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REVIEW

Salvage Treatment for Invasive Aspergillosis and Mucormycosis: Challenges, Recommendations and Future Considerations

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Abstract: Invasive mold diseases are devastating systemic infections which demand meticulous care in selection, dosing, and therapy monitoring of antifungal drugs. Various circumstances regarding PK/PD properties of the applied drug, resistance/tolerance of the causative pathogen or host intolerability can lead to failure of the initial antifungal therapy. This necessitates treatment adaption in the sense of switching antifungal drug class or potentially adding another drug for a combination therapy approach. In the current state of drastically limited options of antifungal drug classes adaption of therapy remains challenging. Current guidelines provide restricted recommendations only and emphasize individual approaches. However, novel antifungals, incorporating innovative mechanisms of action, show promising results in late stage clinical development. These will expand options for salvage therapy in the future potentially as monotherapy or in combination with conventional or other novel antifungals. We outline current recommendations for salvage therapy including PK/PD considerations as well as elucidate possible future treatment options for invasive aspergillosis and mucormycosis.

Keywords: invasive fungal infections, aspergillosis, mucormycosis, salvage therapy

Introduction

Invasive mold infections (IMIs) remain associated with high morbidity and mortality.[1–4] Invasive aspergillosis (IA) and mucormycosis are the two most common IMIs in humans and, even when treated appropriately, associated with mortality rates of 30% and above.[5–10] Failure of first line treatment, which consists of antifungal treatment and often – especially in the case of mucormycosis – also of surgical debridement,[2,6,11] may occur due to (i) absence of clinical response resulting in refractory or breakthrough fungal infection,[12–14] (ii) intolerance/adverse events to first line antifungals,[15] or (iii) insufficient antifungal plasma levels[16–18] remaining below defined thresholds for clinical efficacy.[19–21] As a consequence, failure of first line antifungal treatment necessitating salvage treatment is quite common. Salvage therapy refers to the treatment of infected individuals who are refractory or intolerant to initial therapy administered for at least 7 days. General recommendations include a change in antifungal drug class.[22] However, the current reality of only three available drug classes, in association with intrinsic and acquired resistance complicating treatment of IMIs, renders this approach difficult to implement. Another challenge that we are currently facing is the lack of synergism between most of the available antifungals,[23] contributing to the uncertainties that surround the role of antifungal combination therapy (Table 1).

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Table 1 Antifungal Combination Therapy for Mucormycosis in Mice

Treatment	Model	Effect on Fungal Burden Reduction (Compared to Placebo)	Survival Rate (21-Day)	Ref.
LAmB (5 mg/kg/day) + micafungin or caspofungin (1 mg/kg/day)	Neutropenic mice infected by *Rhizopus oryzae*	< 1 log (kidneys)	< 80%	[60]
LAmB + isavuconazole	Neutropenic mice infected with *Rhizopus delemar* and *Mucor circinelloides*	2.0–3.5 log (lungs and brain)	> 80%	[97]
LAmB (10 mg/kg) + fosmanogepix (78 mg/kg)	Immunosupressed mice infected with *R. arrhizus* var. *delemar*	2-log (lungs and brain)	70%	[87]

Abbreviation: LAmB, liposomal amphotericin-B.

Nevertheless, hope is on the horizon, with a number of new antifungals, often the first compound of entirely new antifungal classes, currently in late stage clinical development.[24] These drugs may change the landscape of salvage therapy for both IA and mucormycosis. Here we review current salvage treatment recommendations, including their pharmacokinetic (PK) and pharmacodynamic (PD) properties, and give an outlook on how antifungal salvage treatment of IA and mucormycosis could present in the future.

