



Guideline

American Society of Transplantation and Cellular Therapy Series: #8-Management and Prevention of Non-*Aspergillus* Molds in Hematopoietic Cell Transplantation Recipients



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The Practice Guidelines Committee of the American Society of Transplantation and Cellular Therapy partnered with its Transplant Infectious Disease Special Interest Group to create a guideline focusing on non-*Aspergillus* invasive molds, which are uncommon yet lethal invasive fungal diseases in the peri-hematopoietic cell transplant (HCT) period. We used a compendium-style approach by dissecting this broad, heterogeneous, and highly complex topic into a series of standalone frequently asked questions (FAQs) and tables. Adult and pediatric infectious diseases and HCT content experts developed, then answered FAQs, and finalized topics with harmonized recommendations. All the evidence for non-*Aspergillus* invasive mold infection is non-RCT and mostly level III, therefore there are no recommendation grades, and instead key references are provided.

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Through this format, this “8th” topic in the series focuses on the relevant risk factors, diagnostic considerations, prophylaxis, and treatment approaches relevant to rare mold infections in the pre- and post-transplant periods.

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INTRODUCTION

Non-*Aspergillus* invasive mold infections (NAIMIs) remain uncommon in the hematopoietic cell transplant (HCT) setting but are associated with high mortality rates, despite advances in diagnostic, preventive, and therapeutic approaches in medical mycology. The exact global cumulative incidence of NAIMIs, individually and collectively, is unclear without any prospective multisite HCT cohort studies in two decades [1,2]. While general guidelines for these complex and unusual invasive fungal diseases (IFDs) exist [3,4], they lack evidence grading, especially in highly immunocompromised HCT recipients. The fact that NAIMI mostly develop on antifungal therapy or prophylaxis compounds is challenging because there is no clear evidence for managing these breakthrough infections. In this current guideline, we organize the approach to NAIMIs in the largely allogeneic HCT setting, by answering 20 frequently asked questions (FAQ) that transplant clinicians encounter in their daily practice. See Table 1 for a list of abbreviations. Due to the paucity of high-level evidence for management of these rare entities, there is little sense to assign evidence gradings for rare molds [5] and instead what is offered is the opinion of subject matter experts based on key provided references.

FAQ1: What are the Key Points About the Epidemiology of NAIMI in HCT?

- Non-*Aspergillus* molds (NAM, please note that we are speaking in this section of the organisms and not the infections) are ubiquitously found in soil, dust, and decaying vegetation, with aerosolization occurring in the context of wind, rain, fires, construction, or other disruption of fungal conidia. While inhalational acquisition is usual, direct inoculation from penetrating trauma is also well described [6,7].
- NAIMIs frequently involve the lungs, sinuses, central nervous system (CNS), skin, and via inoculation, soft tissue; fungemia with dissemination is common, particularly in heavily

immunocompromised HCT recipients. Nosocomial NAIMI outbreaks also occur [8,9].

- The true incidence of NAIMIs is difficult to ascertain due to reporting bias, difficulties with diagnosis and identification of specific causative molds [4], plus regional variation in surveillance and prophylaxis practices. The overall post-HCT 12-month cumulative incidence in the United States (US) is estimated at 0.29%, albeit with significant regional variation [2], but the rank order of frequency are mucormycosis (MCM), fusariosis, scedosporiosis/lomentosporiosis, and then rare NAIMIs:
 1. MCM refers to NAIMI that are caused by molds that belong to the class of Mucomycetes and the order Mucorales, and their incidence may be increasing [1,10]. The most common pathogens of MCM are *Rhizopus* spp., *Mucor* spp., followed by *Lichtheimia*, *Rhizomucor*, *Cunninghamella*, and others depending on geography [2,11].
 2. *Fusarium* spp. NAIMI are most commonly caused by the *F. solani* species complex, followed by *F. oxysporum* species complex [11,12]. *Fusarium* spp. are the third most common cause of invasive mold infection (IMI) after *Aspergillus* spp. and Mucorales, accounting for <5% of IFD in HCT in the US [1,13]. Invasive fusariosis (IF) has been increasing in the US and is an important cause of breakthrough IMI [14,15]. IF can be more frequent in tropical regions, for example, 20% to 30% of IMI in Brazil [16,17]. Acute myeloid leukemia, hyperglycemia, and antithymocyte globulin therapy are recognized risk factors for IF early after allogeneic HCT, while non-myeloablative conditioning, grade III-IV GVHD, and previous IMI have been associated with IF late posttransplant [18].
 3. *Scedosporium/Lomentospora* spp. were previously all under the one genus *Scedosporium* but *Scedosporium prolificans* has been reclassified as *Lomentospora prolificans*, based on a better understanding of mold phylogenetics. Nonetheless, these molds are all broadly resistant to multiple antifungal agents and

Table 1

Abbreviations Used in this Guideline

Abbreviation	Meaning
AMB	Amphotericin B
AST	Antifungal susceptibility testing
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDG	1,3-beta-D glucan
bIMIs	Breakthrough invasive mold infections
CAR T	Chimeric antigen receptor T cell therapy
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
ECV	Epidemiological cut-off values
FAQ	Frequently asked question
FDG	Fluorodeoxyglucose
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVHD	Graft versus host disease
HCT	Hematopoietic cell transplant
IA	Invasive aspergillosis
IF	Invasive fusariosis
IFD	Invasive fungal disease
IFI	Invasive fungal infection
IQR	Interquartile range
IMI	Invasive mold infection
ITS	Internal transcribed spacer
IV	Intravenous
L-AMB	Liposomal amphotericin B
MALDI-TOF	Matrix-assisted laser desorption/ionization time-of-flight
mcf-DNA	Microbial cell-free DNA
MCM	Mucormycosis
MIC	Minimum inhibitory concentration
NAIMI	Non- <i>Aspergillus</i> invasive mold infection
NAM	Non- <i>Aspergillus</i> mold
NGS	Next-generation sequencing
PCR	Polymerase chain reaction
PET/CT	Positron emission tomography/computed tomography
PK/PD	Pharmacokinetic/pharmacodynamic
rhuGM-CSF	Recombinant human granulocyte-macrophage colony-stimulating factor
TDM	Therapeutic drug monitoring

will be discussed together, highlighting any important differences. These molds are particularly common in arid climates including Australia, the southwest US, and Spain [6,19]. IFD with these pathogens are typically seen in the more immunosuppressed (by

underlying condition, iatrogenesis, or GVHD) and are often seen as breakthrough infections [6].

4. *Rare NAIMI* are those other than 1 to 3 above which account for <10% of all IMIs [1,13,20,21]. Their incidence and epidemiology differ according to geographical area [22]. The most frequent pathogenic molds causing this subset of infections are hyalohyphomycetes (non-dematiaceous molds) such as *Acremonium* spp., *Paecilomyces* spp., *Purpureocillium lilacinum*, *Scopulariopsis* spp., and *Hormographiella aspergillata*; and phaeohyphomycetes (dematiaceous molds) such as *Alternaria* spp., *Exophiala* spp., *Aureobasidium* spp., *Cladophialophora* spp. and *Ochroconis gallopavum* (formerly *Dactylaria gallopava*) [1,22–24]. Among the dematiaceous molds, *Cladophialophora bantiana* has a high propensity for infection of the CNS, causing space-occupying masses [25]. Traumatic (including medical) inoculations can occur [9,26], and the increasing use of mold-active antifungal prophylaxis, while effective in reducing IFDs overall, has been associated with an increasing proportion of these rare NAIMIs, which are often refractory to conventional antifungal therapies [27,28]. Novel diagnostics, especially molecular (PCR) approaches, have likely contributed to a better recognition of rare NAIMI [29]. Because they tend to be less pathogenic but more refractory to antifungal drugs compared to *Aspergillus* spp., they predominantly affect patients with refractory or relapsing hematologic cancer, refractory GVHD, and recent mold-active antifungal therapy [22,30,31].

FAQ2: What are the Risk Factors and Highest Risk Periods for NAIMI in HCT Recipients?

Risk factors include:

- Allogeneic HCT higher than autologous HCT [1], and haploidentical, unrelated, and umbilical cord blood grafts are higher risk compared to matched related donor grafts [1].
- Prolonged neutropenia/delayed engraftment [6,11].
- Acute or chronic graft versus host disease [1,32].
- Lymphopenia [33].
- Prior IMI [2].
- Glucocorticoid treatment [33].
- Diabetes, particularly if poorly controlled, particularly a risk for MCM [2,11].

- Voriconazole prophylaxis, particularly a risk for MCM [2,34–36].
- COVID-19, influenza [37].
- Cytomegalovirus infection [38,39].

Highest risk periods are profound and prolonged neutropenia or increased requirement for immunosuppression due to GVHD (especially chronic glucocorticoids); over half of NAIMIs occurred <6 months post-HCT in a large multi-center US study [1,2].

FAQ3: What are the Clinical Manifestations of MCM in HCT?

