



Non-*Aspergillus* mould lung infections

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Invasive fungal disease caused by non-*Aspergillus* moulds is increasing and is associated with exceedingly high mortality. Diagnosis and treatment challenges are discussed in this review.
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Abstract

Non-*Aspergillus* filamentous fungi causing invasive mould infections have increased over the last years due to the widespread use of anti-*Aspergillus* prophylaxis and increased complexity and survival of immunosuppressed patients. In the few studies that have reported on invasive mould infection epidemiology, Mucorales are the most frequently isolated group, followed by either *Fusarium* spp. or *Scedosporium* spp. The overall incidence is low, but related mortality is exceedingly high. Patients with haematological malignancies and haematopoietic stem cell transplant recipients comprise the classical groups at risk of infection for non-*Aspergillus* moulds due to profound immunosuppression and the vast use of anti-*Aspergillus* prophylaxis. Solid organ transplant recipients also face a high risk, especially those receiving lung transplants, due to direct exposure of the graft to mould spores with altered mechanical and immunological elimination, and intense, associated immunosuppression. Diagnosing non-*Aspergillus* moulds is challenging due to unspecific symptoms and radiological findings, lack of specific biomarkers, and low sensitivity of cultures. However, the advent of molecular techniques may prove helpful. Mucormycosis, fusariosis and scedosporiosis hold some differences regarding clinical paradigmatic presentations and preferred antifungal therapy. Surgery might be an option, especially in mucormycosis. Finally, various promising strategies to restore or enhance the host immune response are under current evaluation.

Introduction

Invasive fungal diseases (IFDs) are a major cause of morbidity and mortality worldwide [1]. Over the last few years, an epidemiological change in fungal infections has taken place, with an increase in invasive mould infections (IMIs) and a decrease in yeast infections [2]. Filamentous fungi or moulds typically cause lung infections due to inhalation of spores from the environment, although disseminated infections are not uncommon.

The most common fungi causing IMIs are *Aspergillus* spp. However, extensive use of anti-*Aspergillus* prophylaxis in different settings, together with increased complexity and survival of immunosuppressed patients, has partly driven the emergence of non-*Aspergillus* mould infections [3, 4]. Also, the advent of microbiological molecular techniques has favoured a better recognition of these fungi, typically described in patients with immunosuppression, although there have been reports in immunocompetent patients after natural disasters or viral infections [5]. Of note, most accepted definitions on IFDs are mainly applicable in patients with haematological malignancies or receiving transplants [6, 7]. That stated, non-*Aspergillus* IMIs are probably underrecognised and underreported in several at-risk populations.

Non-*Aspergillus* mould infections are associated with an exceedingly high mortality. This is mainly due to intrinsic resistance to multiple antifungal drugs. However, a lack of proper diagnostic tools has also been



associated with delays in specific treatments, which in turn can lead to a poorer prognosis. In this setting, both improved diagnostic tests and novel antifungals and therapeutic strategies are urgently needed.

In this article, we will review the recent literature concerning data on non-*Aspergillus* mould lung infections, focusing on different at-risk populations, diagnostic challenges, specific causative agents, and current and future therapeutic strategies. We decided to not include other important types of fungi that cause lung infections, e.g. *Pneumocystis jirovecii*, or dimorphic fungi such as *Histoplasma* spp., *Coccidioides* spp. or *Sporothrix schenckii*. The reasons for this include space constraints and a desire to focus the review with a group of more similar mould infections.

Non-*Aspergillus* IMI epidemiology

There are a few studies focusing on the epidemiology of non-*Aspergillus* IMIs, especially in immunosuppressed patients. SLAVIN *et al.* [5] reported 162 non-*Aspergillus* mould infections from across 15 hospitals in Australia and New Zealand. Mucormycosis was the most frequent IMI (46%), followed by scedosporiosis (33%), phaeohiphomycosis (10%) and fusariosis (8%). Mucormycosis was associated with prior voriconazole prophylaxis, while scedosporiosis and fusariosis were more common in solid organ transplant (SOT) and neutropenic patients, respectively. Around 70 patients had pulmonary involvement, with half presenting a disseminated infection. Overall, 90-day mortality was >44%.