PK/PD Considerations

PK properties of agents utilized for salvage therapy of IA and mucormycosis are summarized in Table 2. Azole antifungals inhibit the fungal lanosterol 14-α-demethylase. As mold active azoles are generally strong CYP3A4 inhibitor

Table 2 Overview on Pharmacokinetics of Current Salvage Treatment for Invasive Aspergillosis and Mucormycosis

Fungal Disease	Liposomal Amphotericin B, i.v.	Posaconazole, Per os (tbl.)[$]	Posaconazole, i.v.	Isavuconazole, i.v. or per os	Caspofungin, Intravenous i.v.
	IA, MM	IA, MM	IA, MM	IA, MM	IA in Combination
Standard dose in Adults*	3–4 (5) mg/kg (IA) and 5–10 mg/kg (MM) once daily I.V.	Loading dose, 300 mg b.i.d. on day 1, Maintenance dose 300 mg once daily	Loading dose, 300 mg b.i.d. on day 1, Maintenance dose 300 mg once daily	Loading dose, 200 mg t.i.d. on day 1 and day 2, Maintenance dose 200 mg once daily	Loading dose 70, maintenance dose 50 (70 if body weight > 80 kg)
C_{max} [µg/mL]	14–29 (90)	2	2.6	2.6	10
V_d [L/kg]	0.05–2.2	5	3.7	~6.5	0.3–2.0
Protein binding [%]	95–99 (of amphotericin B, liberated from lipid-encapsulation)	98–99	98–99	98–99	92.4–96.5
$t_{1/2}$[h]	13–24	35	27	80–120	8
CL [mL/h/kg]	1–23	130	100	~30–70	~10

(*Continued*)

Table 2 (Continued).

Fungal Disease	Liposomal Amphotericin B, i.v.	Posaconazole, Per os (tbl.)[$]	Posaconazole, i. v.	Isavuconazole, i.v. or per os	Caspofungin, Intravenous i.v.
	IA, MM	**IA, MM**	**IA, MM**	**IA, MM**	**IA in Combination**
Metabolism and Elimination	Bile, RES long-term disposition, final elimination not yet clear; no metabolism	Metabolisms involving CYP3A4, P-gp substrate		Hepatic metabolism involving UGT, and CYP3A4	Independent from cytochrome, P-450 (CYP)
Renal impairment	No dose adjustment, consider nephrotoxicity	No dose adjustment	Avoid because of SBECD accumulation, When GFR < 50 mL/min	No dose adjustment	Standard dose
Hepatic impairment	No dose adjustment, consider hepatotoxicity	No dose adjustment	No dose adjustment	Mild to moderate, enhanced levels, no dose reduction recommended by the manufacturer	Enhanced exposure in moderate hepatic impairment, dose reduction
Remark	T_{inf} ≥ 4 h recommended	Strong inhibitor of CYP3A4 causing numerous drug-drug interactions	Strong inhibitor of CYP3A4 causing numerous drug-drug interactions	Inhibitor of CYP3A4, P-gp and BCRP	Dose reduction in critically with liver dysfunction may cause underexposure; insufficient efficacy in first-line treatment, limited data for salvage treatment of IA
PK/PD target	C_{max}/MIC	AUC_{0-24h}/MIC	AUC_{0-24h}/MIC	AUC_{0-24h}/MIC	AUC_{0-24h}/MIC or C_{max}/MIC

Notes: *Dosages in pediatric patients are displayed elsewhere {Downes, 2020 #4940}. [$]Posaconazole suspension differs from tablet formulation. For suspension: dosing 4x200mg, intake with fatty meals. Variable oral bioavailability.

Abbreviations: Cmax, peak level; AUC, area under the concentration time curve; Vd, apparent volume of distribution; $t_{1/2}$, half-life; CL, clearance; CYP, cytochrome P 450; SBECD, sulfobutylether-β-cyclodextrin; GFR, glomerular filtration rate; TDM, therapeutic drug monitoring; AUC_{0-24h}, area under the concentration-time curve over 24 hours; MIC, minimal inhibitory concentration; i.v., intravenous; tbl., tablet; CYP, cytochrome P 450; UGT, uridine diphosphate glucuronosyltransferase, P-gp, P glycoprotein, BCRP, breast cancer related protein.

