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MINIREVIEW

Therapeutic Challenges of Non-*Aspergillus* Invasive Mold Infections in Immunosuppressed Patients

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ABSTRACT While *Aspergillus* spp. remain the major cause of invasive mold infections in hematologic cancer patients and transplant recipients, other opportunistic molds, such as *Mucorales*, *Fusarium*, and *Scedosporium* spp. are increasingly encountered in an expanding population of patients with severe and prolonged immunosuppression. High potential for tissue invasion and dissemination, resistance to multiple antifungals and high mortality rates are hallmarks of these non-*Aspergillus* invasive mold infections (NAIMIs). Assessment of drug efficacy is particularly difficult in the complex treatment scenarios of NAIMIs. Specifically, correlation between *in vitro* susceptibility and *in vivo* responses to antifungals is hard to assess, in view of the multiple, frequently interrelated factors influencing outcomes, such as pharmacokinetic/pharmacodynamic parameters determining drug availability at the site of infection, the net state of immune suppression, delay in diagnosis, or surgical debulking of infectious foci. Our current therapeutic approach of NAIMIs should evolve toward a better integration of the dynamic interactions between the pathogen, the drug and the host. Innovative concepts of experimental research may consist in manipulating the host immune system to induce a specific antifungal response or targeted drug delivery. In this review, we discuss the challenges in the management of NAIMIs and provide an update about the latest advances in diagnostic and therapeutic approaches.

KEYWORDS mucormycosis, fusariosis, scedosporiosis, *Mucor*, *Rhizopus*, *Fusarium*, *Scedosporium*, *Lomentospora*, amphotericin B, azole, voriconazole, posaconazole, isavuconazole

Non-*Aspergillus* molds account for a small proportion (10 to 25%) of invasive mold infections in high-risk hematologic cancer and transplant patients (1–3). However, some recent reports suggest that their frequency is increasing as a possible consequence of the expanding spectrum of population with profound and prolonged immunosuppression and the widespread use of anti-*Aspergillus* prophylaxis that may exert a selective pressure (4, 5). Mucormycosis (due to *Mucorales*) is the most frequent of these non-*Aspergillus* invasive mold infections (NAIMIs) (6–8), followed by fusariosis (*Fusarium* spp.) and scedosporiosis (*Scedosporium* and *Lomentospora* spp.). NAIMIs are associated with high mortality rates, attributed in part to their intrinsic level of resistance to multiple antifungal drugs (2, 9). However, many other factors should be taken into account regarding the outcome of NAIMIs, such as the lack of reliable early diagnostic tools, the propensity of these non-*Aspergillus* molds to induce extensive tissue necrosis and to disseminate to multiple organs, and, perhaps most importantly, the net state of immunosuppression of the host. Therefore, antifungal drug efficacy and response to therapy are often difficult to assess. Although international guidelines provide recommendations for the choice of antifungal therapy of mucormycosis,

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TABLE 1 Determinants of outcome in NAIMIs[a]

Parameter	Current strategies	Investigational approach(es)
Diagnosis	Early use of CT scan Invasive procedures to get samples (bronchoscopy, tissue biopsy)	Targeted imaging (immuno-PET/MRI), PET/CT Noninvasive specific biomarkers for NAIMI (e.g., PCR in serum/urine, antigen, or metabolomic detection by POCTs for mucormycosis)
Degree of disease extension/dissemination	Surgical debulking; antifungal therapy	Novel therapies against angioinvasion (anti-CotH antibodies)
In vitro activity of antifungal drugs	Antifungal susceptibility testing by validated methods	Role and significance not well defined; further investigations needed
Penetration of drug at local site	Adjust antifungal drug regimen to PK/PD; debridement surgery for extensive necrosis	Posaconazole-loaded leukocytes
Host immunity	Reduce immunosuppressive therapy if possible; consider additional G-CSF or GM-CSF	Bioengineered genetically modified cytotoxic T cells (CARs)
Metabolic conditions	Correct hyperglycemia; avoid iron overload	Novel therapies targeting iron metabolism (e.g., siderophores)

[a]POCTs, point-of-care tests; PK/PD, pharmacokinetic/pharmacodynamic; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; CARs, chimeric antigen receptors.

fusariosis, and scedosporiosis, robust evidence supporting the superiority of one drug over another is scarce (10, 11).

Indeed, the correlation between *in vitro* MICs and *in vivo* efficacy is difficult to assess. For example, pharmacokinetic and pharmacodynamic parameters come into play when one tries to extrapolate *in vitro* susceptibility data into the actual bioavailability and efficacy of the drug at the infection site. Moreover, because of the multidrug-resistant profile of these molds, nonpharmacologic factors, such as the recovery from immunosuppression, are crucial for outcome, which leads to the concept of the host as the key driver of success. Therefore, it is essential to consider a multilayered approach for the management of these life-threatening infections, including the pathogen, the host and the drug. Antifungal drug factors (selection of a specific antifungal, dose, route of administration) are usually the only parameters that the physician can control best. In this mini-review, we discuss the current thinking of the complexities of treatment of NAIMIs by focusing the main issues in the decision-making: (i) the *in vitro* activity of the drug, (ii) the pathophysiological conditions of the infection, (iii) pharmacokinetic and pharmacodynamic parameters related to the drug bioavailability, host metabolism and site of infection, and (iv) *in vivo* efficacy of the drug (or drug combinations) according to data derived from clinical studies or animal models.