Manifestations are often non-specific but overlap with those seen in other populations. HCT recipients frequently have a rapidly progressive, sometimes fulminant presentation [40,41]. Onset is usually >3 months post-HCT (median 135 days) [1], roughly correlating with augmentation of immunosuppressive therapy for GVHD, especially with high-dose glucocorticoids [42]. Rarely, MCM can manifest before neutrophil engraftment [43]. Symptoms and signs depend on site of involvement, and to some extent, the species of infecting organism [3]. An important hallmark of MCM is hemorrhagic necrosis and destruction of affected tissue. However, the differential diagnosis still includes other mold infections or, rarely, necrotizing bacterial infections. Sites of involvement include:

- Pulmonary involvement is most common [41,44], and fever not responding to broad-spectrum antibiotics may be the only manifestation, especially during neutropenia [40,45]. When present, clinical features include fever, cough, hemoptysis (rarely massive), and pleuritic chest pain due to rapidly progressive pneumonia [46].
- Rhino-orbital-cerebral involvement is primarily seen in diabetic and acidotic patients, classically presenting as “pansinusitis” with fever, headache, nasal congestion, and discharge [47]. Contiguous involvement of the maxillary sinus and palate causes palatal necrosis/eschar. Orbital involvement causes periorbital edema, proptosis, and ophthalmoplegia. Orbital apex infection may present as monocular blindness. Lastly, cavernous sinus involvement can lead to cranial nerve palsies (III, IV, V1 to 2, and VI) with internal carotid artery invasion (hemiparesis) and spread to the cerebrum, typically causing inferior frontal lobe infarction [48].
- Less common is skin and subcutaneous infection [43]; gastrointestinal involvement,

presenting as gastrointestinal bleeding or bowel obstruction [49,50]; and disseminated infection manifesting as thromboembolism and vascular infarction most commonly originating from the lung [48].

FAQ4: How to Diagnose MCM in HCT?

For all potential NAIMIs, it is recommended that clinicians and local laboratories seek support from a fungal reference laboratory to optimize the identification of NAMs and perform susceptibility testing as required.

Diagnosis of MCM is challenging due to the non-specific clinical features, lack of pathognomonic radiological signs, and because the organism does not grow in blood and often does not grow in bodily fluid cultures [51]. MCM should be suspected whenever epidemiological factors, clinical, radiological, and laboratory clues of infection are present [52,53]. Current diagnostic criteria use clinical, radiological, and mycological criteria to assign either a “proven,” “probable” or “possible” MCM diagnosis [54].

- Proven rests on identifying the organism in sterile body fluid or tissue obtained via biopsy.
- Probable rests on identification by microscopy or culture of non-sterile samples (eg, BAL or sinus) in the right clinical/radiological context [54].
- Possible rests on imaging findings alone. No sign, including “reverse halo” (ie, outer rim of denser consolidation with inner region of ground glass consolidation) has adequate diagnostic sensitivity and specificity within the setting of hematological malignancy [55]. However, these signs can provide early clinical clues and empirical treatment in the appropriate context. Other imaging findings include multiple pulmonary nodules ± cavitation ± focal consolidation, pleural effusion, or concomitant pansinusitis.

Importantly, there are no validated biomarkers for MCM, as the organism does not have (1 → 3)- β -D glucan (BDG) in its cell wall and does not produce galactomannan [51] (Table 2). Culture remains the diagnostic gold standard but fungal growth may take weeks and false negatives are common because their delicate hyphae may be damaged during sample collection and/or processing. Histopathology demonstrating characteristic angioinvasive hyphal structures is considered diagnostic but requires expert interpretation. Newer PCR molecular methods show promising results for early diagnosis (and predicting

Table 2

Sensitivity of Non-invasive tests (Blood, Plasma, Serum) for the Diagnosis of Uncommon Invasive Mold Infections*

Mold Infection	Blood Culture	Galactomannan	(1 → 3)-β-D Glucan	PCR	NGS
Mucormycosis	<1% [247–249] (Only <i>Mucor</i> spp., very rare)	ND	ND	75%-80% [56,196–198,250] Commercial kits (MucorGenius, MycoGENIE)	See footnote [†]
Fusariosis	35%-40% [15,18,82,83,85]	25%-30% [15,90,92,93] (variable <10%-80%, species-dependent)	75%-80% [90,91]	90%-95% [92] (single study, in-house PCR)	See footnote [†]
Scedosporiosis/ Lomentosporiosis	~5% (Sce) [19] 40%-50% (Lom) [19,251]	ND	~80% [90]	NA	See footnote [†]
Others	>30% (Acr) [134] 15%-20% (Pur) [137] ~10% (Pae, Sco) [136,252] <10% or unknown (others)	Possible cross-reactions (Pur, Pae, Ras, Pen) [253–255]	Unknown (lacking data, few case reports) [256] No detection of basidio- mycetes (Hor, Sch)	NA	See footnote [†]

Sce indicates *Scedosporium apiospermum* complex; Lom, *Lomentospora prolificans*; Acr, *Acremonium* spp.; Pur, *Purpureocillium lilacinum*; Pae, *Paecilomyces* spp.; Sco, *Scopulariopsis* spp.; Ras, *Rasamsonia* spp.; Pen, *Penicillium*; Hor, *Hormographiella aspergillata*; Sch, *Schizophyllum commune*; ND, no detection (the test is not supposed to detect these molds); NA, not available (no report of specific PCR tests).

* Data about specificity not provided. Specificity of blood cultures is considered 100% (gold standard) but contamination may occur, PCR specificity varies from 90% to 100%, the galactomannan test is designed for detection of *Aspergillus* spp. with possible cross-reaction with few other molds, the (1 → 3)-β-D glucan test is not specific to any fungus (detection of most ascomycetes, no detection of basidiomycetes and zygomycetes).

[†] Plasma microbial free-DNA sequencing (eg, Karius) can be considered in situations where NAIMI is suspected, and conventional PCR approaches fail to identify a pathogen. The stored plasma mcfDNA sequencing assay test has reported moderate sensitivity (79%) and high specificity (95%), NPV, and PPV for pulmonary IMI due to non-*Aspergillus* molds [204]. Results should be interpreted cautiously as sensitivity and specificity data are lacking.

outcomes) [56]. Two commercial PCR assays for mucormycetes show early encouraging data [57]. Plasma microbial cell-free DNA sequencing may be useful for diagnosing MCM, but prospective validation studies are needed [58,59].

FAQ5: What are the Management and Prognostic Determinants of MCM?

Cornerstones of management are: (1) reversal of neutropenia to the extent possible with filgrastim, sargramostim, and/or minimizing myelosuppressive polypharmacy, (2) tapering glucocorticoids to the extent feasible, (3) mitigating hyperglycemia via “2” and/or insulin, (4) low threshold of suspicion plus early effective antifungal therapy (first-line liposomal amphotericin B [L-AMB] or isavuconazole, Table 3) and, in selected cases, surgical debridement [52].

Regarding pharmacological management:

- L-AMB 5 mg/kg IV daily is the preferred first-line treatment over non-lipid formulations because mortality is lower based on retrospective, observational study data [3,60–63], there being no randomized controlled data.
- Higher dosages (7.5 to 10 mg/kg) [3] have been recommended for confirmed or suspected CNS infection but data are limited to murine models and very small case series [64,65].
- The benefit of 10 mg/kg L-AMB in non-CNS infection is debated; strong evidence is lacking and higher nephrotoxicity is a concern [65].
- Urgent initiation of L-AMB on the suspicion of MCM has been associated with improved outcomes and is thus the strongest recommendation [66].
- Isavuconazole was approved in the US and the EU as a first-line therapy based on an open-label single-arm trial of isavuconazole that demonstrated similar survival compared to that of historical controls treated with L-AMB [67]. Posaconazole is used mainly as salvage therapy based on uncontrolled cohort studies [68]. It follows that Mucorales-active triazoles should primarily be used as second-line therapy or as oral step-down consolidation therapy after successful induction with L-AMB.
- The merit of combination therapy is unclear. Although L-AMB plus an echinocandin was beneficial in murine models [69,70] and limited non-HCT clinical data [71,72], this combination can only be marginally recommended because a large retrospective study in patients with hematological cancer, including HCT recipients,

did not find benefit [73]. Similarly, clinical data from that study did not support L-AMB plus posaconazole suspension and thus this combination is not recommended [73].

Surgical debridement is strongly recommended where possible, particularly for invasive fungal sinusitis, CNS disease, and skin and soft tissue infections, as it has been associated with survival benefit [60,74]. Disfiguring surgical management of craniofacial structures can be minimized by direct examination of intraoperative selected biopsies [75]. Surgical management of pulmonary MCM should be considered, particularly in the setting of lesions close to critical structures such as large blood vessels [76]. Local instillation of antifungals, intraconal irrigation with AMB, AMB-soaked gauze surgical packing, transcutaneous retrobulbar AMB injections in rhino-orbital MCM, and adjunctive hyperbaric oxygen have been used in selected patients, without robust supporting data [77–79].