numerous drug-drug interactions must be considered.[25,26] Amphotericin-B is fungicidal to most *Aspergillus* species by interacting with ergosterol in the fungal cellular membrane causing leakage of substrates. Additional mechanisms are lipid peroxidation and inhibition of the fungal proton-ATPase.[27] The conventional deoxycholate formulation of amphotericin B causes renal damage and infusion-related adverse effects such as nausea, chill, fever and hypokalaemia in almost half of the patients. Amphotericin is a concentration-dependent antimicrobial, but the conventional formulation requires infusion over at least four hours for limiting adverse effects. Amphotericin B deoxycholate has been administered at doses of 0.6–1.0 mg/kg. Because of its poor tolerability its use can be justified only in settings with highly limited resources.[28] Lipid formulation of amphotericin B are less toxic than the conventional deoxycholate formulation. The mechanisms underlying this improved safety are not yet fully elucidated. It had been hypothesized that the active compound is only released following the contact with the fungus. In plasma of patients and of healthy subjects, however, amphotericin B is partially released from lipid-encapsulation. Pharmacokinetics of this liberated amphotericin B fraction resembles that of conventional amphotericin B. Different binding to plasma lipoproteins and rapid uptake by the reticuloendothelial system (RES) were other explanations of the lower toxicity of lipid-formulated amphotericin B.[29,30] Nowadays, liposomal amphotericin B (LAmB) is the only formulation available in most countries which is infused at a daily standard-dose of 3–4 mg/kg, with higher dosages for eg IA of the central nervous system (CNS, up to

10 mg/kg)[31] and for mucormycosis (5 mg/kg).[6] Amphotericin B does not undergo any biotransformation but it is eliminated via urine and bile. LAmB is eliminated from the plasma mainly by cells of the reticular endothelial system with $t_{1/2}$ of 13-24h. Accordingly, no relevant pharmacokinetic drug-drug interactions with amphotericin-B have been identified so far, and no dose adjustment is required for patients with renal impairment.[32] Amphotericin-B accumulates in liver and spleen, while its concentrations are intermediate in lung (lower in pulmonary epithelial lining fluid) and kidney, but low in the brain, cerebrospinal fluid, pleural effusion and in ascites fluid.[33–39] Acquired resistance to amphotericin-B is rare.[29,40,41] For this reasons, amphotericin-B is an important option for salvage therapy of IA. However, there are still some challenges that need to be considered. Despite its improved safety, LAmB treatment has been associated with deterioration of renal function in more than 20%.[42,43] Similiar to other antimicrobials, distribution of the drug in humans may be very variable as it depends on age, fitness, physiological conditions, and underlying diseases eg ketoacidosis and hyperlipidemia as mostly seen in diabetic patients. Studies in different laboratory animals showed that PK of LAmB is linear, however, in tissue they are more complex and depend on the species, organ type, and tissue studied.

Echinocandins are fungistatic to *Aspergillus* by inhibition of the synthesis of ^{1,3}-ß-D-glucan which is an essential constituent of fungal cell walls.[44–46] Three echinocandins are commercially available (ie anidulafungin, caspofungin, micafungin) which are applied once daily by intravenous infusion. Their binding to plasma proteins exceeds 95%. Only caspofungin has been licensed for salvage treatment of IA.[47–49] This is based on an open non-comparative trial of 83 patients who did not respond to standard therapy (LAmB, itraconazole, or voriconazole) or did not tolerate it. A complete response to caspofungin was observed in 5%, a partial response in 40%.[50] Caspofungin is not licensed for first-line treatment of IA because of its unsatisfying efficacy in clinical studies, ie 50% or more of the patients on first-line treatment with caspofungin experienced progression of IA.[51–53] Caspofungin has an elimination half-life of 8–10 h. Importantly, it does not influence the activity of CYP enzymes, but it is a strong inhibitor of breast cancer related protein (BCRP) and a weak P-glycoprotein inhibitor in-vitro.[54] Caspofungin achieves its highest tissue levels in liver, where it persists for weeks, followed by spleen, kidney and lung. Because of its poor CNS penetration, it has no role in treatment of cerebral mycoses.[55] Thus, currently available clinical and pharmacological data do not encourage caspofungin monotherapy for IA neither as first-line nor as salvage treatment. Azole-amphotericin-B combinations are controversial because of the common molecular target.[29] However, a meta-analysis of 16 studies on combinations of echinocandins with mold-active azoles or with LAmB, shows that combination antifungal therapy increases the likelihood of therapeutic response and improves the 12-week survival rate, as compared with monotherapy in a salvage setting of invasive aspergillosis.[56–59] Although echinocandins have minimal activity against *Mucorales* when tested in vitro, the combination of micafungin with LAmB improved survival compared to monotherapy in a murine model.[60]