IN VITRO ACTIVITY OF ANTIFUNGALS

Despite the existence of standardized testing protocols, antifungal susceptibility testing (AST) is not recommended for the clinical management of NAIMIs (10, 11). Specifically, there is no established correlation between *in vitro* MIC and outcome for NAIMIs and thus no defined interpretive breakpoints. The fact that NAIMIs are uncommon diseases and that the outcome depends on multiple factors (Table 1) with a key role of nonpharmacologic parameters (e.g., stage of the fungal infection at time of diagnosis, activity of underlying disease, comorbidities, and recovery of immunosuppression) renders this assessment particularly difficult. Indeed, studies attempting to correlate MICs and outcome in opportunistic mold infections, including NAIMIs, in high-risk hematology patients are scarce (9, 12–14). Differences between *in vitro* artificial AST conditions and the complexity of *in vivo* infections are illustrated in Fig. 1. Specifically, AST is performed with high inocula of conidia in a glucose-rich medium devoid of immune cells. These conditions differ from the *in vivo* mode of growth of molds (hyphal formation, low oxygen and PH, limited nutrient sources, and small populations of invading fungi that are exposed to immune cells).

Despite the absence of interpretive criteria for non-*Aspergillus* molds, some thoughts may be helpful when considering the possible role of AST in clinical practice. One

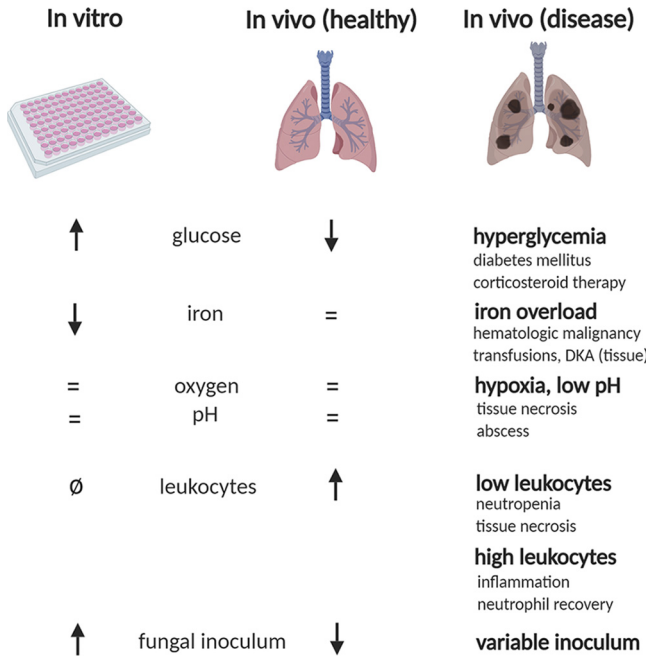

FIG 1 Factors affecting antifungal activity: comparison of *in vitro* versus *in vivo* conditions.

should first distinguish situations where the susceptibility of a mold to a given antifungal drug is predictable (narrow range of MIC distribution) or unpredictable (wide range of MIC distribution). This pattern may be genus or species-specific. The susceptibility profiles of the most clinically relevant non-*Aspergillus* molds (Fig. 2) can be categorized in situations where the antifungal activity of the drug is predictable and either (i) highly active *in vitro* with evidence of clinical efficacy, (ii) displaying intermediate level of *in vitro* activity with uncertain clinical efficacy, or (iii) inactive or poorly active *in vitro* with absence of clinical efficacy (in preclinical models of infection and/or clinical data). In some cases, the activity of the drug is defined as "unpredictable," which means that a wide range of MICs are observed, and this variability can be (i) interspecies

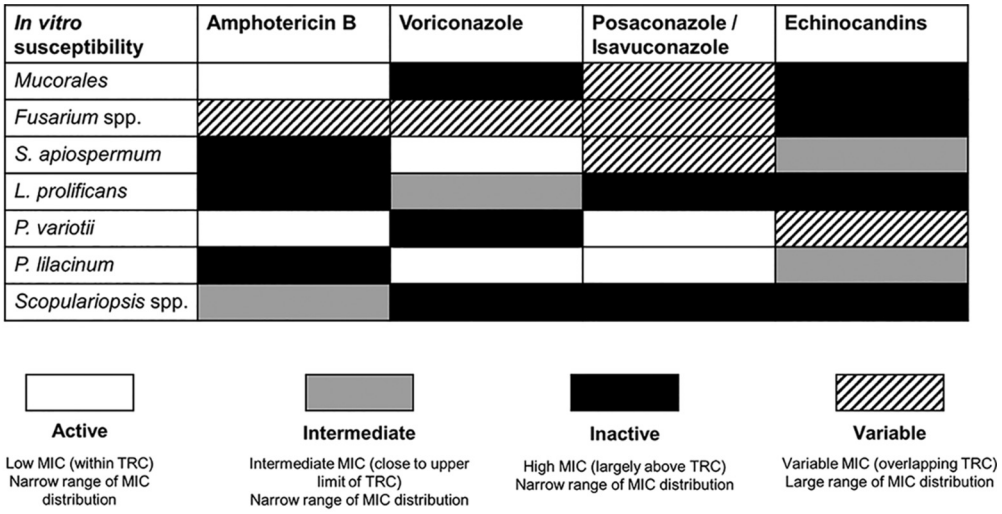

FIG 2 *In vitro* antifungal activity of antifungal drugs against non-*Aspergillus* molds. The *in vitro* activity of the different antifungal drugs against a given pathogenic mold is classified in four different categories: active (white), intermediate (gray), inactive (black), or variable (hatched).

within a same genus or (ii) intraspecies. A potential utility of AST is thus limited to these latter categories where *in vitro* activity of the drug cannot be predicted on the basis of the mold identity. Because conventional diagnostic phenotypic methods usually achieve identification of non-*Aspergillus* molds at the genus level only, it is often not possible to predict antifungal susceptibility when interspecies variability exists within a same genus. Novel diagnostic tools (matrix-assisted laser desorption ionization--time of flight [MALDI-TOF] and sequencing analyses) can be helpful for more accurate identification at the species level.

