moore CB et al. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. *Clin Infect Dis*. 2009; 49: 928–930.
29. Hostetler JS, Heykants J, Clemons KV et al. Discrepancies in bioassay and chromatography determinations explained by metabolism of itraconazole to hydroxyitraconazole: studies of interpatient variations in concentrations. *Antimicrob Agents Chemother*. 1993; 37: 2224–2227.
30. Law D, Moore CB, Denning DW. Bioassay for serum itraconazole concentrations using hydroxyitraconazole standards. *Antimicrob Agents Chemother*. 1994; 38: 1561–1516.

31. Kim MM, Vikram HR, Kusne S, Seville MT, Blair JE. Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. *Clin Infect Dis*. 2011; 53: 1060–1066.
32. Freifeld A, Proia L, Andes D et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. 2009; 53: 1648–1651.
33. Kim SH, Kwon JC, Park C et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether beta-cyclodextrin in haematological patients with renal impairment. *Mycoses*. 2016; 59: 644–651.
34. Johnson RH, Einstein HE. Coccidioidal meningitis. *Clin Infect Dis*. 2006; 42: 103–107.
35. Kinoshita J, Iwata N, Ohba M, Kimotsuki T, Yasuda M. Mechanism of voriconazole-induced transient visual disturbance: reversible dysfunction of retinal ON-bipolar cells in monkeys. *Invest Ophthalmol Vis Sci*. 2011; 52: 5058–5063.
36. Voriconazole package insert. Available at: http://www.pfizer.com/files/products/uspi_vfend.pdf. Accessed Dec 7.
37. Pascual A, Calandra T, Bolay S et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis*. 2008; 46: 201–211.
38. Epaulard O, Villier C, Ravaud P et al. A multistep voriconazole-related phototoxic pathway may lead to skin carcinoma: results from a French nationwide study. *Clin Infect Dis*. 2013; 57: e182–188.
39. Haylett AK, Felton S, Denning DW, Rhodes LE. Voriconazole-induced photosensitivity: photobiological assessment of a case series of 12 patients. *Br J Dermatol*. 2013; 168: 179–185.
40. Malani AN, Kerr L, Obear J, Singal B, Kauffman CA. Alopecia and nail changes associated with voriconazole therapy. *Clin Infect Dis*. 2014; 59: e61–65.
41. Thompson GR, 3rd, Bays D, Cohen SH, Pappagianis D. Fluoride excess in coccidioidomycosis patients receiving long-term antifungal therapy: an assessment of currently available triazoles. *Antimicrob Agents Chemother*. 2012; 56: 563–564.
42. Wermers RA, Cooper K, Razonable RR et al. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. *Clin Infect Dis*. 2011; 52: 604–611.
43. Gerber B, Guggenberger R, Fasler D et al. Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole. *Blood*. 2012; 120: 2390–2394.
44. Trifilio S, Pennick G, Pi J et al. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. *Cancer*. 2007; 109: 1532–1535.
45. Park WB, Kim NH, Kim KH et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis*. 2012; 55: 1080–1087.
46. Luong ML, Al-Dabbagh M, Groll AH et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *J Antimicrob Chemother*. 2016; 71: 1786–1799.
47. Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; 356: 348–359.
48. Thompson GR, 3rd, Rinaldi MG, Pennick G et al. Posaconazole therapeutic drug monitoring: a reference laboratory experience. *Antimicrob Agents Chemother*. 2009; 53: 2223–2224.
49. Pham AN, Bubalo JS, Lewis JS, 2nd. Comparison of posaconazole serum concentrations from haematological cancer patients on posaconazole tablet and oral suspension for treatment and prevention of invasive fungal infections. *Mycoses*. 2016; 59: 226–233.
50. Thompson GR, 3rd, Chang D, Wittenberg RR, McHardy I, Semrad A. In vivo 11beta-hydroxysteroid dehydrogenase inhibition in posaconazole-induced hypertension and hypokalemia. *Antimicrob Agents Chemother*. 2017; 61: e00760–17.