Prognosis remains poor despite improvements in early diagnosis, availability of newer MCM-active triazoles, and multidisciplinary interventions [80]. Retrospective allogeneic HCT studies have identified the following negative prognostic factors: age <45 years, female sex, active malignancy, severe lymphopenia, delayed L-AMB treatment, and breakthrough to Mucorales-active agents [32,41,66,81]. Neutrophil recovery is an independent predictor of favorable outcome [66].

FAQ6: What are the Clinical Manifestations and Diagnosis of Fusariosis?

Overall, 50% to 70% of IF cases manifest with cutaneous lesions that may be primary (eg, onychomycosis, paronychia, intertrigo, lymphangitis, cellulitis) or secondary (painful embolic nodules ± central necrosis) during fungemia [15,18,82–86]. In Brazil, skin is the primary site of entry, and lung involvement does not exceed 50% [18,83,85,86]. Lung involvement was 70% to 80% in US cohorts [15,82]; lesions are predominantly nodules or masses, but the halo sign is usually absent [87].

Diagnosis is mostly made by:

- Clinical suspicion (eg, paronychia or skin lesion (s) consistent with secondary emboli).
- Culture and/or tissue histopathology (usually skin) and/or blood cultures which are positive for fungemia in 35% to 40% of cases [15,18,82,83,85,88,89].

Table 3

Recommendations for Antifungal Therapy of Uncommon Invasive Mold Infections in Adult and Pediatric Patients

Mold Infection	First-Line Therapy	Alternative*	Comment
Mucorales	L-AMB or ISA	PCZ	Variable in vitro activity of ISA and PCZ without correlation with clinical outcomes [68,146,160,257,258] L-AMB treatment associated with better outcome compared to other AF regimens [60,61] ISA therapy associated with similar outcomes compared to AMB (historical cohort) [146] PCZ mainly used as secondary or salvage therapy [68,258] Synergism between AMB and echinocandins in murine models, but no impact on clinical outcomes [69–73,259]
<i>Fusarium</i> spp.	VRC or L-AMB alone or in combination	PCZ VRC or L-AMB combined with TBF	Variable in vitro activity for triazoles (VRC, PCZ) without correlation with clinical outcomes [97] In vitro synergism of VRC and TBF [99] VRC and L-AMB equally effective in clinical studies [85,97,260] PCZ effective in salvage therapy [98] TBF may improve cutaneous lesions, but not overall outcome [102]
<i>Scedosporium apiospermum</i> complex	VRC	PCZ or ISA according to AST results Drug combination with mold-active triazole and/or echinocandin and/or TBF	VRC most active in vitro [123,261] Variable in vitro activity of other triazoles (PCZ, ITZ, ISA) [19,123,261] Poor in vitro activity of AMB [19,123,261] AMB formulations associated with significantly worse outcomes compared to VRC and other AF [19]
<i>Lomentospora prolificans</i>	VRC + TBF	Combination including either VRC or TBF with another AF	Poor in vitro activity of all AF [19,123,261] VRC + TBF tended to be associated with better outcomes [127,262] Combination including VRC or TBF associated with better outcomes [127,262] AMB associated with worse outcomes [19]
<i>Acromonium/Sarocladium</i> spp.	VRC	PCZ or L-AMB according to AST results ($\pm$ TBF)	Very limited clinical data and low-quality of evidence VRC and TBF displays the highest in vitro activity [134,263] TBF might be considered adjunctive therapy if susceptible isolate [134]
<i>Hormographiella aspergillata</i>	VRC	L-AMB	Very limited clinical data and low-quality of evidence Most experience with VRC and L-AMB (most active in vitro) [139] Avoid PCZ [139]
<i>Paecilomyces</i> spp.	L-AMB	PCZ (2nd choice) ITZ (3rd choice)	VRC not recommended (poor in vitro activity) [4,96,136] Flucytosine might be considered adjunctive therapy in selected cases [96,136]
<i>Purpureocillium lilacinum</i>	VRC	ITZ or PCZ	L-AMB not recommended (poor in vitro activity, higher mortality rates) [4,96,137] Terbinafine might be considered adjunctive therapy in skin infections [4]
<i>Schizophyllum commune</i>	L-AMB or VRC	PCZ or ISA	Very limited clinical data and low-quality of evidence Low in vitro MIC to L-AMB and mold-active triazoles [264,265]

(continued)

Table 3 (Continued)

Mold Infection	First-Line Therapy	Alternative*	Comment
<i>Scopulariopsis</i> spp.	L-AMB, VRC, or PCZ alone or in combination	AF combination involving CAS and/or TBF (in addition to L-AMB or a triazole)	High in vitro MICs to most licensed antifungal agents [266] Very limited clinical data and low-quality of evidence Poor in vitro activity of all AF [267] In vitro synergism reported for PCZ-TBF, PCZ-CAS, AMB-CAS, PCZ-TBF-CAS [268,269] L-AMB, VRC, and PCZ prolonged survival of mice infected with <i>Scopulariopsis brumptii</i> (but not <i>Scopulariopsis brevicaulis</i>) [270]
<i>Rasamsonia</i> spp.	Echinocandin + triazole (VRC, PCZ) or L-AMB	Monotherapy with echinocandin, VRC, PCZ or L-AMB, according to AST results	Very limited clinical data and low-quality of evidence Variable and relatively high MIC for VRC, PCZ, and AMB [138] Echinocandins most active in vitro (fungistatic effect) [138]
<i>Trichoderma</i> spp.	Echinocandin + triazole (VRC or PCZ)	Echinocandin monotherapy or in combination with L-AMB VRC, PCZ, or L-AMB monotherapy according to AST results	Very limited clinical data and low-quality of evidence Moderate activity of VRC, PCZ, and AMB [271] Echinocandins most active in vitro (fungistatic effect) [271]
Black molds (agents of phaeohyphomycosis)	L-AMB or triazole (VRC, PCZ, ITZ)	Combination therapy of triazoles or L-AMB + echinocandin or TBF (skin lesions), according to AST results	AMB most active drug in vitro with some exceptions (eg, <i>Rhinocladiella</i> spp.) [131] Variable activity of mold-active triazoles [131] No evidence supporting superiority of L-AMB or mold-active triazoles [131,272–274] VRC recommended for brain infection (higher penetration) [131,275]

L-AMB indicates liposomal formulation of amphotericin B; ISA, isavuconazole; PCZ, posaconazole; AMB, amphotericin B; VRC, voriconazole; AST, antifungal susceptibility testing; TBF, terbinafine; ITZ, itraconazole; AF, antifungal drug; CAS, caspofungin.

* In case of contraindication, toxicity, or failure of first-line therapy.

- Although not specific for *Fusarium* spp., serum BDG has 75% to 80% sensitivity for IF and mostly preempts culture positivity [90,91]. Serum galactomannan is variably positive (25% to 30% overall) [15,90,92,93], and may be elevated with other invasive mold diseases (eg, *Aspergillus* spp.). Infection of the CNS by *Fusarium* spp. can be detected and monitored by cerebrospinal fluid (CSF) BDG [94].
- As *Fusarium* spp. initially grow in culture as hyaline hyphae without characteristic macroconidia, which may require several days to develop, laboratories equipped with matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) spectroscopy may be able to rapidly identify these organisms at an early stage of growth [95].
- Non-culture diagnostic tools such as a quantitative PCR specific for *Fusarium* spp. that detected 14 of 15 cases several days prior to positive culture shows promise [92], however, commercialized assays are not yet available.

FAQ7: What are the Management and Prognostic Determinants of Fusariosis?

Cornerstones of management are: (1) voriconazole or L-AMB as first-line therapy irrespective of antifungal susceptibility testing (AST) results [4,85,88,96], (2) reversal of neutropenia, (3) careful withdrawal of glucocorticoids and (4) surgical debridement, whenever possible. For refractory IF, posaconazole monotherapy or combination therapy (triazole + L-AMB or terbinafine) can be used. Higher dosages of L-AMB and voriconazole may be required for CNS disease.

Regarding pharmacological management:

- In vitro, susceptibility to amphotericin B or triazoles is variable across *Fusarium* spp. but also across isolates of the same species. However, the value of AST is debated because correlations between MIC and clinical outcomes have not been demonstrable [88,97]. Recovery from neutropenia and immunosuppression may be more critical determinants of outcome.

- Outcomes were similar for voriconazole and L-AMB but mortality was higher with deoxycholate amphotericin B [85].
- Posaconazole is not recommended as first-line treatment [4,96] because IF is a frequent breakthrough IMI during posaconazole prophylaxis [14,15]. However, posaconazole is considered a limited rescue therapy (success rates <20%) in persistent neutropenia [98].
- Combination triazoles with L-AMB or terbinafine are recommended by guidelines but evidence for superior benefit is limited in clinical as well as murine studies [4,82,99–106]. It is worth mentioning that terbinafine undergoes irreversible protein binding and is thus unlikely to be available to exert antifungal activity at most sites of IFD except skin and nails [107].

Surgical debridement of localized infection is usually recommended to prevent dissemination and improve outcome [4,84,88,96], however, debridement of multiple cutaneous lesions is not recommended. In the rare cases where an intra-vascular catheter is the clear source of fungemia, it should be removed [88,108].