However, interspecies and intraspecies variability of MIC often coexist among non-*Aspergillus* molds. For instance, a wide range of voriconazole MICs can be observed for all individual *Fusarium* spp., although *F. solani* tends to exhibit higher MIC_{90}s than other pathogenic species (e.g., *F. oxysporum* and *F. verticilloides*) (15). The same phenomenon can be observed for posaconazole susceptibility among *Mucorales* spp. While some species (e.g., *Mucor circinelloides*) are known to display higher posaconazole MICs compared to others, important intraspecies variability has also been reported among *Rhizopus oryzae* and other pathogenic species (16, 17). These large ranges of intraspecies MIC distribution suggest that mechanisms of innate or acquired resistance may exist in non-*Aspergillus* molds, which remains unknown and unexplored (18). Whether variability in *in vitro* MICs can influence outcome is actually unclear. However, AST results could be taken into account if alternative therapeutic choices exist and/or in the assessment of possible causes of nonresponse to therapy in follow-up. Most importantly, MIC results should be interpreted in conjunction with multiple parameters that may affect the activity of the drug *in vivo* (Table 1), which will be discussed in the next section.

PHARMACOKINETIC/PHARMACODYNAMIC PARAMETERS

Besides the inherent *in vitro* activity of the drug, a key factor for therapeutic success is the bioavailability of the drug at the site of infection. For this purpose, there are several aspects of NAIMIs which differ from invasive aspergillosis and should be taken into account. First, extrapulmonary spread of these infections to other organs (e.g., soft tissues and bone, skin, eye, or brain) is frequently observed. Second, these molds have enhanced tropism to invade blood vessels and cause extensive tissue necrosis in a microenvironment of low-pH and low-oxygen conditions, which does not favor drug penetration. Both immune cells and antifungal agents have limited access to this necrotic tissue, and antifungal drug penetration is often limited to the lipid-rich membrane of macrophages outside the necrotic center of the fungal lesions (19). Third, diagnosis is frequently delayed, which means that a high fungal burden and/or injurious inflammatory response may already be present when therapy is started.

Again, all of these *in vivo* conditions are not taken into account during *in vitro* testing. For example, hypoxic conditions have been observed in a murine model of invasive aspergillosis (20), and Binder et al. showed that the effect of hypoxia was *Aspergillus* species dependent with altered activity of antifungals against *A. terreus* but not against *A. fumigatus* or *A. flavus* (21). However, such data are scarce for non-*Aspergillus* molds. One study analyzing the transcriptomic profile of *Mucor irregularis* under hypoxic conditions found a pattern of gene expression that was unique to this fungus and different from *Aspergillus* spp., which suggests that adaptation to hypoxia is a fungal genus- and species-specific process (22). Another study found that a culture protocol simulating the physiologic conditions of hypoxia and human body temperature during invasive mucormycosis increased the recovery rate of *Mucorales* (23).

The tissue distribution of antifungal agents has been extensively studied in animal models (24). Drug penetration in tissues is influenced by multiple factors, such as the drug formulation and mode of administration, the lipophilicity of the drug, the degree of protein binding, and the inflammatory response (24). There may be considerable variations between the concentrations of antifungals in bloodstream and the different targeted organs, not only in terms of absolute concentration but also relative to the concentration over time. Other characteristics specific to drug classes should be taken

into account, such as the targeted delivery of amphotericin B liposomes, which makes the actual significance of free serum or tissue concentrations unclear. Moreover, important differences in pharmacokinetic properties may be observed between antifungal drugs within a same class. For instance, triazoles display a wide range of lipophilicity indexes (log D from 0.5 to >5) and percentages of protein binding (12 to >99%), and the properties of amphotericin B are influenced by the type of formulation (24, 25). Overall, mold-active azoles and amphotericin B formulations achieve concentrations in lung tissue that are at least equal to or higher than those in plasma, but important differences may be observed relative to the type of lung compartment (epithelial cells, alveolar macrophages, lung parenchyma, and pleural fluid) and the type of drug (24). For example, posaconazole was shown to accumulate in pulmonary epithelial cells and transfer to *Aspergillus* conidia upon contact with the respiratory epithelium, which may explain its particular role for antifungal prophylaxis (26).

Most mold-active antifungals achieve good penetration in skin, soft tissues, or other internal organs, such as the liver, spleen, or kidney, but there are discordances in their concentration-time profiles between plasma and tissues (24). As an example, liposomal amphotericin B exhibits nonlinear accumulation in these organs, with prolonged persistence in tissues and half-lives of several weeks (27). However, penetration in sanctuary sites, such as the brain and eye, is problematic. Voriconazole is the treatment of choice for cerebral aspergillosis (28, 29), while posaconazole achieves modest brain concentrations (50 to 80% of serum) (30). The new broad-spectrum triazole isavuconazole can achieve brain concentrations comparable to that of voriconazole (about twice that in plasma) (31–33). Brain concentrations are relatively low for all formulations of amphotericin B (24, 34), although they are effective and recommended for treatment of cryptococcal meningitis and represent an alternative for cerebral aspergillosis (29).

Another important issue is the targeted serum concentration that should be achieved for triazoles in the treatment of NAIMIs (e.g., posaconazole for mucormycosis or voriconazole for fusariosis or scedosporiosis). For invasive aspergillosis, therapeutic drug monitoring is recommended for the adjustment of voriconazole dosing. A trough serum concentration of voriconazole of >1 μg/ml (for an MIC distribution of *Aspergillus* spp. usually between 0.25 and 1 μg/ml) has been associated with better outcomes (35). Petraitiene et al. demonstrated that sustained plasma posaconazole concentrations of ≥1 μg/ml were effective for the prevention and treatment of invasive aspergillosis in a rabbit model (36), which was further supported by a clinical study of posaconazole as salvage therapy of invasive aspergillosis with improved response rates for average plasma concentrations of >1 μg/ml (37). However, there is no established therapeutic range for triazoles in the treatment of NAIMIs, and targeted levels are usually extrapolated from those defined for invasive aspergillosis. Because these molds usually exhibit higher MICs compared to *Aspergillus* spp., there might be a rationale to target higher concentrations (38), but evidence from clinical studies is lacking.