LEE *et al.* [8] reported another large cohort of 689 patients with IMIs from a South Korean tertiary centre. Only ~7% of IMIs were due to moulds other than *Aspergillus*, with Mucorales being the most frequent causative agent once again, followed by *Fusarium* spp. The most common site of IMIs was pulmonary, with 18% being disseminated infections and 24% being breakthrough episodes. Interestingly, almost 20% of patients had a mixed fungal infection (all with *Aspergillus*) and >50% presented a coexisting infection other than IMIs, a reflection of the severe net state of immunosuppression in patients. Finally, 12-week mortality was 39%. The authors did not find a significant increase in the rate of non-*Aspergillus*/*Aspergillus* infections over the 7-year study period.

The Transplant Associated Infections Surveillance Net (TRANSNET), a multicentre network of 23 transplantation hospitals in the USA, reported IFD epidemiology during 2001–2006 [9]. Of the 1208 cases of proven or probable IFDs in SOT recipients and the 983 cases in haematopoietic stem cell transplant (HSCT) recipients, 169 (7.7%) cases were due to non-*Aspergillus* moulds. Mucorales (105 patients) were the most common, followed by *Fusarium* spp. (37 patients) and *Scedosporium* spp. (27 patients). The lower respiratory tract was the most commonly involved site and 17.4% of all cases had disseminated infection. The overall crude mortality rate at 90 days was 56.6% (90 out of 169). Globally, cumulative 12-month incidence was low, with allogenic HSCT (0.2–0.8%, depending on human leukocyte antigen relatedness) and lung and liver transplants (~0.15%) being the most elevated [9]. Interestingly, high variability was observed between centres in both incidence and agents causing non-*Aspergillus* IMIs. This outlines the importance of environmental and climate conditions as these relate to growth and sporulation of these moulds. It underpins, at the same time, the expectable variability of certain species predominance between distant regions. That stated, in a prospective cohort of eight Brazilian transplant centres, the leading IFD was fusariosis (35%), followed by aspergillosis (30%), invasive candidiasis (17%) and hyalohyphomycosis (12%) [10].

Some other cohorts also report data on IFDs caused by non-*Aspergillus* moulds [11–15]. The Prospective Antifungal Therapy (PATH) Alliance Registry documented proven or probable IFDs in HSCT recipients from across 16 North American medical centres between 2004 and 2007 [11]. 14% of the episodes were caused by Mucorales (half of them) or other moulds. In another study conducted in Taiwan [14], the investigators reported 27 diagnosed cases of non-*Aspergillus* IMIs throughout a 9-year period; 12 (44.4%) were caused by *Fusarium* spp., seven (25.9%) by *Paecilomyces* spp., five (18.5%) by Mucorales and three (11.1%) by *Scedosporium* spp. Overall, 12-week mortality was 40.7%, reaching 76.9% in patients with haematological malignancies.

Table 1 summarises some of the most important studies regarding non-*Aspergillus* IMIs. In all of these studies, reported clinical features among the different moulds were almost indistinguishable (except for that of bloodstream infection, which was more frequent in fusariosis). In this sense, thorough knowledge of local epidemiology is mandatory. Additionally, the presence of a non-*Aspergillus* mould could result from antifungal selection pressure. For that reason, expected breakthrough IFD epidemiology per prior antifungal therapy has been suggested [2]. Importantly, mortality rates were variable, although commonly stated as >50%. This variability could be explained by the wide variety of hosts involved in the different studies, as well as the potentially different virulence of the various causative moulds.

TABLE 1 Important studies regarding non-*Aspergillus* invasive mould infections (IMIs)