Posaconazole is a highly lipophilic long-tailed triazole antifungal agent currently available as an oral suspension, a delayed-release tablet, and an intravenous formulation. Delayed release tablets or infusions of posaconazole are the preferred treatment option compared to the less reliable oral suspension.[6] Considering differences between the formulations in frequency of dosing, administration with food and plasma drug concentrations, it is important to note that they should not be used interchangeably. Models suggest intake of the oral solution with a meal due to better absorption and 20% higher plasma concentrations. A fatty meal may increase AUC 0–72 h and C_{max} for 51% and 16%, respectively, compared to application of the drug during fasting.[61] As the absorption of the oral suspension is unreliable its use is discouraged. Unresolved are the observations regarding time-dependent increase of posaconazole plasma concentrations. In up to 11% of elderly patients (> 80 y) a decrease in clearance was observed. Caution is necessary in overweight (> 120 kg) and underweight patients (< 40 kg) as a negative correlation of the clearance and weight was observed.[62] Therapeutic drug monitoring should be performed in order to avoid sub-therapeutic exposure but also (less frequently observed) toxic concentrations. Following oral administration posaconazole has a large mean apparent volume of distribution ranging from 5–25 L/kg.[63] Posaconazole is well distributed in skin, alveolar cells, kidneys, liver, and heart.[62] Current PK evidence regarding CNS distribution, does not support its use for the treatment of fungal CNS infections as the penetration of posaconazole in human CNS was demonstrated to be lower than in murine models of invasive fungal infection.[62,64,65] High lipophilicity suggest low bioavailability of posaconazole in eyes, however in one ex vivo permeation study was shown that micellar formulation may positively affect its efficacy.[66] Posaconazole is a CYP3A4 enzyme inhibitor, hence co-medication with benzodiazepines, venetoclax, vinca alkaloids and other CYP3A4

substrates should be avoided if possible.[67] Posaconazole is metabolized mainly by Phase II enzymes, ie uridine diphosphate glucuronosyltransferase and it also a substrate of P glycoprotein (P-gp). Therefore, administration glucuronide or P-gp inhibitors (eg verapamil, cyclosporin, quinidine, clarithromycin, erythromycin) may result in an increase of posaconazole plasma levels. The inducers of glucuronidation or P-gp on the other hand (eg rifampin, rifabutin, some anticonvulsant drugs) may decrease the plasma concentration of Posaconazole.[63] Repeated dose-toxicity studies showed inhibition of steroid hormone synthesis similar to effects observed for other azoles. Posaconazole should not be used in pregnant women as animal models have suggested reproductive toxicity. PD related data is scarce and there is no clear understanding of PK-PD relation enabling better understanding of the treatment efficacy.[62] However, the ratio AUC_{0-24h} /MIC appears to correlate with therapeutic efficacy.[63] Posaconazole shows primarily fungistatic activity against *Aspergillus* spp.[63] However, the combination of posaconazole and caspofungin resulted in remarkable synergistic efficacy against azole-resistant *Aspergillus* spp.[68] Even though posaconazole showed better in vitro activity than other azoles against many zygomycetes including *Rhizomucor* spp. it is less active than amphotericin B.[63]

Isavuconazole, the most recent azole, shows some significant advantages compared to other azoles, including more predictable PK and a less complicated drug interaction profile.[69] Isavuconazole is cleaved by plasma esterases from isavuconazonium, its water-soluble prodrug. Therefore, no solvent is required for the intravenous formulation.