Another condition that may affect the response to therapy despite sufficient levels of active drug at the site of infection is the development of biofilms and fungal persister cells. This phenomenon has been well described with *Candida* spp. (39). Persisters consist of subpopulations of dormant cells that are adherent to biotic surfaces or implanted devices and exhibit high tolerance or resistance to antifungals, including the fungicidal drugs. *Aspergillus* spp. are able to form biofilms *in vitro* and *in vivo* (40, 41). *Aspergillus* biofilms can be observed on bronchial epithelium and be responsible for chronic colonization, for instance in patients with cystic fibrosis. The activity of all antifungal drug classes was shown to be considerably decreased against sessile biofilms of *Aspergillus fumigatus* on bronchial epithelial cells (42). Similarly, *Scedosporium* spp., which are frequent persistent colonizers in patients with cystic fibrosis, are able to form biofilms with decreased susceptibility to antifungals and possibly higher virulence (43). Biofilm formation has also been described for *Fusarium* spp. in the pathogenesis of keratitis with contact lenses and onychomycosis and for the pathogenic species of the order *Mucorales in vitro* (44, 45). The role of biofilms in chronic fusariosis or mucormycosis is, however, not yet established.

TABLE 2 Recommendations for the management of NAIMIs[a]

Type of NAIMI	Treatment	Comments
Antifungal therapy		
All (general principles)	Early start of empirical antifungal therapy with broad-spectrum antifungals	High index of suspicion. Crucial for outcome, e.g., L-AMB or ISA; until identification of fungal pathogen
Mucormycosis	L-AMB at 5 to 10 mg/kg QD	First line (first choice)
	ISA, 200 mg TID (days 1 to 2), then 200 mg QD[b]	First line (second choice) or second line[c]
	POS, 300 mg BID (day 1), then 300 mg QD	Second line[c,d]
	L-AMB combined with CAS or POS	Severe cases (low clinical evidence)
Fusariosis	L-AMB, 5 to 10 mg/kg QD	First line or second line
	VOR, 6 mg/kg BID (day 1), then 4 mg/kg BID	First line or second line[c,d]
	L-AMB combined with VOR	Severe cases (low clinical evidence)
Scedosporiosis		
S. apiospermum complex	VOR 6 mg/kg BID (day 1), then 4 mg/kg BID	First line (first choice)[d]
	CAS, 70 mg QD (day 1), then 50 mg QD	Second line (if VOR not possible, low evidence)
	VOR combined with TBF or CAS	Severe cases (low clinical evidence)
L. prolificans	VOR 6 mg/kg BID (day 1), then 4 mg/kg BID	First line (first choice)[d]
	VOR combined with TBF	Severe cases (low clinical evidence)
Adjuvant therapy		
All types	Reduce immunosuppression if possible	Taper corticosteroids if feasible
	GM-CSF (or G-CSF), IFN-γ, WBC transfusion	If neutropenia
	Surgery	Selected cases
Mucormycosis	Surgery	To consider for most cases (timing to assess individually)
	Control hyperglycemia	In particular for patients with diabetes
	Hyperbaric oxygen (selected cases)	Single site infection (e.g., sinusitis, soft tissue), ideally in conjunction with surgery
	Iron chelators: not recommended	Lack of clinical evidence

[a]POS, posaconazole; ISA, isavuconazole; VOR, voriconazole; L-AMB, liposomal amphotericin B; CAS, caspofungin; TBF, terbinafine; WBC, white blood cell; GM-CSF, granulocyte macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; IFN, interferon. QD, once daily; BID, twice daily; TID, three times daily.

[b]For isavuconazole, 200 mg of active drug corresponds to 372.6 mg of isavuconazonium sulfate.

[c]Consider results of antifungal susceptibility testing if available (favor alternative antifungal regimen if MIC ≥8 μg/ml). Experts' recommendations (no evidence).

[d]Consider therapeutic drug monitoring. Suggested targeted serum concentrations: ≥1 μg/ml and <5 μg/ml (based on recommendations for invasive aspergillosis, no evidence for NAIMIs).

Symbiosis and interactions of fungi with the rest of the microbiome could also be determinant for disease containment or progression. Bacteria could be in competition with fungi and produce signal molecules that will influence the rate of fungal growth and propagation. Such interactions have been described for *Scedosporium* spp. and *Pseudomonas aeruginosa* (46). While direct contact with the bacteria resulted in fungal growth inhibition, the presence of *P. aeruginosa* could enhance the growth of the fungus when the two microorganisms were cultured "plate to plate" with a physical separation. Indeed, *Scedosporium* spp. are frequently recovered from the lungs of patients with cystic fibrosis, and concomitant colonization with mucoid *P. aeruginosa* has been identified as a predisposing factor (47).

EFFICACY OF ANTIFUNGALS *IN VIVO*

Most recommendations for the treatment of NAIMIs rely on observations derived from uncontrolled and mostly retrospective small clinical studies. However, some particular features should be highlighted: (i) the absence of comparative randomized trials because of the rarity of the disease, and the heterogeneity of site of infection, underlying hosts, and NAIMIs, and (ii) the crucial role of nonpharmacologic parameters in the outcome of these infections, such as the feasibility, timing, and extent of surgical interventions and recovery from immunosuppression. In addition, because these infections are due to multiresistant fungi and are associated with high mortality rates, combination antifungal therapies represent attractive options, but their actual benefit is very difficult to demonstrate (14). Clinical studies assessing antifungal drug efficacy for the three most relevant NAIMIs will be discussed below. General and specific recommendations for the management of NAIMIs, including antifungal therapy and adjuvant treatments, are summarized in Table 2.