First author [ref.], year [#]	Country	Study type, period	Infections (n)	Baseline disease	IMI epidemiology	Mortality
NEOFYTOS [11], 2009	USA and Canada	Prospective, 2004–2007	250 IFDs, 35 non- <i>Aspergillus</i> mould infections	HSCT recipients	51% Mucorales, 11% <i>Fusarium</i> spp., 38% other moulds (not specified)	12-week mortality: 72%
HSIUE [14], 2009	Taiwan	Retrospective, 2000–2008	27 non- <i>Aspergillus</i> mould infections	58% haematological malignancies, 12% solid tumour, 12% SOT, 8% diabetes mellitus, 8% HIV	44% <i>Fusarium</i> spp., 26% <i>Paecilomyces</i> spp., 19% Mucorales, 11% <i>Scedosporium</i> spp.	12-week mortality: 41%
KONTOYIANNIS [9], 2010	USA	Prospective, 2001–2005	1208 IFDs, 169 non- <i>Aspergillus</i> mould infections	73% HSCT, 27% SOT	62% Mucorales, 25% <i>Fusarium</i> spp., 13% <i>Scedosporium</i> spp.	90-day mortality: 56.6%
NUCCI [10], 2013	Brazil	Prospective, 2007–2009	66 IFDs, 35 non- <i>Aspergillus</i> mould infections	61% HSCT, 39% acute leukaemia	69% <i>Fusarium</i> spp., 23% hyaline moulds, 8% Mucorales	6-week mortality: 47%
GIRMENIA [15], 2014	Italy	Prospective, 2008–2010	164 IFDs, 11 non- <i>Aspergillus</i> mould infections	HSCT recipients	54% Mucorales, 27% <i>Fusarium</i> spp., 9% <i>Scedosporium</i> spp., 9% other hyaline moulds	100-day mortality: 75%
SLAVIN [5], 2014	Australia and New Zealand	Retrospective, 2004–2012	162 non- <i>Aspergillus</i> mould infections	46% haematological malignancies, 23% diabetes mellitus, 17% HSCT, 16% COPD, 15% no comorbidities, 14% SOT	46% Mucorales, 33% <i>Scedosporium</i> spp., 10% phaeohyphomycetes, 8% <i>Fusarium</i> spp., 5% other hyaline moulds	90-day mortality: 44.4%
FOX [12], 2014	Spain	Retrospective, 2009–2011	7 non- <i>Aspergillus</i> mould infections	HSCT recipients	72% Mucorales, 14% <i>Scedosporium</i> spp., 14% other hyaline moulds	Overall mortality: 85%
PEGHIN [13], 2016	Spain	Retrospective, 2003–2013	10 non- <i>Aspergillus</i> mould infections	Lung transplant recipients	40% <i>Purpureocillium lilacinum</i> , 40% <i>Scedosporium apiospermum</i> , 20% other hyaline moulds	Overall mortality: 40%
LEE [8], 2020	South Korea	Retrospective, 2011–2018	689 IMIs, 46 non- <i>Aspergillus</i> mould infections	All cases in patients with haematological diseases	57% Mucorales, 19% <i>Fusarium</i> spp., 4% <i>Scedosporium</i> spp., 15% other hyaline moulds, 4% phaeohyphomycetes	12-week mortality: 39.1%

IFD: invasive fungal disease; HSCT: haematopoietic stem cell transplant; SOT: solid organ transplant. #: publications listed in chronological order.

Non-*Aspergillus* mould infections in specific populations and settings

Patients with haematological malignancies and HSCT recipients

IFD is a common cause of morbidity and mortality in patients with haematological malignancies and HSCT recipients. Highly toxic chemotherapies associated with profound and prolonged aplasia, along with an increased survival of patients, make this population highly susceptible to fungal infection [16]. Classically, patients with acute myeloid leukaemia (AML) and allogeneic HSCT recipients have comprised the groups associated with the highest risk of fungal infection. However, in recent years, IFD has been increasingly reported in other populations, such as those with acute lymphoblastic leukaemia, lymphoma or multiple myeloma. This holds especially true in those patients who have received multiple prior lines of treatment [17, 18]. IFD epidemiology in patients with haematological malignancies has been highly influenced by the widespread introduction of antifungal prophylaxis in high-risk populations [2]. At the beginning of the current century, fluconazole prophylaxis became the standard of care in neutropenic patients with haematological malignancies, since some trials had demonstrated a reduction in fungal infection and mortality [19–21]. After fluconazole prophylaxis, IFD epidemiology shifted from the clear predominance of invasive candidiasis (reaching ~90% of all fungal infections in some older studies) to a scenario in which invasive aspergillosis became the most frequent IFD [9, 11, 15]. As previously presented, non-*Aspergillus* moulds already caused ~6–14% of all fungal infections in such studies. However, later trials also showed that anti-*Aspergillus* prophylaxis with posaconazole or voriconazole lowered the risk of IFD in both high-risk patients with either AML or myelodysplastic syndrome and allogeneic HSCT recipients with graft-versus-host disease receiving corticosteroid therapy [22–24]. Large cohorts describing breakthrough IFD epidemiology in patients receiving posaconazole or voriconazole prophylaxis are missing. However, these episodes will be expected to be associated with an increase in non-*Aspergillus* resistant fungi rates. For example, LAMOTH *et al.* [25] compared 24 microbiologically