Neutrophil recovery is a key factor for survival [15,82,85]. Conversely, persistent neutropenia and/or receipt of glucocorticoids have been associated with poor prognosis [15,82,85]. Some studies reported better prognosis for localized skin lesions and worse prognosis for pulmonary or disseminated IF [15,82]. Mortality rate remains high at 60% to 70% with outcome primarily determined by host immune status [109,110]. Mortality might be higher with *F. solani* and *Fusarium proliferatum* compared to other species [111].

FAQ8: What are the Clinical Manifestations and Diagnosis of Scedosporiosis in HCT?

L. prolificans infections are often disseminated at presentation (lung, blood, CNS, skin), with a median time to death of 6 days in one large study [6]. Pulmonary and CNS lesions appear similar to other IMIs. Skin lesions are violaceous and necrotic and signify dissemination. *Scedosporium* spp. presents similarly, either disseminated, or as a localized infection after traumatic inoculation; median time to death was 131 days [6,112]. Both pathogens can also affect paranasal sinuses and can cause hematogenous endophthalmitis. Less commonly, other deep organ infection (eg, liver, spleen, kidneys, bone) and rarely endocarditis can be observed [6,19,113,114]. Bone infection by *Lomentospora/Scedosporium* spp. may be the result

of hematogenous dissemination or direct traumatic inoculation.

Regarding diagnosis of *Lomentospora/Scedosporium* spp. infections:

- Traditionally this relies on blood cultures or tissue biopsy [4], noting that blood cultures, whilst highly specific, are <50% sensitive for invasive scedosporiosis [6,19]. Species identification from cultures is subsequently achieved through macroscopic and microscopic colony examination and can be confirmed by internal transcribed spacer gene sequencing using a “panfungal PCR,” which may also be performed on formalin-fixed paraffin-embedded samples, although fresh tissue is preferred [115,116]. For those clinical laboratories using MALDI-TOF technology, a mycological diagnosis of *Lomentospora/Scedosporium* spp. may be rapidly made directly from an early colony growth [117]. There are no commercially available PCR assays specific for *Lomentospora/Scedosporium* spp. at present [29].
- Regarding biomarkers, galactomannan will be negative; BDG may be elevated but is neither sensitive [90] nor specific [118].

FAQ9: What are the Management and Prognostic Determinants of Scedosporiosis?

Cornerstones of management are: (1) voriconazole is first-line for *Scedosporium* spp. [19,119,120], but combination voriconazole plus terbinafine is first-line for *L. prolificans*; (2) reversal of neutropenia [121], (3) glucocorticoid tapering as much as feasible and (4) surgical debridement whenever possible for either species.

Regarding pharmacological management:

- Treatment options are limited due to intrinsic resistance of *Lomentospora/Scedosporium* spp. to most commonly available antifungals [122,123]. The relative rarity of these fungi also means recommendations are based on low-quality evidence from just observational studies:
 - Against *Scedosporium* spp., voriconazole performed better than amphotericin B, including improved survival [19,120,124].
 - Against *L. prolificans*, L-AMB should be avoided as first-line therapy due to its inferior performance compared to voriconazole [120]. However, voriconazole is variably successful, with just 44% successful response to therapy in the voriconazole global trial registry [119]. Limited preclinical [125,126] and observational clinical data suggests improved

survival with the combination of voriconazole and terbinafine, and this has become a standard of care in many centers [4,106,127]. It follows that contemporary cohorts often lack power to compare combination to now rarely used monotherapy [6]. It is worth again mentioning (see FAQ7) that unlike skin and subcutaneous adipose tissue, terbinafine may not achieve adequate levels in lung and CNS/eye [107]. Thus, any observed benefit of combining terbinafine in any disseminated NAIMI needs to be interpreted with caution [102].

Where possible, surgical debridement is recommended given observed survival association [4,6,127] despite the cautionary caveat that debridement may be used more frequently in those with lower acuity, localized versus disseminated infections.

Prognosis is poor for disseminated infections, which are often rapidly fatal [2,19]; *L. prolificans* has a higher mortality rate (60% to 70% at 1 month) compared to that of *Scedosporium* spp. (20% to 50%) [6,19], in part explained by the latter's higher rates of localized infection [6].

FAQ10: What are the Clinical Manifestations, Diagnostic Methods, Treatments, and Outcomes of Other Unusual Molds?

Clinical presentation of rarer NAIMIs may be indistinguishable from those more frequent NAIMI discussed in FAQ3-9; interpretation of serum galactomannan and BDG results may be confusing and consultation with Infectious Disease is recommended (see FAQ1 and Supplement).

The standard diagnostic approach utilizes cultures, but non-culture methods, specifically pan-fungal PCR and MALDI-TOF, should be used whenever possible to improve diagnostic sensitivity and accuracy. Fungal PCR testing that targets conserved ribosomal regions (eg, internal transcribed spacer, 26-28S, 18S) is not widely available, commercialized, or standardized [29]; contact with a fungal reference laboratory is recommended. Metagenomic next-generation sequencing is another novel promising diagnostic approach [29,128]. However, once an organism is recovered, MALDI-TOF technology can rapidly identify the organism at an early stage of growth before any diagnostic mycological structures are present.

Because these rare molds have very specific resistance profiles, invasive procedures should be

undertaken to obtain a deep tissue isolate for identification and AST (AST should be used as a rough guide, however). Blood cultures may be useful to detect some species causing fungemia, but a propensity for slow growth means results are often delayed by days or weeks.

Cornerstones of management are: (1) Fungal speciation [4,96,129] and AST results (fungal reference laboratory involvement is advised) to inform antifungal therapy in the absence of established therapeutic recommendations (Table 3) [129,130]. (2) Careful clinical staging, and antifungal dosage, end-organ toxicity, drug-drug interactions, therapeutic drug monitoring, and antifungal drug distribution and penetration should be carefully considered given the propensity for disseminated disease including brain abscesses. (3) Surgical debridement is considered whenever feasible, especially for extrapulmonary foci [131–133]. Lastly, (4) immunosuppressive therapies should be reduced whenever possible [129].

Despite limited data, duration of therapy follows other IMIs according to site of infection [4,96,131].

Paradoxically, although less virulent, these rare NAIMIs tend to occur in the most immunosuppressed patients, are broadly resistant to antifungals, and thus are often refractory [30,129]. Overall mortality rates are 40% to 70%, except 20% to 30% for *Purpureocillium* and *Paecilomyces* infections [134–139].

FAQ11: What are the Primary and Secondary Prophylaxis Issues of NAIMI?

Intrinsic antifungal resistance significantly complicates prophylactic strategies. Because there is no perfect prophylactic agent for NAIMIs, primary prophylaxis is tailored to the most likely pathogens (*Candida*- and *Aspergillus* spp.). Posaconazole has good efficacy against *Aspergillus* spp. and the commonest NAIMIs (especially Mucorales), is reasonably well-tolerated with mostly manageable drug-drug interactions [140], and hence it remains the preferred agent in most cases [141]. For secondary prophylaxis, it is recommended to select the prophylactic agent with the best in vitro activity against the specific NAM encountered [142]. Optimal duration of antifungal prophylaxis is not defined but should continue at least until engraftment, beyond which additional risk factors contribute to the individualized decision to continue prophylaxis, including presence of GVHD, active malignancy, cytomegalovirus reactivation, and poor graft function [143].

In addition to primary and secondary antifungal prophylaxis, minimization of environmental exposures against molds both during hospitalization and in the outpatient setting is important as previously published regarding the much more common mold infection, that of aspergillosis [144]. In addition, education and practical recommendations targeting both clinicians and patients regarding potential sources of fungal infections outside the hospital are useful [145].

FAQ12: How do We Assess Treatment Response and Determine Duration of Therapy in NAIMI?

The natural course of NAIMIs is not well described and response assessment and duration of therapy decision-making is extrapolated from invasive aspergillosis (the commonest IMI) [144]. Treatment is very individualized but includes an initial phase, followed by consolidation or secondary prophylaxis, and may last months, or years [68,146,147]. Considerations include site and extent of infection, whether surgical debridement occurred, neutrophil recovery, status of underlying condition, type of transplant, presence of GVHD, and corticosteroid dose-regimen [147,148]. A minimum 3 months of systemic therapy is recommended in disseminated NAIMI, longer in sanctuary sites such as bone, joint, and CNS infection. Response is assessed based on a combination of clinical and radiological factors, and rarely mycological data. Ideally, there should be complete resolution of infection manifestations, with diminishing or complete resolution of radiological signs and reversal of the net state of immunosuppression [3,148]. Complete radiological resolution may be elusive in clinical practice because confounding factors may contribute to imaging findings like postinfectious scarring, organizing pneumonia, postsurgical changes, and observer variability in assessing lung lesions [149]. Importantly, neutrophil recovery can result in “pseudo-progression” in the early clinical course [150]. When symptoms resolve, but lung imaging findings persist, positron emission tomography/computed tomography may be reassuring [151,152] if there is a decrease or normalization of fluorodeoxyglucose uptake [153]. Due to risk of relapse, secondary prophylaxis should be considered in those with ongoing risk factors (see FAQ11).