Mucormycosis. Amphotericin B formulations are the mainstay of treatment for mucormycosis. Liposomal amphotericin B therapy was associated with lower mortality rates compared to other antifungal regimens and was a significant factor associated with survival in large cohorts (48, 49). The potential benefit of administering high doses of liposomal amphotericin B (10 mg/kg instead of 5 mg/kg) is debated and has not been demonstrated until now, but it has been associated with a higher incidence of nephrotoxicity (50). Experience with other formulations of amphotericin B (lipid complex) is more limited (49). Posaconazole is mainly used as a second-line therapy in cases of refractory disease or intolerance to amphotericin B, with a reported success rate of about 60% (51). Its use as first-line treatment has been limited by variable bioavailability of oral suspensions but should be further investigated with the advent of the new intravenous formulation and the more stable gastroresistant tablets. Posaconazole is recommended as antifungal prophylaxis in high-risk hematologic patients (52, 53). However, it is noteworthy that its efficacy has been mainly demonstrated for the prevention of invasive aspergillosis. Indeed, studies reported a predominance of mucormycosis among breakthrough IMIs under posaconazole prophylaxis (5, 54). Recently, isavuconazole has been approved as first-line treatment for mucormycosis on the basis of a single-arm open-label trial showing a 67% rate of survival at day 42, which was similar to that of matched controls treated by amphotericin B formulations from an international registry (55). Experience with isavuconazole for antifungal prophylaxis is limited, but breakthrough mucormycoses have been reported, especially in the setting of refractory leukemia with persistent neutropenia (56). Correlation between *in vitro* MICs and clinical efficacy remains an open question regarding the *Mucorales*-active triazoles. Despite the absence of known mechanisms of resistance, *Mucorales* exhibit a wide range of intraspecies MIC distribution for posaconazole and isavuconazole, with some pathogenic species, such as *Mucor circinelloides*, exhibiting higher MICs compared to the others (16, 57). Differences between testing methods have been reported for isavuconazole (58). In murine models of invasive infection by *Mucor circinelloides* or *Rhizopus oryzae*, posaconazole showed poor efficacy irrespective of MIC values (59, 60). While there are no clinical breakpoints, AST results, when available, suggest caution for the use of triazole monotherapy as the initial treatment of mucormycosis in case of high MIC values. For amphotericin B, MICs are distributed in a narrower range, with values rarely exceeding 4 μg/ml (16). One small retrospective study suggested that amphotericin B MICs of $\leq$0.5 μg/ml were associated with a better response to therapy (9). Most importantly, prompt initiation of amphotericin B therapy is crucial for outcome, with a rate of mortality that was twice higher among patients for which therapy was delayed ($\geq$6 days from diagnosis) (61).

The poor outcomes of mucormycosis with currently available monotherapies, has stimulated interest in studying various antifungal combinations (62). While echinocandins *per se* do not display significant antifungal activity against *Mucorales*, they may act synergistically with amphotericin B. This effect may be related to an activation of the immune system. Indeed, a small amount of beta-glucan is present in the cell wall of *Mucorales*, but echinocandins can induce unmasking of beta-glucan, which triggers the activity of polymorphonuclear neutrophils against the molds (63). Both *Aspergillus* and *Rhizopus* spp. were shown to trigger interleukin-23 production by dendritic cells following activation of dectin-1 by unmasked beta-glucan (64). The positive interaction between amphotericin B and echinocandins was first described in murine models of mucormycosis, with improved survival in the combination therapy group compared to treatment with amphotericin B alone (65, 66). Few clinical data tend to support the benefit of this combination, which is possibly limited to diabetic patients (67, 68). Combined therapy of amphotericin B with posaconazole has also been suggested, but a murine model failed to demonstrate the superiority of this combination over monotherapies, and clinical evidence is also lacking (59, 69). Overall, the potential benefit of any drug combination for the treatment of mucormycosis remains doubtful and two large retrospective studies of over 100 cases did not demonstrate a significant im-

provement in survival (70, 71). Whether the availability of a better-absorbed posaconazole formulation (posaconazole tablets) or isavuconazole in combination with lipid amphotericin B and the promise of earlier diagnosis of mucormycosis would result in benefits of combination therapy remains to be seen.

Besides early initiation of antifungal therapy, surgical debridement is another cornerstone in the treatment of mucormycosis, which emerged as a significant predictor of improved survival in several studies (49, 72, 73). Patient selection is important for improved outcomes since underlying diseases (hematologic malignancies, neutropenia, and active malignancy), age, comorbidities, localization, and extent of disease are other important factors associated with mortality (49, 71, 72, 74).

Fusariosis. Amphotericin B lipid formulations and voriconazole are the two treatments of choice of disseminated fusariosis, and there is no evidence supporting the benefit of one drug over the other (11). Analysis of 233 cases from an international registry showed similar 90-day survival for patients treated with voriconazole and amphotericin B lipid formulations, but amphotericin B deoxycholate was associated with a lower probability of survival (75). A French series of 73 cases of invasive fusariosis treated with voriconazole as primary or salvage therapy reported a 90-day survival of 42% (76). No antifungal susceptibility data were available in these studies, and there is no evidence whether variations in voriconazole MIC may impact outcome. However, one study reported a high rate of failure of therapy (11/12, 87.5%) among patients with disseminated fusariosis who received voriconazole first-line treatment despite lack of *in vitro* activity of this drug (MIC $\geq$16 μg/ml) (9). Actually, *in vivo* experiments in mice showed that neither voriconazole nor amphotericin B lipid formulations demonstrated any benefit compared to the untreated groups for the treatment of invasive fusariosis, irrespective of the MIC values (77). Indeed, the only factors that were significantly associated with improved outcomes in clinical studies were nonpharmacologic parameters, such as the recovery of neutropenia and the absence of concomitant corticosteroid therapy (75, 78–80). These observations lead to the conclusion that immune reconstitution is the cornerstone for success in the management of invasive fusariosis.