documented breakthrough IMIs (eight for posaconazole and 16 for voriconazole) with 66 non-breakthrough episodes. They showed a clear increase in rates of IMIs caused by Mucorales and other moulds. Importantly, >50% of breakthrough episodes were due to voriconazole- and posaconazole-resistant species, and 17% of strains were also amphotericin B resistant. Larger prospective studies reporting current breakthrough fungal infection epidemiology in patients with haematological malignancies are needed.

SOT recipients

IFDs pose a significant threat to patients undergoing SOT. Risk and features of fungal infection vary widely depending on the organ transplanted, surgery performed, baseline disease and comorbidities, and type of immunosuppression. Over the last few years, mucormycosis and other non-aspergillosis IMIs have been increasingly reported in SOT, especially in those of heart and lung, and typically late after transplantation [26–28]. The most common presentation forms are fungal pneumonia and rhino-sinus infection. Lung transplant recipients are at a particularly higher risk of IMIs for several reasons: 1) the transplanted lung has decreased mucociliary function and lymphatic drainage dysfunction, 2) the graft is directly exposed to the ubiquitous environmental mould spores, 3) an altered blood supply complicates the delivery of antifungal treatments, and 4) immunosuppression therapies are frequently more intense than in other SOTs. Remarkably, mortality as high as 40–80% has been reported [29–31]. In this setting, antifungal prophylaxis is often used in these patients, often with nebulised amphotericin B-based regimens. However, there is a lack of consensus as it relates to the best prophylactic agent or duration of treatment. A Spanish cohort recently reported the epidemiology of non-*Aspergillus* IMIs in patients undergoing lung transplantation [13]. Of the 412 lung transplantations, 10 (2.42%) patients developed non-*Aspergillus* mould infections: three (30%) cases of simple tracheobronchitis, three (30%) ulcerative tracheobronchitis, two (20%) bronchial stent infections and two (20%) invasive pulmonary infections. Median time from transplantation to the first non-*Aspergillus* mould infection was 420 days, and the most common causative agents included *Purpureocillium lilacinum* (40%) and *Scedosporium apiospermum* (40%). Of note, four of the 10 patients (40%) were co-infected with *Aspergillus* species and three (30%) had a bronchial stent. Although the overall incidence of non-*Aspergillus* IMIs was relatively low, related mortality was 60%, reaching 100% in pulmonary forms.

Patients with viral infections

Respiratory viruses disrupt local innate immunity and harm mucociliary activity and bronchial mucosa, favouring fungal invasion [32–34]. The reported association between invasive aspergillosis and patients with severe influenza requiring intensive care unit (ICU) admission has constituted the prime example of the aforementioned relationship [35–37]. More recently, severe coronavirus disease 2019 (COVID-19) cases associated with pulmonary aspergillosis have also been reported with varying incidence rates [38]. Information on non-*Aspergillus* moulds associated with both influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is scarce and basically restricted to cases of mucormycosis. A review published at the beginning of 2021 reported eight and seven cases of mucormycosis related to influenza and COVID-19, respectively [39]. Most cases occurred in patients with underlying conditions and either severe influenza or COVID-19. Also, common risk factors included corticosteroid therapy and uncontrolled diabetes. The only difference found regarding the predisposing viral infection was a higher presence of rhino-orbito-cerebral mucormycosis in patients with severe COVID-19. As the pandemic has advanced, and particularly spread further into India, more case series of COVID-19-associated mucormycosis have been reported [40–43]. Again, corticosteroid therapy, uncontrolled diabetes and haematological malignancies comprised the most frequent risk factors. Reported mortality due to COVID-19-associated mucormycosis stands at ~50%, making it mandatory to undertake a prompt antifungal treatment and surgical approach [44]. Of note, an Iranian study focused on COVID-19-associated pulmonary mould infections in patients requiring mechanical ventilation for ≥4 days [45]. As many as 40 (38%) patients were reported to have an associated pulmonary IMI. Although invasive aspergillosis was the most common infection, *Fusarium* spp. was isolated in six out of 29 (21%) of the culture-positive samples. Finally, as already known, local damage and immune alteration is probably common to all respiratory viruses. In this sense, we believe that the described association for influenza and SARS-CoV-2 may be extrapolated to other respiratory viruses, as long as they present in a sufficiently severe form.