Studies in healthy subjects have demonstrated that PK of isavuconazole is proportional up to 600 mg per day. In contrast to posaconazole, food intake does not impact the bioavailability of isavuconazole.[70] Due to metabolism involved CYP enzymes, this drug should not be combined with strong CYP3A4/5 inducers (eg rifampicin, rifabutin, carbamazepine, phenytoin and St. John's wort), moderate CYP3A4/5 inducers (eg efavirenz, nafcillin, etravirine) as well as strong CYP3A4/5 inhibitors.

To date, there are no studies conducted in patients with severe hepatic impairment, while dose adjustment is unnecessary in subjects with mild or moderate hepatic impairment.[71] In the subjects with mild, moderate or severe renal impairment no relevant differences in the total C_{max} and AUC of isavuconazole was observed compared to those with normal renal function.[72] The trial designed to assess the efficacy and safety of isavuconazole for the treatment of patients with IA and renal impairment suggested efficacy and no drug-specific safety concerns in those patients.[73] As sufficient antifungal concentrations are crucial for therapeutic response, therapeutic drug monitoring of azoles is highly recommended during salvage therapy, in order to avoid sub-therapeutic or toxic concentrations.

Salvage Treatment for Invasive Aspergillosis

Current Guideline Recommendations

Current and future salvage treatment options for invasive aspergillosis are depicted in Figure 1. Voriconazole or isavuconazole are recommended for first-line treatment of IA.[22] Posaconazole is still licensed for IA in case response to amphotericin-B treatment is absent, although this will likely change soon due to results of a recent clinical trial giving clinicians another first-line option.[74] Future salvage treatment options for IA are depicted in Figure 1. With sparse high-quality evidence, current guidelines provide unsatisfactory recommendations for IA salvage treatment options listing currently available drugs (ie polyenes, azoles, echinocandins) in different rotations.[40,75–77] If a refractory or progressive disease is confirmed, the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID)/ European Confederation of Medical Mycology (ECMM) guidelines both emphasize the importance of microbiological confirmation to lead further therapeutic decisions.[40,77] This corresponds to an escalation in diagnostic methods like bronchoscopy, CT-guided biopsy or video assisted thoracoscopic surgery to enable the confirmation of the causative pathogen, as well as susceptibility testing and ruling out/confirming potential differential diagnosis or co-infections (eg mucormycosis). Importantly, in settings of clinically suspected treatment failure/progression of disease, combination of multiple biomarkers may increase the diagnostic performance, as performance of every single mycological test/biomarker is reduced in the presence of antifungal treatment.[78–82]

The IDSA guideline recommends an individualized approach based on the patient's circumstances and co-morbidities, while also taking local epidemiological data into account, and – most importantly the prior antifungal therapy. Furthermore, a reduction in immunosuppression should be considered when clinically feasible.[40] The ESCMID/