Because of the poor outcome of invasive fusariosis, many clinicians opt for combinations therapies, for which there is no demonstrated benefit apart from case reports (75, 76, 81, 82). In one study of 44 cases of invasive fusariosis treated primarily by combined amphotericin B and triazole therapy, mortality still remained as high as 66% (78). *In vitro* interactions between voriconazole and amphotericin B against *Fusarium* spp. show variable results with fractional inhibitory concentration indexes (FICI) classified as indifferent or antagonistic for the majority of strains and synergistic for only a few isolates (83–85). The drug combinations showing the highest percentage of positive interactions *in vitro* were (i) amphotericin B plus caspofungin or 5-flucytosine and (ii) voriconazole plus terbinafine (83–85). The clinical efficacy of these combinations is only supported by a few case reports, with an apparent publication bias (86). While terbinafine is usually not recommended for the treatment of invasive mycoses, its propensity for accumulation in skin and soft tissues might be interesting as adjuvant therapy for fusariosis because of the high frequency of primary or secondary skin lesions.

Some positive *in vitro* interactions between amphotericin B or voriconazole and nonantifungal drugs (rifampin, ibuprofen, ciprofloxacin, metronidazole, and miltefosine) have been reported (85, 87, 88). Activity of pentamidine (*in vitro* studies and animal models) against *Fusarium* spp. has also been described (89, 90). The mechanistic explanations and the clinical relevance supporting these potential synergisms are unclear.

Scedosporiosis. Species of the *Scedosporium apiospermum* complex and *Lomentospora* (formerly *Scedosporium*) *prolificans* are the main etiological agents of scedosporiosis. Voriconazole has potent *in vitro* activity against *S. apiospermum*, whereas posaconazole is less active and isavuconazole or itraconazole only have marginal activity (91, 92). Echinocandins display some degree of activity, but the minimal effective

concentrations are 5- to 10-fold higher than those observed for *Aspergillus* spp., and their efficacy was not demonstrated in a murine model (91, 93). Resistance to amphotericin B is intrinsic among these species. *L. prolificans* is notoriously resistant to all antifungal agents, with voriconazole being the most active *in vitro* (92). Interestingly, an association between voriconazole MIC and outcome has been suggested by a murine model of disseminated scedosporiosis (94). Scedosporiosis has a high potential for cerebral involvement and dissemination and is associated with high mortality rates. Voriconazole is the recommended therapy and has been associated with significant improved survival compared to amphotericin B (95, 96). Again, nonpharmacologic factors play an important role in the outcome of infection. Disseminated infection and severe immunosuppression (i.e., hematologic cancer) are associated with poor prognosis, while surgery may improve outcome (95, 96).

Synergistic interaction between voriconazole or itraconazole and terbinafine against *L. prolificans* has been reported (97–99). However, a recent analysis combining all cases from an international registry and previous published reports did not demonstrate any benefit of the voriconazole-terbinafine combination compared to voriconazole monotherapy (55% versus 50% mortality rates, respectively) (96). One case report mentioned successful treatment of *L. prolificans* osteomyelitis in an immunocompetent child with a triple combination of voriconazole, terbinafine, and miltefosine (100). The combination of triazoles and echinocandins displayed various types of *in vitro* interactions against *S. apiospermum* complex, with synergism in some cases, but failed to demonstrate a significant benefit in a murine model of scedosporiosis (93, 97). It is also interesting to note that nonantifungal drugs, such as colistin and some psychotropes (e.g., chlorpromazine and trifluoperazine), exert some *in vitro* activity against *Scedosporium* spp. (101–103). Voriconazole could potentiate the effect of colistin, although the combination did not meet criteria for synergism in most cases (102). A potentiating effect of a mucolytic agent (*N*-acetyl-L-cysteine) with conventional antifungals has also been suggested (104).

NOVEL ANTIFUNGAL AGENTS

For many years, the treatment of severe invasive mold infections relied solely on amphotericin B-based regimens. Despite the development of novel triazoles and echinocandins, as well as less toxic formulations of amphotericin B, our antifungal armamentarium is still limited to only three antifungal drug classes. Because fungi are eukaryotes like humans, it is difficult to identify specific targets outside the cell wall and the ergosterol component of the fungal cell membrane. Glycosylphosphatidylinositol (GPI)-anchored proteins are important for cell wall integrity and attachment to host cell surfaces (105). APX001A (E1210) is an inhibitor of fungal GPI biosynthesis (Gwt1p) with broad *in vitro* antifungal activity against *Aspergillus*, *Fusarium*, and *Scedosporium* spp. but inactive against *Mucorales* (106, 107). Albeit only fungistatic, this compound recently proved to be effective in the treatment of murine invasive pulmonary aspergillosis and may be contemplated for clinical applications in the future (108). Another investigational agent belonging to the orotomide class of antifungals, F901318 (F2G, olorofim), which inhibits pyrimidine biosynthesis, exhibited potent fungicidal activity against a large variety of multiresistant pathogenic molds, including *Scedosporium*/*Lomentospora* spp. and *Scopulariopsis* spp. and variable activity against *Fusarium* spp. (only fungistatic against *F. solani*) (109, 110). An extensive review of these compounds can be found elsewhere (111).

Repurposing of old agents to treat NAIM has also been reported. For example, miltefosine, a membrane phospholipid analogue used against leishmaniasis and displaying modest antifungal activity *per se*, demonstrated synergistic interactions with posaconazole or voriconazole against some isolates of *Mucorales*, *Fusarium* spp., and *L. prolificans* (87). Another antiprotozoal agent, pentamidine, also demonstrated *in vitro* activity and efficacy in murine models against *Fusarium* spp. (89, 90). In addition, colistin has been shown to display modest *in vitro* and *in vivo* fungicidal activity against *Mucorales* (112). Several other potential candidates for

novel antifungal therapies are contemplated but have not yet reached the stage of clinical use.