51. Sanchez-Ortega I, Vazquez L, Montes C et al. Effect of posaconazole on cyclosporine blood levels and dose adjustment in allogeneic blood and marrow transplant recipients. *Antimicrob Agents Chemother*. 2012; 56: 6422–6424.
52. Patterson TF, Thompson GR, 3rd, Denning DW et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 63: e1–e60.
53. Lutz JE, Clemons KV, Aristizabal BH, Stevens DA. Activity of the triazole SCH 56592 against disseminated murine coccidioidomycosis. *Antimicrob Agents Chemother*. 1997; 41: 1558–1561.
54. Gonzalez GM, Tijerina R, Najvar LK et al. In vitro and in vivo activities of posaconazole against Coccidioides immitis. *Antimicrob Agents Chemother*. 2002; 46: 1352–1356.
55. Stevens DA, Rendon A, Gaona-Flores V et al. Posaconazole therapy for chronic refractory coccidioidomycosis. *Chest*. 2007; 132: 952–958.
56. Catanzaro A, Cloud GA, Stevens DA et al. Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. *Clin Infect Dis*. 2007; 45: 562–568.
57. Anstead GM, Corcoran G, Lewis J, Berg D, Graybill JR. Refractory coccidioidomycosis treated with posaconazole. *Clin Infect Dis*. 2005; 40: 1770–1776.
58. Vo E, Jolliff J, Heidari A, Johnson R. *Evaluation of posaconazole in the treatment of severe coccidioidomycosis*. IDWeek 2015. San Diego, CA. Poster no. 266.
59. Marty FM, Ostrosky-Zeichner L, Cornely OA et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis*. 2016; 16: 828–837.
60. Donnelley MA, Zhu ES, Thompson GR, 3rd. Isavuconazole in the treatment of invasive aspergillosis and mucormycosis infections. *Infect Drug Resist*. 2016; 9: 79–86.
61. Maertens JA, Raad, II, Marr KA et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016; 387: 760–769.
62. Thompson GR, 3rd, Rendon A, Ribeiro Dos Santos R et al. Isavuconazole Treatment of Cryptococcosis and Dimorphic Mycoses. *Clin Infect Dis*. 2016; 63: 356–362.
63. Wiederhold NP, Kovanda L, Najvar LK et al. Isavuconazole is effective for the treatment of experimental cryptococcal meningitis. *Antimicrob Agents Chemother*. 2016; 60: 5600–5603.
64. Maertens JA, Raad, II, Marr KA et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2015; 387: 760–769.
65. Anderson TM, Clay MC, Cioffi AG et al. Amphotericin forms an extramembranous and fungicidal sterol sponge. *Nat Chem Biol*. 2014; 10: 400–406.
66. Sawaya BP, Weihprecht H, Campbell WR et al. Direct vasoconstriction as a possible cause for amphotericin B-induced nephrotoxicity in rats. *J Clin Invest*. 1991; 87: 2097–2107.
67. Sawaya BP, Briggs JP, Schnermann J. Amphotericin B nephrotoxicity: the adverse consequences of altered membrane properties. *J Am Soc Nephrol*. 1995; 6: 154–164.
68. Metzger NL, Varney Gill KL. Nephrogenic diabetes insipidus induced by two amphotericin B liposomal formulations. *Pharmacotherapy*. 2009; 29: 613–620.
69. Roden MM, Nelson LD, Knudsen TA et al. Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. *Clin Infect Dis*. 2003; 36: 1213–1220.
70. Yeo EJ, Ryu JH, Cho YS et al. Amphotericin B blunts erythropoietin response to hypoxia by reinforcing FIH-mediated repression of HIF-1. *Blood*. 2006; 107: 916–923.
71. Twarog M, Thompson GR, 3rd. Coccidioidomycosis: recent updates. *Semin Respir Crit Care Med*. 2015; 36: 746–755.
72. Mistro S, Maciel Ide M, de Menezes RG et al. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis. *Clin Infect Dis*. 2012; 54: 1774–1777.
73. Clemons KV, Capilla J, Sobel RA et al. Comparative efficacies of lipid-complexed amphotericin B and liposomal amphotericin B against coccidioidal meningitis in rabbits. *Antimicrob Agents Chemother*. 2009; 53: 1858–1862.