FAQ13: What are the Special Considerations in Approach to Breakthrough NAIMIs?

Breakthrough IMIs (bIMIs) are commonly defined as new IMIs developing after ≥ 7 days for

mold-active azoles and polyenes [154] and are becoming more prevalent as the use and duration of antifungals increases [155]. When bIMI is suspected, diagnostic workup should include CT imaging, early bronchoscopy with bronchoalveolar lavage (BAL) or biopsy of the affected site (if possible), and AST if an isolate grows from culture [155]. Therapeutic drug monitoring is necessary for posaconazole or voriconazole to verify appropriate exposure at the time of suspected breakthrough [155]. Experts generally recommend switching to a different broad-spectrum triazole or to L-AMB, but if bIMIs occur while on L-AMB, resistant infections caused mainly by *Scedosporium/Lomentospora*, *Scopulariopsis* and *Paecilomyces* should be considered, and L-AMB would be switched to voriconazole or isavuconazole $\pm$ echinocandin [155].

FAQ14: Can We Transplant Patients with a History of NAIMI?

Clinical decision-making on transplant candidacy must be individualized and leverages multidisciplinary input [156], especially consultation from infectious diseases and surgery. Considerations include patient comorbidities, malignancy, conditioning, stem cell source, antifungal treatment, and fungus-specific issues that affect the risk of recurrent post-HCT IMI. Supporting literature is mostly uncontrolled and derived from the more familiar setting of invasive aspergillosis. Literature specific to NAIMI is scarce, mostly older, and highlights poor outcomes due to the propensity for tissue invasion, early dissemination, and broad antifungal resistance [32,129,157]. However, improvements in early diagnosis and use of potent broad-spectrum triazoles have made successful allogeneic HCT feasible [158]. Achievement of hematologic remission, evidence of at least partial response to antifungal therapy, and when feasible, surgical debulking of residual infectious foci factor into the HCT candidacy decision-making [156]. Selection of conditioning intensity must balance IMI relapse-related mortality against concerns for hematologic malignancy relapse-related mortality. Peripheral blood stem cell grafts are preferred over marrow or umbilical cord blood grafts due to more rapid neutrophil engraftment [159].

In contrast, patients at highest risk for post-HCT IMI relapse (refractory hematological malignancy, cord blood, and mismatched grafts, prolonged cytopenias, severe or refractory GVHD, infection with rare $\pm$ drug-resistant mold, disseminated or extensive sinopulmonary IMI, comorbidities, <4

weeks antifungal treatment), if transplanted, need to be very closely monitored. Secondary prophylaxis should be highly individualized, and involvement of a mycology expert is recommended.

FAQ15: Which Antifungal Drug-Drug Interactions During HCT Should Clinicians be Aware of?

When treating NAIMIs, antifungal drug-drug interactions cannot be overemphasized (Tables 4 to 6) and close collaboration with an HCT pharmacist is strongly recommended to determine appropriate monitoring and/or preemptive dose adjustments to minimize adverse events. The main practice points relate to significant inhibition of CYP3A4, especially with posaconazole and voriconazole, and to a lesser extent with isavuconazole, which can exacerbate conditioning toxicity, especially with busulfan, cyclophosphamide, and etoposide. Substantial preemptive dose reductions of immunosuppressants may be strongly recommended, for example, 90% for sirolimus, 67% for tacrolimus if concomitantly receiving voriconazole (Tables 5 and 6). Due to potentially serious drug-drug interactions, antifungal agents with significant inhibition of CYP3A4 should not be administered concomitantly in HCT conditioning regimens.

FAQ16: What is the Role of Antimicrobial Susceptibility Testing for Management of NAIMIs?

AST has a limited role except in selected cases. This is because neither Clinical and Laboratory Standards Institute nor European Committee on Antimicrobial Susceptibility Testing have established clinical breakpoints for NAM [129,130]. Epidemiological cut-off values have been assessed for Mucorales and *Fusarium* spp. [160,161] but without known resistance mechanisms and lack of clinical data for these rare pathogens, epidemiological cut-off values should be interpreted cautiously. In murine models, MIC outcome correlations for Mucorales, *Fusarium* spp., and *Scedosporium* spp. yielded controversial results

[162–166]; clinical studies addressing the same question are scarce and demonstrated correlations in the setting of complex confounders [97,167]. Current clinical guidelines support using AST mainly for epidemiological purposes with a low/marginal recommendation for guiding antifungal therapy [3,96]. However, AST results might help in selected cases of refractory infection, when therapy recommendations are absent (ie, very rare molds), or drug intolerance.

FAQ17: Are There Special Considerations for NAIMI in Pediatric HCT Recipients?

Epidemiology—Children do not differ fundamentally from adults in terms of risk factors, clinical presentation, or the most commonly reported pathogens (Mucorales, *Fusarium*-, *Scedosporium*- and *Lomentospora* species) [1,11,168–173], and association with breakthrough infections [27,28]. However, patients undergoing HCT for primary immunodeficiencies have distinctive risks for IFDs in their pretransplant care [174]. In combined series of pediatric cancer and HCT patients, NAIMIs have accounted for a variable 0% to 35% of all proven/probable IFDs [175,176]. Analysis of 18 retrospective, single- and multicenter cohort study publications from 2000 to 2024 shows that pediatric NAIMIs account for 0% to 29.7% after allogeneic HCT and none of the proven/probable IFIs after autologous HCT (Supplementary Table 1). Trends in incidence, geographic patterns, or mortality rates over time cannot be deduced from these mostly unsystematic data.

Diagnostic approaches—Imaging and standard diagnostic microbiological approaches mirror those in adults with an emphasis on culture and microscopic examination of appropriate liquid and tissue specimens [177]. One detail is that pediatric validation of non-culture-based methods for NAIMI detection do not exist, albeit there is little rationale to assume fundamental differences from adult studies [176,178].

Evaluation of antifungals—Based on current concepts of pediatric drug development reflected in pediatric guidelines [3,4,176,179,180],

Table 4
Triazole Metabolism/Transport Effects

	Isavuconazonium	Itraconazole	Posaconazole	Voriconazole
Substrate	CYP3A4 (major)	CYP3A4 (major)	UGT1A4	CYP2C19 (major) CYP2C9 (minor)
Inhibitor	CYP3A4 (moderate) OCT1, OCT2, P-gp	CYP3A4 (strong) P-gp	CYP3A4 (strong) P-gp	CYP3A4 (strong) CYP2C19 (moderate) CYP2C9 (weak)
Inducer	CPY2B6 (weak)			

Table 5

Drug-Drug Interactions with Antifungal Therapy and Commonly Use Medications in Stem Cell Transplant [276–322]