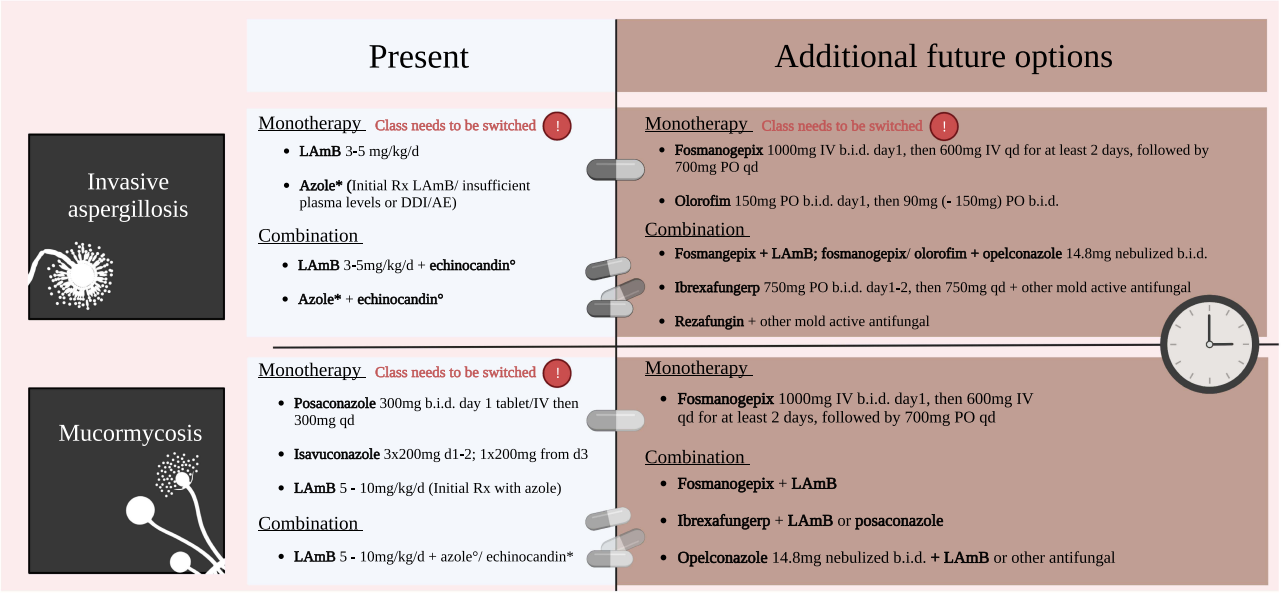

Figure 1 Present salvage therapy recommendations for invasive aspergillosis/ mucormycosis and additional future options. *Voriconazole (4–6mg/kg/d), isavuconazole (3x 200mg d1+2, then 200mg qd), posaconazole (300mg b.i.d. day 1 table/IV then 300mg qd) caspofungin (70mg/d IV day 1 then 50mg/d), micafungin (100mg - 150mg/d), anidulafungin (200mg qd day1 the 100mg qd).
Notes: Created with BioRender.com.
Abbreviations: LAmB, liposomal amphotericin B; Rx, medical prescription; DDI, drug-drug interaction; AE, adverse event; IV, intravenous; b.i.d., twice daily; qd, once daily.

ECMM guideline gives a strong recommendation for voriconazole only, but again emphasizes the need for changing drug class. Moderate recommendations are given for LAmB, posaconazole and caspofungin. Weak recommendations are given for Amphotericin-B lipid complex (ABLC), micafungin and itraconazole with recommendation against itraconazole in case of prior voriconazole therapy.[77] The European Conference on Infections in Leukemia (ECIL)-6 guideline gives BII recommendations for LAmB, ABLC, caspofungin, posaconazole, voriconazole and combination therapy, and a lower recommendation (CIII) for itraconazole.[76]

Importantly, a switch in antifungal class is recommended from the IDSA, as well as the ESCMID/ECMM guideline (eg switch to LAmB in case of established voriconazole therapy).[40,77] In clinical practice, following this recommendation poses huge challenges, especially in light of missing microbiological evidence and susceptibility testing. Given the current data, most patients with IA will assumably receive initial antifungal therapy with a triazole (voriconazole, posaconazole, isavuconazole).[74,75,83] In refractory disease the two viable options are lipid formulations of amphotericin-B or, less established, an echinocandin (always in combination with another *Aspergillus* active antifungal). Both agents are applied intravenously only and the long therapy duration of minimally 6 weeks renders this alternative unpracticable, frequently requiring another switch of antifungal drug class back to an azole or long-term ambulatory parenteral therapy.

To date, no firm conclusions can be drawn whether a specific combination therapy may be beneficial as salvage treatment. This is reflected in the vague recommendations made on combination therapy. ESCMID/ECMM and ECIL-6 guidelines give CIII, BII recommendations, respectively, both stating insufficient evidence to recommend combination- over monotherapy. The IDSA guideline recommends an individualized approach, with potential benefits in some patients.[40,76,77]

Of note, not all antifungals are available in all parts of the world, limiting salvage treatment options in many geographic areas outside Europe and the United States.[84–86]

Future Treatment Options

Availability of only three antifungal drug classes for the treatment of IA is drastically restricting options for salvage therapy and guideline recommended switch of drug class. Especially in settings of difficult to treat IA, a change of drug

class is infeasible. These settings include the presence of drug tolerance/resistance, limiting drug-drug interactions, and/or severe underlying organ dysfunction.