Other at-risk populations

Some other groups of immunosuppressed patients are also at risk of pulmonary IMIs. These include those with solid tumours [46], autoimmune diseases and immunosuppressants [47, 48] or chronic granulomatous disease [49]. Also, IFD frequency appears to be on the rise in patients admitted to the ICU. However, it is important to bear in mind that IMIs due to non-*Aspergillus* moulds can also present in otherwise healthy patients. In the Australia and New Zealand Mycoses Interest Group (ANZMIG) cohort [5], 15.4% of

patients with a non-*Aspergillus* IMI had neither underlying immunosuppression nor comorbidity. Nonetheless, it should be noted that European Organisation for Research and Treatment of Cancer/ Mycoses Study Group host criteria [6] were not required in the ANZMIG study due to their low applicability outside of the haematological and transplant setting. Eliminating host criteria while maintaining (and probably restricting) clinical and microbiological criteria would likely result in a better depiction of the real-world landscape of invasive fungal infections.

Diagnostic challenges in non-*Aspergillus* lung IMIs

There are several challenges in diagnosing non-*Aspergillus* IMIs. First, it is extremely difficult to clinically differentiate invasive aspergillosis from other IMIs. Although some characteristics are typically associated with a particular mould (e.g. cutaneous lesions and fusariosis or rhino-sinus compromise and mucormycosis), these are largely unspecific and any mould could be the causative agent. Second, although the presence of macronodules and the halo sign are commonly associated with invasive aspergillosis [50], these findings are again non-specific and could also be found in infections caused by other moulds. A work conducted at the MD Anderson Cancer Center (Houston, TX, USA) comparing radiological findings between pulmonary mucormycosis and pulmonary aspergillosis showed that the presence of multiple (≥ 10) nodules and pleural effusion were both associated with pulmonary mucormycosis [51]. However, no differences were noted with respect to the frequency of other computed tomography findings such as masses, cavities, halo sign or air crescent sign. Third, there are no specific fungal biomarkers for mould infections other than *Aspergillus*. Serum or bronchoalveolar galactomannan is a useful marker for the diagnosis and treatment monitoring of invasive aspergillosis. Although galactomannan can be elevated in some patients with invasive fusariosis or other fungi [52, 53], a positive result will be logically interpreted to indicate invasive aspergillosis unless a culture for another mould tests positive. 1,3- β -D-glucan is a component of the cell wall of many fungi that may be detectable in the serum of patients with non-*Aspergillus* IMIs, excluding mucormycosis. However, its use is limited due to its complete lack of specificity. In this complex scenario, direct visualisation and/or culture of these moulds remains essential. This is also challenging, given that the yield of cultures is often $< 50\%$ for non-*Aspergillus* moulds, and invasive sample collection (e.g. lung biopsy) is typically constrained due to patient instability and/or profound thrombocytopenia. Once a mould is detected in histopathology or culture, molecular methods can confirm the infection and identify the causative strains [54]. In the last few years, quantitative PCR (qPCR) assays to detect fungal DNA have been investigated. These techniques, ranging from pan-fungal to species-specific, may be used in histopathological samples, but also in blood and urine [55], and have a fast turnaround time (~ 3 h), moderate sensitivity and high specificity [56]. In fact, some studies showed that specific Mucorales qPCR may diagnose mucormycosis earlier than conventional mycological methods or imaging in susceptible patients [57–60].

The most frequent non-*Aspergillus* IMIs and available antifungal treatments

Table 2 shows the main characteristics and treatment recommendations for the most frequent non-*Aspergillus* moulds causing lung infections.

Mucormycosis

Invasive mucormycosis is caused by Mucorales, ubiquitous fungi commonly found in decaying organic matter. Mucorales cause severe infections with frequent angioinvasion, tissue infarction and necrosis [61, 62]. The most frequently involved species include *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, *Lichtheimia* and *Apophysomyces*. Poor glycaemic control has been shown to diminish neutrophil activity against Mucorales, thus resulting in its classical recognition as an important risk factor [63–65]. Other common risk factors include haematological malignancies, HSCT, prolonged and profound neutropenia, and trauma [64, 66, 67]. Although rhino-sinus and orbital involvement is characteristic, the lung is the most commonly involved site, especially in immunosuppressed patients [3].