	Isa v	Itra	Pos a	Vori	L- AMB*	Echid	Metabolism/Transport Effects Clinical Considerations
Conditioning Regimen Chemotherapy(278, 279)							
Busulfan	▲	▲	▲	▲	◆	◆	-Extensive hepatic metabolism; glutathione via GST catalysis • Triazoles may decrease Busulfan clearance, increasing serum concentration. • PK analysis with Busulfan strongly recommended if need to continue concomitant triazole
Carboplatin	◆	◆	◆	◆	◆	◆	-Minimal hepatic metabolism
Cyclophosphamide (280-284)	▲ ▼	▲ ▼	▲ ▼	▲ ▼	◆	◆	-Substrate: CYP3A4, CYP2C9, CYP2C19, CYP2B6 , CYP2A6 -Prodrug: Hepatic metabolism to active metabolites • Bi-directional interaction concerns given hepatic metabolism via CYP450 enzymes to active metabolites. • Triazole may inhibit metabolism to active metabolites. • Triazole may increase serum concentration of active metabolites, such as hydroxycyclophosphamide, which is further metabolized to the toxic acrolein degradation product
Etoposide	▲	▲	▲	▲	◆	◆	-Substrate: CYP3A4 , P-gp , CYP1A2, CYP2E1 • Given high doses of VP16 used during SCT, recommend avoiding concomitant triazole use if able
Fludarabine	◆	◆	◆	◆	◆	◆	-Rapid dephosphorylation
Melphalan	◆	◆	◆	◆	◆	◆	-Hepatic metabolism via chemical hydrolysis
Thiotepa	▼	▼	▼	▼	◆	◆	-Substrate: CYP3A4 , CYP2B6 -Inhibits: CYP2B6 -Prodrug: Hepatic metabolism to active metabolites • Triazole may decrease thiotepa metabolism to active metabolites (TEPA), decreasing efficacy.
Graft-Versus-Host Disease (GVHD)(278, 279, 285, 286)							
Cyclosporine (287)	●	●	●	●	◆	●	-Substrate: CYP3A4 , P-gp -Inhibits: BCRP/ABCG2, BSEP/ABCB11, CYP2C9, CYP3A4, OATP1B1/1B3, P-gp • See table 4C for empiric dose adjustment considerations. • CSA may increase serum concentration of caspofungin, possibly through competitive inhibition of P-gp. Monitor for adverse events (e.g. hepatotoxicity)
Tacrolimus	●	●	●	●	◆	▼	-Substrate: CYP3A4 , P-gp • See table 4C for empiric dose adjustment considerations. • Not typically clinically significant, however caspofungin may dec. tacro conc, continue tacro TDM-no empiric dose adjustment recommended
Sirolimus (288)	●	●	●	●	◆	▼	-Substrate: CYP3A4 , P-gp • See table 4C for empiric dose adjustment considerations. • Not typically clinically significant, however caspofungin may dec. siro conc, continue siro TDM- no empiric dose adjustment recommended
Mycophenolate Mofetil	▲	◆	◆	◆	◆	◆	-Substrate: OAT1/3, OATP1B1/1B3 (SLCO1B1/1B3), UGT1A10, UGT1A8, UGT1A9, UGT2B7 • Isav inhibits UGT-mediated mycophenolic acid conjugation, increased serum conc. of MMF
Belumosudil (289, 290)	◆	◆	◆	◆	◆	◆	-Substrate: CYP3A4 , P-gp, CYP2C8 CYP2D6, UGT1A9 -Inhibits: BCRP/ABCG2, OATP1B1/1B3 (SLCO1B1/1B3), P-glycoprotein/ABCB1 • No clinically significant interaction seen when co-administered with itraconazole in healthy subjects
Ibrutinib (291-293)	▲	■	●	●	◆	◆	-Substrate: CYP3A4 , CYP2D6 • For Chronic GVHD: Decrease to 140 mg/day. May consider 280 mg/day with voriconazole 200 mg twice daily (higher doses not studied) • Strong CYP3A4 inhibitors (excluding posa and vori) are not recommended for co-administration
Ruxolitinib (294)	▲	▲	▲	▲	◆	◆	-Substrate: CYP3A4 , CYP2D6 • For acute or chronic GVHD, no initial dose adjustment recommended
Antimicrobial Agents							
Letermovir (295-298)	◆	◆	◆	●	◆	◆	-Substrate: CYP3A, CYP2D6, UGT1A1, UGT1A3, P-gp , OATP1B1/3 -Inhibits: CYP3A, CYP2C8, P-gp, OAT3, OATP1B1/3 -Inducer: CYP2C9, CYP2C19, CYP2B6, CYP3A • LTV dec. vori serum conc. via CYP2C19/2C9 induction • Vori TDM strongly recommended. Onset of induction interactions are days to weeks, will need to continue vigilant monitoring with concomitant therapy. • Currently, no empiric dose adjustment recommended. • Consider stopping LTV if concerned for vori therapeutic failure due to drug-drug interaction if unable to use alternate anti-fungal
Rifampin (Rifamycin class) (299)	■	■	■	■	◆	●	-Substrate: OATP1B1/1B3 (SLCO1B1/1B3), P-glycoprotein/ABCB1 -Inhibits: OATP1B1/1B3 (SLCO1B1/1B3) -Induces: CYP3A4 , CYP2C19 , BCRP/ABCG2, CYP1A2, CYP2B6 CYP2C8, CYP2C9, OATP1B1/1B3 (SLCO1B1/1B3), P-gp, UGT1A1, UGT1A9 • Rifampin should be avoided.

(continued)

							- Alternative rifamycin class agent should be considered if absolutely needed, however will still have significant impact on triazoles dec serum conc./inc risk for therapeutic failure. - Caspo dose should be increased to 70 mg/day
Maintenance Chemotherapy(300-303) <i>-Post-SCT maintenance chemotherapy with allogeneic SCT is still being studied; recommendations for dose adjustments are based on data extrapolated from leukemia dosing or drug pharmacokinetics when SCT data unavailable.</i>							
Venetoclax (304)	●	●	●	●	◆	◆	-Substrate: CYP3A4 , P-gp, BCRP/ABCG2 • Venetoclax length of therapy per cycle cannot be recommended at this time. Dosing recommendations based on known interactions and available tablet size. • Posa/ltra: 50 mg/day; Vori: 100 mg/day; Isav: 200 mg/day
Azacitidine (305)	◆	◆	◆	◆	◆	◆	-Hepatic metabolism; hydrolysis and deamination
Decitabine and Cedazuridine (306)	◆	◆	◆	◆	◆	◆	-Decitabine, cytidine deaminase; Cedazuridine, physiochemical degradation
Gilteritinib (307, 308)	▲	▲	▲ [†]	▲ [†]	◆	◆	-Substrate: CYP3A4 , P-gp • Triazole may increase serum conc. of gilteritinib • Available maintenance trial utilized 120 mg/day but noted increased myelosuppression that could be contributed to concomitant azole. Consider starting at 80 mg/day to account interaction with triazoles.
Midostaurin (309-311)	▲	▲	▲ [†]	▲ [†]	◆	◆	-Substrate: CYP3A4 -Inhibits: BCRP/ABCG2, OATP1A1/SLCO1A1, OATP1B1/1B3 (SLCO1B1/1B3) -Induces: CYP2B6, MRP2 • Triazole may increase serum conc. of midostaurin • Available maintenance trial utilized 50 mg twice daily
Quizartinib (312)	▲	●	● [†]	● [†]	◆	◆	-Substrate: CYP3A4 , P-gp, BCRP/ABCG2 • Triazole may increase serum conc. of quizartinib • Dose adjustment recommendations based on goal dose
Sorafenib (313-315)	◆	▲	▲	▲	◆	◆	-Substrate: CYP3A4 , UGT1A9 -Inhibits: BSEP/ABCB11, UGT1A1, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A4, P-gp -Prodrug: Hepatic metabolism to active metabolites • Available PK data demonstrated although ketoconazole (strong CYP3A4 inhibitor) decreased concentration of active N-oxide formation noted, did not increase sorafenib exposure; albeit low dose sorafenib was utilized for this study. • Patient should be monitored closely with used in combination with strong CYP3A4 inhibitors. • Available maintenance trial utilized dose-escalation to goal of 800 mg/day of sorafenib; about half the patients required dose modification.
Bosutinib (316)	■	■	■	■	◆	◆	-Substrate: CYP3A4 • Triazole may increase serum conc. of bosutinib. • Prescribing information recommends avoiding use with moderate/strong CYP3A4 inhibitors • Currently lack of data to recommend potential dose adjustment
Dasatinib (317)	▲	●	● [†]	● [†]	◆	◆	-Substrate: CYP3A4 • Triazole may increase serum conc. of dasatinib • Dose adjustment recommendations based on goal dose
Nilotinib (318)	▲	●	● [†]	● [†]	◆	◆	-Substrate: CYP3A4 , P-gp -Inhibits: CYP3A4 • Triazole may increase serum conc. of nilotinib • Dose adjustment recommendations based on goal dose
Ponatinib (319)	▲	●	●	●	◆	◆	-Substrate: CYP3A4 , P-gp, BCRP/ABCG2, CYP2C8, CYP2D6 -Inhibits: BSEP/ABCB11 • Triazole may increase serum conc. of ponatinib • Dose adjustment recommendations based on goal dose
Enasidenib (320)	●	●	●	●	◆	◆	-Substrate: CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B15, UGT2B7 -Inhibits: CYP1A2 , BCRP/ABCG2, CYP2C19, CYP2D6, OATP1B1/1B3 (SLCO1B1/1B3) -Induces: CYP3A4 • Enasidenib may dec. triazoles serum concentration via CYP3A4 induction • Vori/Posa TDM strongly recommended. Onset of induction interactions are days to weeks, will need to continue vigilant monitoring with concomitant therapy.
Ivosidenib (321, 322)	▲	●	● [†]	■ [†]	◆	◆	-Substrate: CYP3A4 , P-gp -Induces: CYP3A4, CYP2C9 • Bi-directional interaction given substrate and induction properties of ivosidenib • Strong CYP3A4 inhibitors: Reduce to Ivosidenib 250 mg/day • Ivosidenib dec. voriconazole serum concentration via CYP2C9 and CYP3A4 induction and unlikely to achieve therapeutic levels. Recommend alternative antifungal if able. • Ivosidenib dec. other triazoles serum concentration via CYP3A4 induction

(continued)

								Posa TDM strongly recommended. Onset of induction interactions are days to weeks, will need to continue vigilant monitoring with concomitant therapy.
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*Although no drug interactions are observed, L-AMB is metabolize hepatically and known to be nephrotoxic. Caution should be used when using in combination with other medications as overlapping toxicity increases the risk for hepatotoxicity and renal failure.