Innovative antifungals in the pipeline not only show significant advantages in PK/PD properties, but also feature new mechanisms of action which will both substantially enhance treatment options for salvage therapy.[24]

Fosmanogepix, a new Gwt1 inhibitor, with broad activity against Aspergillus spp. including azole resistant strains, will likely come into play as an option for monotherapy or combination therapy with intravenous LAmB. This particular combination seems notably encouraging, as synergistic effects with LAmB were observed in a mouse model, leading to reduced lung and brain fungal burden as well as increased survival rates.[87] Further, in a phase II trial including 66 patients with renal insufficiency, administration of fosmanogepix neither resulted in worsening of renal function, nor was a dose adjustment required, outlining the potential safety of adding fosmanogepix to LAmB therapy.[88]

Another representative of a new antifungal drug class is olorofim. The dihydroorotate dehydrogenase inhibitor, which is an enzyme involved in pyrimidine synthesis, shows good activity against various *Aspergillus* spp. including azole-resistant strains and difficult to treat cryptic species.[89] Potential applications for salvage therapy could be administration as monotherapy or in combination with another novel azole.

The oral glucan synthase inhibitor ibrexafungerp has broad antifungal activity including azole-resistant and cryptic *Aspergillus* species.[90] The mechanism of action is similar to echinocandins, yet the binding site slightly differs resulting in low cross-resistance. Its spectrum of activity together with favorable PK/PD properties (ie high tissue penetration, limited drug-drug interactions) render it a valuable option for salvage therapy. Applications could be monotherapy or combination therapy with conventional azoles or LAmB.

An innovative azole called opelconazole, which was particularly designed for inhalation therapy (adapted particle size), could be a most welcome add-on in settings where systemic administration paralleled by toxicity is a limiting factor. Opelconazole shows broad activity against *Aspergillus* spp. and enables high local concentrations while avoiding systemic adverse effects. Synergism has been observed together with systemically administered azoles, commending itself for a combination approach in salvage therapy.[91] The combination with all above mentioned agents could be a feasible option also including the addition of opelconazole as a third acting agent, however, potential synergism/antagonism remains to be evaluated.

Lastly, rezafungin, a second-generation echinocandin with optimized pharmacokinetics (eg mean half-life of ~150h after two dosages), will allow, amongst other options, outpatient salvage therapy in combination with oral agents.[92] These could include combinations with fosmanogepix, olorofim, LAmB or conventional azoles, with data on potential synergistic/antagonistic effects needed.

To summarize, LAmB will remain an essential option for salvage therapy in the future, however, not as monotherapy but most likely in combination with new antifungals. Potential combinations could include the addition of fosmanogepix, ibrexafungerp or opelconazole. Alternatives will include fosmanogepix or olorofim as monotherapy, or combination therapy by echinocandins/ibrexafungerp together with azoles.

Salvage Treatment for Mucormycosis

Current Guideline Recommendations

The preferred initial treatment for mucormycosis is high-dose LAmB. Isavuconazole and posaconazole are strongly recommended for salvage treatment.[6] The rarity and complexity of diagnosing mucormycosis potentially leads to misdiagnoses and LAmB might not always be the initial treatment administered. Hence, all three drugs could be potential options for salvage therapy of mucormycosis.

Current and future salvage treatment options for mucormycosis are depicted in Figure 1. Current guidelines recommend for salvage treatment primarily a change in drug class. Given that LAmB is strongly recommended as first line treatment, isavuconazole[93] or posaconazole [parenteral or tablet formulation[94]] are usually the preferred options for salvage treatment.[6] Salvage antifungal therapy should, however, be adapted to the resistance profile and/or species identification, as some genera such as *Cunninghamella* or *Mucor* may exhibit poor in vitro susceptibility to azoles. In those patients where azoles were used for first line treatment (eg because of compromised renal function), salvage

treatment would consist of LAmB, for which small case series have indicated that it can be safely administered even in patients with renal compromise, justifying its use in such a desperate clinical situation where benefit outweighs the risk.[95,96] Combination treatment is not generally recommended, but sometimes used in the salvage treatment setting, including combinations of isavuconazole/ posaconazole with LAmB.[97,98]