NOVEL THERAPEUTIC APPROACHES

Because of the limited efficacy of antifungal drugs against non-*Aspergillus* molds, various adjuvant therapies have been proposed with the goal to favor the activity of antifungals by their action on the biological conditions of infection within the host. These approaches may consist in: (i) modulation of the tissue microenvironment (hypoxia, pH, iron, glucose, or nutrient availability) to the detriment of the fungus and/or in favor of the host immune defenses, and (ii) nonspecific or specific enhancement of the host immune response against the fungus (Table 1).

Despite the lack of activity in murine models (113), the use of hyperbaric oxygen has been anecdotally reported for the treatment of mucormycosis with the rationale to combat hypoxia associated with extensive tissue necrosis (10, 114). This approach seems to be more beneficial among diabetic patients who are in ketoacidosis as acidic environment contributes to fungal growth (114). It is unclear whether the reports regarding the benefit of hyperbaric oxygen in mucormycosis represent publication bias and concrete evidence for improved outcomes is still lacking.

Maintaining iron homeostasis is crucial for fungal survival and virulence in an environment with low iron availability such as the human body. The iron chelator deferasirox was effective in treating murine mucormycosis in diabetic ketoacidotic mice (115). Because deferasirox demonstrated synergistic effect with liposomal amphotericin B, this combination was tested in small placebo-controlled trial of neutropenic and heavily immunosuppressed patients (116). Patients treated with adjunctive deferasirox exhibited higher mortality rate compared to those treated by liposomal amphotericin B alone, but were also more likely to present other factors of bad prognosis (active malignancy, neutropenia, corticosteroid therapy). It is possible that deferasirox exerts its efficacy best in the setting of diabetic ketoacidosis, where there is free excess tissue iron (117).

Decompensated diabetes mellitus with hyperglycemia and ketoacidosis are well-known risk factors of mucormycosis. Glycosylation of proteins (e.g., ferritin, transferrin) and altered pH conditions may affect iron metabolism. Indeed, ketone bodies (β-hydroxy-butyrate), glucose and iron favor growth of *Mucorales* and also enhance the expression of the host receptor GRP78 of endothelial cells, which facilitate angioinvasion (118). Hyperglycemia was also associated with invasive fusariosis in hematologic cancer patients (119). Control of glycemia and prevention of iron overload thus remain important measures in patients at risk or treated for NAIMI.

As mentioned earlier, the quality of the host immune response is crucial for the containment and resolution of invasive fungal infections. Because neutrophil recovery is a factor of better prognosis in mucormycosis or fusariosis (79, 120), nonspecific approaches to boost the host response, such as administration of granulocyte-macrophage or granulocyte colony-stimulating factor (GM-CSF or G-CSF), are occasionally recommended, but their efficacy remains to be demonstrated. Adjuvant G-CSF therapy did not demonstrate any benefit for the treatment of murine mucormycosis compared to posaconazole monotherapy (121). One prospective nonrandomized study suggested good efficacy of granulocyte transfusions (GTX) for the control or the prevention of recurrence of invasive fungal infections (122). However, GTX did not demonstrate any benefit in addition to antifungal therapy for the treatment of invasive aspergillosis and was even associated with worse outcomes due to pulmonary reactions in a retrospective clinical study (123). Addition of recombinant interferon γ1b (rIFN-γ1b) to GTX has also been tested without clear evidence of benefit (124). However, a combination of IFN-γ and nivolumab was successful for the treatment of refractory mucormycosis in one case report (125). A study also showed some effect of IFN-γ and GM-CSF in enhancing the activation of polymorphonuclear neutrophils against *S. apiospermum* and *L. prolificans* (126). GM-CSF could be more potent than

G-CSF. Its use as adjuvant therapy was reported to be successful in a small case series of rhinocerebral mucormycosis (127).

Besides these broad adjuvant therapies, more targeted approaches are under development to achieve the goal of a specific and potent enhancement of the host immune response specifically directed against the pathogenic fungus. Novel strategies used against cancer, which consists in bioengineering genetically modified cytotoxic T cells *ex vivo* to express CD19-specific chimeric antigen receptors (CARs) against tumors, can also be applied for the treatment invasive fungal infections. Using the pattern recognition receptor dectin-1, such T cells were generated to target specifically the beta-glucan component of fungi (128). This approach was effective in reducing fungal burden in murine models of pulmonary and cutaneous aspergillosis. Hijacking the host immune system for targeted drug delivery is another innovative approach. Posaconazole is a lipophilic drug that accumulates within the cell membrane of human cells. Transfusion of leucocytes loaded *ex vivo* with posaconazole can deliver very high drug concentrations directly to hyphae, which was demonstrated *in vitro* and in a murine model of invasive aspergillosis (129).

Another specific approach may consist in disrupting the interaction between the fungus and the host cells to prevent tissue invasion. Pathogenesis of mucormycosis is characterized by angioinvasion and even dead fungal hyphae are able to induce vascular damages (130). *Mucorales* exhibit spore coat protein homologs (CotH), which are absent from noninvasive fungi (131). Binding of CotH to the glucose-regulated protein 78 (GRP78) of human endothelial allows angioinvasion (132). Treatment with anti-CotH antibodies was able to prevent mucormycosis in diabetic ketoacidotic mice (131).

Finally, a better understanding of the mechanisms of innate immunity against fungi may also bring interesting perspectives for improved preventive strategies. An individualized approach of antifungal prophylaxis with stratification of risk factors for invasive mold infections based on genetic analyses is contemplated for the future. Several single nucleotide polymorphisms in pattern recognition receptors of host immune cells, such as Toll-like receptor 4 (TLR4), dectin-1, and pentraxin-3 (PTX3), have been associated with increased risk of invasive aspergillosis (133–135). Their association with NAIMIs is unknown because of the rarity of the disease.