†Increase risk for QTc prolongation with concomitant therapy; need close monitoring with EKGs

Bold=Major; Isav=Isavuconazolum; Itra=Itraconazole; Posa=Posaconazole; Vori=Voriconazole; L-Amb=Liposomal Amphotericin B; Echid=Echinocandin; PK=Pharmacokinetic; P-gp=P-glycoprotein; VP16=Etoposide; CSA=Cyclosporine; Caspo=caspofungin; Tacro=tacrolimus; TDM=therapeutic drug monitoring; Siro=Sirolimus ; LTV=letermovir

Color Legend

◆	No clinically significant interaction expected
▲	Known drug-drug interaction with increase in co-administered medication serum concentration with no empiric dose adjustments. Close monitoring recommended. Potential risk for increased adverse events
▼	Known drug-drug interaction with decrease in co-administered medication serum concentration with no empiric dose adjustments. Close monitoring recommended. Potential risk for therapeutic failure.
▲▼	Known drug-drug interaction with potential for either increase or decrease in co-administered medication serum concentration attributed to bi-directional interaction with no empiric dose adjustments. Close monitoring recommended. Potential risk for increased adverse events or therapeutic failure.
●	Known drug-drug interaction with expected increase in serum concentration of co-administered medication. Requires dose adjustment, altered timing of administration, and/or additional monitoring. Increased risk for toxicity/adverse events
●	Known drug-drug interaction with expected increase or decrease in serum concentration of anti-fungal therapy. Requires dose adjustment, altered timing of administration, and/or additional monitoring. Potential risk for increased adverse events or therapeutic failure.
■	These drugs should not be co-administered

recommendations for prophylaxis and therapy are based on (1) efficacy evidence from adult studies; (2) quality pediatric pharmacokinetic data; (3) pediatric data on safety and, where available, efficacy; and (4) regulatory approval for use in children.

While recommendations for children may mirror those for adults, selection of antifungal prophylaxis or treatment should be guided by the aforementioned points 2 to 4 when data are available [176]. Current recommendations for pediatric dosing of antifungal agents are provided in Table 7.

Treatment—Recommendations for MCM are based on small phase II studies and, for other NAIMs, just case series and individual case reports [176].

- MCM: Similar to adults, first-line treatment is with L-AMB, [3,176,181]. For CNS infections, L-AMB is preferred for pharmacokinetic and

pharmacodynamic reasons [176,181]. Isavuconazole is an alternative to L-AMB for age ≥ 1 year based on US and EU drug approvals [182–185]. Second-line treatment does not differ from that of adults [3,176].

- Other rare NAIMs are treated as for adults. Recently updated international guidelines headed by the European Confederation of Medical Mycology include pediatric-specific considerations [4].

Ancillary management, as in adults, includes prompt initiation of antifungals, reduction of glucocorticoids, filgrastim, and granulocyte transfusions (where feasible), and/or surgical debridement in selected patients.

Prophylaxis does not differ from that of adults and should consider local epidemiology, and also cover *Aspergillus* and *Candida* spp. as the major risk factors overlap.

Table 6

Empiric Dose Adjustment Considerations for Immunosuppressive Therapy and Triazoles

	Tacrolimus		Cyclosporine		Sirolimus	
Antifungal	Dose ↓		Dose ↓		Dose ↓	
Isavuconazonium	25%	Consider	25%	Consider	50%	Consider
Itraconazole	50%	Consider	50%	Consider	Not studied	
Posaconazole suspension*	50%-67%	Consider	25%	Consider	50%	Consider
Posaconazole tabs/IV	50%-90%	Strongly consider	25%-50%	Strongly consider	50%-90%	Essential
Voriconazole	67%	Strongly consider	50%	Strongly consider	90%	Essential

* Posaconazole suspension is NOT recommended if patients are able to take posaconazole DR tablets given the erratic absorption. Posaconazole suspension $\neq$ posaconazole tablets/IV.

Table 7

Summary of Approved Indications, Pediatric Dosing, and Pediatric Approval of Antifungal Agents Used for Management of NAIMIs*

Antifungal Agent	Summary of FDA Approved Indications [†]	Pediatric Dosage Range	Comments
Amphotericin B deoxycholate	Treatment of IFDs	0.7–1.5 mg/kg/d IV in one single dose	PK and dosing not different relative to adults; infusion-related reactions and nephrotoxicity curtail clinical usefulness
Liposomal amphotericin B	Treatment of IFDs and empirical therapy in granulocytopenic patients	3–5 mg/kg/d IV in one single dose	PK and dosing not different relative to adults; infusion-related reactions and nephrotoxicity less frequent relative to amphotericin B deoxycholate
Itraconazole	Treatment of superficial <i>Candida</i> infections; treatment of blastomycosis and histoplasmosis; 2nd line treatment of invasive candidiasis, aspergillosis and cryptococcosis, and antifungal prophylaxis in granulocytopenic patients (European Union)	5 mg/kg/d PO of the suspension in two divided doses +TDM 2.5 or 5 mg/kg IV on one single dose +TDM	Limited pediatric PK data in 2–17 year old subjects, no principal differences relative to adults. Similar problems with absorption. High PK variability requires TDM. High potential for relevant drug-drug interactions. Not licensed in subjects <18 years, no PK data for children <2 years
Isavuconazole	Treatment of invasive aspergillosis and treatment of mucormycosis	≥1 year old: 10 mg/kg of isavuconazonium sulfate (days 1 and 2: three times daily); followed by 10 mg/kg of isavuconazonium sulfate once daily IV 6 years of age and older weighing ≥16 kg, age and weight-based PO dosing (capsules)	Linear pharmacokinetics without principal differences relative to adults. Potential for relevant drug-drug interactions. TDM suggested. Not licensed in subjects <1 year (IV solution) and in subjects <6 years of age weighing <16 kg (PO capsules)
Posaconazole	Treatment of invasive aspergillosis; 2nd line treatment of fusariosis, chromo-blastomycosis, and coccidioidomycosis (European Union); treatment of oropharyngeal candidiasis; antifungal prophylaxis in AML/MDS and allogeneic HCT patients	≥2 years old: 6 mg/kg once daily (maximum 300 mg; day 1: twice daily) IV; >40 kg: 300 mg once daily (day 1: twice daily) PO (delayed-release tablets); ≤40 kg: weight-based once daily dosing (day 1: twice daily) PO (powder for delayed-release oral suspension)	Sufficient pediatric PK data; no principal differences relative to adults. Potential for relevant drug-drug interactions. TDM suggested. Not licensed in subjects <13 years for treatment of invasive aspergillosis (results of the phase II study of the Pediatric Investigation Plan not available yet)
Voriconazole	Treatment of invasive aspergillosis, fusariosis, scedosporiosis; treatment of candidemia in non-granulocytopenic patients; treatment of esophageal candidiasis; antifungal prophylaxis in allogeneic HCT patients (European Union)	2–<12 years/12–14 years and <50 kg: 8 mg/kg BID (day 1: 9 mg/kg BID) IV and 9 mg/kg BID PO; ≥15 years and 12–14 years and ≥50 kg: 4 mg/kg BID (day 1: 6 mg/kg BID) IV; 200 mg BID PO +TDM (all)	Optimal dose uncertain, and age-dependent; high PK variability requires TDM, at least in the setting of treatment. Relevant potential for drug-induced adverse events, and high potential for relevant drug-drug interactions. Not licensed in subjects <2 years of age.

(continued)

Table 7 (Continued)

Antifungal Agent	Summary of FDA Approved Indications [†]	Pediatric Dosage Range	Comments
Caspofungin	Treatment of invasive candidiasis, invasive aspergillosis (2nd line), and for empirical antifungal therapy in granulocytopenic patients	50 (d1:70) mg/m ² /d IV in one single dose; max. dose 70 mg/d	Robust pediatric PK datasets/models and safety data
Micafungin	Treatment of esophageal and invasive candidiasis, prophylaxis of invasive <i>Candida</i> infections in patients undergoing HCT	1–4 mg/kg/d IV (≥ 50 kg: 50–200 mg) in one single dose	Robust pediatric PK dataset/models and safety data; black box warning in the SPC, clinical relevance remains uncertain
Terbinafine	Treatment of tinea capitis in patients ≥ 4 years of age; treatment of onychomycosis and various forms of tinea in adults	<25 kg 125 mg/d PO; 25–35 kg 187.5 mg/d PO; >35 kg 250 mg/d PO in one single dose	Not licensed in subjects <4 years. PK data in subjects 2–17 years of age indicate higher weight-based doses in younger children; several clinical studies have documented the principal safety of terbinafine in pediatric patients.

IV indicates intravenously; PO, orally; TDM, therapeutic drug monitoring; PK, pharmacokinetics.

* For source data, please see Groll et al. [176]; reference appendix, section 3, antifungal agents; and Groll et al. [323].

[†] Summarized tabulation; for specific wording, please refer to the respective summary of product characteristics (SPCs).

FAQ18: Are There Special Considerations for NAIMI in Chimeric Antigen Receptor T Cell Therapy Recipients?

Overall rates of proven/probable IMIs (includes Aspergillosis) have been $\sim 2\%$ to 3% [186]; NAIMIs are thought to occur only sporadically based on reported cases of MCM [187]. NAIMI risk factors after CAR-T include number of prior therapies (including allogeneic HCT), underlying malignancy remission status, cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome with consequent receipt of glucocorticoids and tocilizumab, neutropenia, and history of IMI [186,188–190]. Immune-mediated cytopenias including granulocytopenia may persist for several weeks after chimeric antigen receptor T cell therapy administration; cellular immunity is impaired for at least a year, with half of patients having <200 CD4 cells/ μL at 18 months post-infusion [191]. Finally, profound B cell aplasia may play a more insidious role in contributing to IMI [186]. In summary, routine prophylaxis against molds is not recommended [192] but yeast-active antifungal prophylaxis is generally adopted [193]. However, when aforementioned risk factors accumulate, especially prolonged neutropenia, an individual may warrant mold-active prophylaxis on a case-by-case basis [192,194].