Future Treatment Options

Despite a loaded antifungal pipeline, new antifungals with broad spectrum activity when used as monotherapy against mucormycosis to complement surgery remain an unmet need.[24] First line choices for primary and salvage monotherapy are therefore unlikely to change, and recommendations will likely continue to favor either LAmB or isavuconazole/ posaconazole for first line salvage monotherapy,[6,86,94,99,100] depending on which drug-class was selected for first line monotherapy (switch of drug-classes preferred for salvage therapy).[13] That said, some of the new drugs in the antifungals pipeline, particularly fosmanogepix[101,102] and opelconazole show some activity against Mucorales,[24,103] and may present important components of combination antifungal therapy in the future. Given the pharmacokinetic properties of some of these new antifungals, with eg, fosmanogepix showing strong synergism with LAmB in animal models[6,87] antifungal combination therapy may even become first line for salvage therapy, if not first line treatment. In an immunocompromised mouse model, combination of fosmanogepix with LAmB showed strong synergism, significantly enhancing survival (survival rate >80%) and reducing tissue fungal burden over antifungal monotherapy (30% survival) and also placebo (10% survival).[87] Opelconazole may also be very attractive as an inhaled antifungal combination partner, that may be utilized broadly, particularly for patients with pulmonary disease.

While ibrexafungerp and rezafungin as well as olorofim are not thought to have activity against Mucorales, preliminary data from a *Rhizopus delemar* mouse model[104] indicated that survival with ibrexafungerp (35%) was not different from survival with any other antifungal monotherapy but that survival could be markedly improved once ibrexafungerp was combined with LAmB (65% survival) or posaconazole (50%) survival, indicating synergism and outlining that – if confirmed - there may be a role for ibrexafungerp in salvage antifungal combination therapy in the future.

Given that treatment duration for mucormycosis is often several months, sometimes years, oral/long-acting treatments that allow for treatment continuation after discharge are needed. Currently only isavuconazole and posaconazole are available as oral formulations with activity against Mucorales. New antifungals that come as oral formulations (fosmanogepix, ibrexafungerp), inhaled formulations (opelconazole) or with a once-a-week parenteral administration (rezafungin),[24] may therefore also play an important role in stepdown salvage therapy.

Discussion & Conclusion

A successful management of invasive fungal diseases is a multiple lane road. Even though substantial efforts were taken to improve diagnostic and therapeutic approaches, late diagnoses and treatment failures remain a serious consequence coming along with even worse patient outcomes.[84,105,106] Continuous monitoring of response to therapy is needed to recognize potential treatment resistance or intolerance, which are adequately addressed by the implementation of salvage therapy. Antifungal susceptibility testing and/or molecular testing for resistance mutations to monitor eg azole resistance in *Aspergillus fumigatus* can be effective tools to guide optimal treatment.[107] Currently available drugs originate from three drug classes only, which frequently restricts practicability of the proposed change in drug class. Evidence for combination therapy is scarce and limited by mostly absent synergism between drugs. Interindividual PK/PD variances, especially in azoles, make clear guidelines for therapeutic drug monitoring in different settings necessary. Overall, the current armamentarium is insufficient in order to properly address salvage therapy for IA and mucormycosis.

The loaded antifungal pipeline however leaves room for cautious optimism. Novel mechanisms of action paired with improved PK/PD properties open up a number of new possibilities for salvage treatment. For IA these include monotherapy approaches with fosmanogepix, olorofim or ibrexafungerp as well as combinations with LAmB, conventional azoles, or the addition of locally acting inhaled opelconazole. For mucormycosis, the synergism between LAmB and fosmanogepix/ ibrexafungerp could render this combination first option in salvage- or even first-line settings.

Stepdown to oral therapy will be possible due to the oral availability of fosmanogepix, olorofim and ibrexafungerp. Opelconazole as an inhaled antifungal and rezafungin as a once-a-week parenteral antifungal will offer further options.

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