74. Clemons KV, Sobel RA, Williams PL, Pappagianis D, Stevens DA. Efficacy of intravenous liposomal amphotericin B (AmBisome) against coccidioidal meningitis in rabbits. *Antimicrob Agents Chemother*. 2002; 46: 2420–2426.
75. Albert MM, Adams K, Luther MJ, Sun SH, Graybill JR. Efficacy of AmBisome in murine coccidioidomycosis. *J Med Vet Mycol*. 1994; 32: 467–471.
76. Gonzalez GM, Tijerina R, Najvar LK et al. Efficacies of amphotericin B (AMB) lipid complex, AMB colloidal dispersion, liposomal AMB, and conventional

AMB in treatment of murine coccidioidomycosis. *Antimicrob Agents Chemother* 2004; 48: 2140–2143.
77. Mathisen G, Shelub A, Truong J, Wigen C. Coccidioidal meningitis: clinical presentation and management in the fluconazole era. *Medicine (Baltimore)*. 2010; 89: 251–284.
78. Stevens DA, Shatsky SA. Intrathecal amphotericin in the management of coccidioidal meningitis. *Semin Respir Infect*. 2001; 16: 263–269.
79. Hodge G, Cohen SH, Thompson GR, 3rd. In vitro interactions between amphotericin B and hydrocortisone: potential implications for intrathecal therapy. *Med Mycol*. 2015; 53: 749–753.
80. Day JN, Chau TTH, Wolbers M et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. 2013; 368: 1291–1302.
81. Marr KA, Schlamm HT, Herbrecht R et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med*. 2015; 162: 81–89.
82. Rex JH, Pappas PG, Karchmer AW et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clin Infect Dis*. 2003; 36: 1221–1228.
83. Gonzalez GM, Gonzalez G, Najvar LK, Graybill JR. Therapeutic efficacy of caspofungin alone and in combination with amphotericin B deoxycholate for coccidioidomycosis in a mouse model. *J Antimicrob Chemother*. 2007; 60: 1341–1346.
84. Glenn TJ, Blair JE, Adams RH. Coccidioidomycosis in hematopoietic stem cell transplant recipients. *Med Mycol*. 2005; 43: 705–710.
85. McCarty JM, Demetral LC, Dabrowski L et al. Pediatric coccidioidomycosis in central California: a retrospective case series. *Clin Infect Dis*. 2013; 56: 1579–1585.
86. Levy ER, McCarty JM, Shane AL, Weintrub PS. Treatment of pediatric refractory coccidioidomycosis with combination voriconazole and caspofungin: a retrospective case series. *Clin Infect Dis*. 2013; 56: 1573–1578.
87. Seyedmousavi S, Rafati H, Ilkit M et al. Systemic Antifungal Agents: Current Status and Projected Future Developments. *Methods Mol Biol*. 2017; 1508: 107–139.
88. Lindsay J, Sandaradura I, Wong K et al. Serum levels, safety and tolerability of new formulation SUBA-itraconazole prophylaxis in patients with haematological malignancy or undergoing allogeneic stem cell transplantation. *J Antimicrob Chemother*. 2017; 72: 3414–3419.
89. Wiederhold NP. Antifungal resistance: current trends and future strategies to combat. *Infect Drug Resist*. 2017; 10: 249–259.
90. Osherov N, Kontoyiannis DP. The anti-*Aspergillus* drug pipeline: is the glass half full or empty? *Med Mycol*. 2017; 55: 118–124.
91. Wiederhold NP, Patterson TF, Srinivasan A et al. Repurposing auranofin as an antifungal: in vitro activity against a variety of medically important fungi. *Virulence*. 2017; 8: 138–142.
92. Valentine M, Chow D, Driebe E et al. Establishing a low-cost, high-throughput screening assay for compounds efficacious against the fungus *Coccidioides*, the causative agent of Valley fever. *Proceedings of the 58th Annual Coccidioidomycosis Study Group Meeting* 2014.