FAQ19: What is the Role of Molecular Diagnostics for NAIMIs?

Molecular diagnostics (Table 2) continue to be refined and compared to conventional cultures and can offer earlier detection through increased sensitivity, applicability, and acceptable performance in blood and a possible role in monitoring response [29]. Their main limitations are lack of standardization and low availability without commercialized kits [29]. The focus of PCR diagnostics has been MCM, given the poor diagnostic yield of cultures [29]. A real-time multiplex PCR for the most frequent pathogenic Mucorales (*Rhizopus* spp., *Mucor* spp., *Rhizomucor* spp., and *Lichtheimia* spp.) has $>80\%$ sensitivity for diagnosing MCM in blood or serum [56,195–197]. A recently commercialized PCR assay with a similar spectrum of detection (MucorGenius, PathoNostics, Maastricht, The Netherlands) has 75% sensitivity in serial blood samples of patients with proven MCM [198]. Both approaches mostly resulted in earlier diagnosis than that by culture or histopathology [56,195,198] and demonstrated some role in assessing therapeutic response [56,196]. Sensitivity of these PCRs in BAL fluid was $>90\%$ and superior to culture [199,200]. PCR assays for detecting other rare molds remains limited (eg, an in-house pan-*Fusarium* PCR that has $>90\%$ sensitivity [92]).

More novel is the detection of fungal cell-free DNA in plasma by next-generation sequencing, which may detect virtually all pathogenic fungi [29], including non-*Aspergillus* molds such as the Mucorales [201]. A commercialized version using the Karius platform (Redwood City, CA, USA) has suggested some utility for early detection and management of pneumonia (including fungal pneumonia) in immunocompromised patients, including HCT recipients [58,202,203]. In a single-center retrospective study mcfDNA-Seq had moderate but better sensitivity in pulmonary IMI caused by non-*Aspergillus* species (compared to *Aspergillus* species) and the test was complementary to serum galactomannan index testing when used in combination [204]. Although the approach remains limited by cost and how to interpret potential false positive results, when available, it might be considered in selected cases where diagnosis is particularly challenging [205].

FAQ20: What Future Investigational Therapies Are There in NAIMI?

These potentially include several antifungal agents that are in the later stages of development (olorofim, fosmanogepix, encochleated amphotericin B) [206]. In addition, preclinical data and limited clinical anecdotes support the promise of various immunomodulating therapies such as adoptive T cell therapy [207] and immune checkpoint inhibitors [208], as well as recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF; sargramostim) [209].

- *Olorofim* is a first-in-class novel antifungal targeting dihydroorotate dehydrogenase which affects fungal pyrimidine synthesis [210] and has US orphan drug and breakthrough therapy drug designation status [206]. Its IV and oral formulations can achieve therapeutic concentrations in all target organs including CNS and eye [211]. It is furthest along in the development pipeline and most promising for *Scedosporium/Lomentospora* spp. [212], and has good activity against *Aspergillus* spp. and some *Fusarium* spp. [213,214]. Importantly, it has no activity against yeasts or Mucorales. A paradoxical inflammatory worsening of musculoskeletal and pulmonary lesions during the course of successful therapy with olorofim has been observed with *Scedosporium* infection and other mycoses [215].
- *Fosmanogepix* is a first-in-class antifungal that inhibits the enzyme Gwt1 in the glycosylphosphatidylinositol biosynthesis pathway [206]

and has broad in vitro activity against most fungi including *Lomentospora/Scedosporium* spp., *Aspergillus* spp., and most *Fusarium* spp., but only marginal activity against Mucorales [216–218]. After IV or oral administration it has >90% bioavailability [219], and penetrates CNS and the eye in mouse models [220]. Although a Phase 2 trial (NCT04240886) was terminated for strategic reasons, results from an expanded access program study in resistant fungal infections including *Lomentospora/Scedosporium* spp. (NCT06433128) and *Fusarium* spp. are awaited. Fosmanogepix was also used successfully as salvage therapy in three of the four patients who survived during the Matamoros *F. solani* meningitis outbreak [221]. Recent case reports demonstrate encouraging therapeutic responses in patients with refractory fusariosis [222].

- *Encochleated amphotericin B* (a.k.a. MAT2203) is a novel formulation of the polyene amphotericin B, whereby the drug is conditioned into a lipid nanocrystal cochleate. In principle, this formulation allows for oral administration, with its unaltered absorption in the bloodstream and uptake by reticuloendothelial cells, where it then unfolds to reveal the active drug [223]. The resulting very low serum amphotericin B levels reduces nephrotoxicity [224]. Because the antifungal spectrum is comparable to that of L-AMB, it is anticipated to have broad activity against Mucorales and *Fusarium* spp., but not *Scedosporium/Lomentospora* spp. and rabbit models demonstrate activity in pulmonary MCM [225]. In combination with flucytosine, it was effective and relatively well tolerated compared to L-AMB in treating HIV-associated cryptococcosis [226]. Data for NAIMI are confined to successful treatment of two patients with invasive *Fusarium* spp. infection [227].
- *Adoptive T cell therapy* uses *ex vivo* expansion of T cells (autologous or donor-derived) specific to fungal antigens of interest, which are then infused into the patient to boost pathogen-specific immunity [228,229]. At present, this approach has focused on *A. fumigatus* [229–231], with a small phase 1 trial suggesting safety and persistent in vivo expansion of the T cell product [232]. Preclinical studies have also demonstrated the ability to also isolate T cells specific to *Rhizopus oryzae* [233–235] but clinical application has not yet followed.
- *Immune checkpoint inhibitors*: In the context of IFI, in vitro data has suggested T cell exhaustion

via activation of immune checkpoint pathways [208] which has sparked interest in a mitigation approach using immune checkpoint inhibitor therapy. So far, there are only case reports (in non-HCT recipients) of successfully treating invasive molds with nivolumab $\pm$ interferon-gamma as adjunctive therapy to antifungals and surgery in the salvage setting [236–239]; further studies are required to explore potential benefits and risks of this approach.

- *rhuGM-CSF* improved in vitro fungicidal activity alone and in combination with antifungal agents, as well as reversing glucocorticoid-induced suppression of phagocytic cells against medically important molds [209,240–242]. Published case series have reported its variable successful use in IFIs [243–245]. A multicenter study in China randomized 206 patients to GM-CSF, G-CSF or both beginning at Day 5 after allogeneic HCT [246]. Although the three groups had similar incidences of proven/probable IFI, GM-CSF was associated with greater antifungal treatment response, lower 100-day all-cause mortality and lower IFI-related mortality out to 600 days median follow-up compared to G-CSF. GM-CSF use has not become routine, possibly due to concerns about negative effects on the underlying hematologic malignancy.

CONCLUSIONS

The HCT landscape for NAIMIs is highly heterogeneous and evolving but common themes emerge.

- A) NAIMI must be managed in a multilayered, multidisciplinary, and highly individualized approach, considering multiple parameters as outcome determinants.
- B) Frequent clinical assessment, plus high index of suspicion for any suggestive clinical manifestations, and knowledge of local NAIMI epidemiology are important for effective preemptive therapy that can be critical for good outcomes.
- C) Besides appropriate use of a limited number of antifungal drugs with activity against NAIMIs, recovery of underlying host immune deficiency and remission of the underlying disease indication for HCT are key positive determinants of prognosis.
- D) Imaging to stage fungal disease and, when feasible, microbiological, molecular, proteomic (MALDI-TOF)/histopathological diagnosis to the genus and ideally at species level, are important in order to select the best treatment.
- E) Non-culture-based diagnostics, especially PCR

for MCM, are promising but not yet routine, and serum/BAL fungal biomarkers (galactomannan and BDG) lack sensitivity and specificity.

- F) While AST is not routinely recommended because interpretive criteria are lacking and host factors strongly confound responses to antifungal therapy, AST might inform management for selected rare NAIMIs.
- G) Pharmacokinetic and pharmacodynamic parameters related to antifungal drug bioavailability, tissue distribution, host metabolism, and site of infection are important; and development of first-in-class new antifungals are greatly needed additions to our limited armamentarium.
- H) As persistent immunosuppression of the host is a key driver of success, source control of sequestered necrotic lesions and secondary antifungal prophylaxis should be entertained, and perhaps immunotherapy strategies in selected cases should be considered.

Future epidemiological studies dissecting the complex epidemiology and the burden of NAIMIs [2] could be helpful. In addition, preclinical research studying the pathobiology of these infections, accelerating drug discovery of potent antifungal drugs, and devising effective and safe immunoenhancement strategies are important to improve outcomes.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jctc.2025.01.892.

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