ADVANCES IN DIAGNOSTIC STRATEGIES

Early detection of NAIMI and start of effective antifungal therapy is crucial for improving outcome. These infections are often characterized by the paucity and nonspecificity of clinical signs at early stages, becoming apparent at the stage of advanced tissue destruction (e.g., mucormycosis) or bloodstream dissemination (e.g., fusariosis). Current recommendations for the diagnostic approaches of NAIMIs are presented in Table 3. The limited number of diagnostic tools and their poor sensitivity, in particular for mucormycosis, is challenging. The yield of direct examination and culture is particularly low, with the exception of disseminated fusariosis and scedosporiosis due to *L. prolificans* that can be detected in blood cultures in about 40% cases (75, 96). Currently available serum biomarkers (galactomannan and beta-glucan) do not detect *Mucorales*. However, these biomarkers can be most useful for the early diagnosis of fusariosis. Galactomannan cross-reacts with *Fusarium* spp. and was found to have a sensitivity of 83% for the detection of invasive fusariosis (136). A similar sensitivity has been observed for the beta-glucan test (137). Both markers were found to anticipate diagnosis of fusariosis by cultures by several days (136, 137), which may be crucial for prompt initiation of antifungal therapy and possibly improved outcomes. The role of serum biomarkers for the diagnosis of other NAIMIs is unclear because of lacking data. The galactomannan test can cross-react with some pathogenic species closely related to *Aspergillus* spp. (e.g., *Paecilomyces* spp.) (138). The beta-glucan test should theoretically detect most pathogenic mold species other than *Mucorales*, but data about its actual performance are scarce (139).

Recent advances in molecular diagnosis may improve the rate of detection of

TABLE 3 Recommendations for the diagnostic approach of NAIMIs[a]

Type of NAIMI	Diagnostic approaches	Comments
All (general principles)	Daily clinical assessment for high risk patients	High index of suspicion for any suggestive clinical signs/symptoms
	Low threshold for imaging (e.g., CT)	Stage the disease and assess extent of dissemination
	Histopathology/culture of deep respiratory specimens (BAL) and/or tissue samples	Obtain deep tissue sample whenever possible
	Diagnosis at the genus and ideally at species level	MALDI-TOF, sequencing (selected cases)
	Antifungal susceptibility testing (reference lab)	Consider in specific situations (see below)
	Fungal biomarkers (galactomannan and beta-glucan)	Consider in specific situations (see below)
	Molecular tests (PCR), immunohistochemistry and in situ hybridization in tissue (reference lab)	Investigational
Mucormycosis	Molecular tests (PCR)	Pan-*Mucorales* PCR in tissue or serum (reference lab, currently limited availability)
	Antifungal susceptibility testing	POS and ISA, large MIC distribution (clinical relevance unknown); AMB, possible association MIC/outcome (limited retrospective data)
Fusariosis	Blood cultures	Sensitivity about 40%
	Galactomannan test (serum, BAL)	Sensitivity about 80% (serum)
	Beta-glucan test (serum)	Sensitivity about 80%
	Antifungal susceptibility testing	VOR, POS, ISA, and AMB, large MIC distribution (clinical relevance unknown)
Scedosporiosis	Beta-glucan test (serum)	Sensitivity unknown (lacking data)
	Blood cultures: *L. prolificans* only	Sensitivity about 40%
	Antifungal susceptibility testing	
	S. apiospermum complex	Not indicated (predictable MIC)
	L. prolificans	Usually not indicated. VOR: possible association with outcome (animal model only)

[a]BAL, bronchoalveolar lavage; MALDI-TOF, matrix-assisted laser desorption ionization–time of flight; POS, posaconazole; ISA, isavuconazole; VOR, voriconazole; AMB, amphotericin B.

NAIMIs, in particular mucormycosis. Lack of standardization and limited availability of these "in-house" PCRs still represent limitations (140). Millon et al. have developed a multiplex quantitative PCR targeting the most relevant pathogenic *Mucorales* with a sensitivity of about 80% for direct detection of mucormycosis in serum (141, 142). CotH also represents a specific marker of mucormycosis that can be detected by PCR in urine with a good sensitivity and specificity, as suggested by a murine model and a small case series of proven mucormycosis in humans (143). The cell wall polysaccharide α-1,6-mannan, common to both ascomycetous fungi and *Mucorales*, may also represent an interesting target for serological tests, such as lateral-flow immunoassays, for "point of care" diagnosis of NAIMI, including mucormycosis (144). Analyses of volatile metabolite profiles in breath samples of mice or human patients with mucormycosis showed distinct signatures for each *Mucorales* species (145). These latter findings could open new possibilities for rapid and noninvasive detection of mucormycosis. Advances in radiological technologies also deserve mention. Use of *Aspergillus*-specific tracers (e.g., siderophores and monoclonal antibodies) for immuno-PET detection is investigated, but such approaches for NAIMIs are still lacking (146–148). The immuno-PET approach shows promise as a theragnostic tool in mold infections (148).

CONCLUSIONS

NAIMIs remain uncommon diseases that are still associated with desperately high mortality rates despite advances in diagnostic and therapeutic approaches in medical mycology. These infections must be managed in a multilayered and multidisciplinary approach considering multiple parameters as determinants for outcome (Tables 1 and 2). Besides the inherent activity of antifungal drugs, the potential of recovery of the host immune system and the evolution of the underlying medical disease are key determinants of prognosis. Surgery also plays an important role for some of them. The attending physician should keep in mind that the outcome will be mainly dependent on these nonpharmacologic parameters and only modestly influenced by the choice of

the antifungal drug. While continuous efforts in research of new fungal targets are warranted, it is time to enter in a new concept of antifungal therapeutic approach, which includes the dynamic interactions between the drug, the fungus, and the host and to consider the host immune system as a major ally that can be used for more efficient and targeted therapeutic strategies.

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