With the current and widespread use of antifungal prophylaxis, reporting of both primary and breakthrough mucormycosis has been on the rise [26, 68–70]. The microbiological diagnosis is particularly challenging in mucormycosis due to low culture susceptibility and a lack of useful biomarkers. In this setting, specific antifungal treatment should be started as soon as there is clinical suspicion, since delayed treatment has been associated with significantly increased mortality [62].

Amphotericin B-based therapies form the basis of mucormycosis treatment, with liposomal amphotericin B being associated with the lowest mortality [67, 71]. Doses between 5 and 10 mg·kg⁻¹ per day are usually recommended, with the highest dose associated with increased nephrotoxicity and often kept for central nervous system involvement [71]. Isavuconazole has been licensed as a first-line treatment for mucormycosis on the basis of similar efficacy to an external matched control group treated with

TABLE 2 Main characteristics and treatment recommendations for the most frequent non-*Aspergillus* moulds causing lung infections

Fungal agent	Main species	Microbiological diagnosis [130] [#]	Treatment [¶]	Comments [¶]
Mucorales [71]	<i>Rhizopus</i> spp., <i>Mucor</i> spp., <i>Rhizomucor</i> spp., <i>Cunninghamella</i> spp., <i>Lichtheimia</i> sp., <i>Apophysomyces</i> spp.	Thick, ribbonlike, non-septate hyphae; no available biomarkers; molecular diagnosis (pan-fungal or quantitative species-specific PCR)	Liposomal amphotericin B 5–10 mg·kg ⁻¹ per day (first choice) or isavuconazole (second choice); posaconazole (second line); liposomal amphotericin B combined with echinocandins or posaconazole in severe cases (low evidence)	CT scan showing reverse halo sign, multiple nodes (>10) or pleural effusion; perform surgery whenever feasible; AST is recommended; rigorous glycaemic control; strategies to restore immunity; consider deferasirox in diabetic ketoacidosis; consider hyperbaric oxygen
<i>Fusarium</i> spp. [94]	<i>F. solani</i> species complex, <i>F. oxysporum</i> species complex, <i>F. verticillioides</i> , <i>F. fujikuroi</i>	Narrow, septate hyphae with acute angle branching (like <i>Aspergillus</i> spp.); canoe-shaped macroconidia; conidiophores with single or clustered conidia, with potential reniform adventitious conidia; galactomannan and 1,3-β-D-glucan may be positive; positive blood cultures in ~50% of cases (adventitious sporulation); molecular diagnosis	Liposomal amphotericin B or voriconazole; consider initial combination of both liposomal amphotericin B and voriconazole; adding an echinocandin or terbinafine may be considered in severe cases (very low evidence)	Typically disseminated skin lesions; AST is recommended; perform surgery whenever feasible; strategies to restore immunity; importance of neutropenia recovery
<i>Scedosporium</i> spp. [94]	<i>S. apiospermum</i> , <i>S. aurantiacum</i> , <i>S. boydii</i> , <i>S. dehoogii</i>	Narrow, septate hyphae with acute angle branching (like <i>Aspergillus</i> spp.); lateral branching off at 60–70° angle may be observed; annellides with a swollen base and elongated neck; oval conidia with truncated base; distinctive coremia or an ascocarp may be seen; molecular diagnosis	Voriconazole (first line); echinocandins (second line); voriconazole combined with echinocandins or terbinafine in severe cases (low evidence)	Consider performing MRI; resistant to amphotericin B; AST is recommended; perform surgery whenever feasible; strategies to restore immunity
<i>Lomentospora prolificans</i> (formerly known as <i>Scedosporium prolificans</i>) [94]		Narrow, septate hyphae with acute angle branching (like <i>Aspergillus</i> spp.); black colour colonies; flask-shaped and annellated conidiogenous cells with a swollen base and elongated neck; smooth olive conidia cluster at the apex; molecular diagnosis	Voriconazole (first line); consider voriconazole combined with terbinafine or/and echinocandins (very low evidence); consider the use of olorofim (current lack of evidence and not commercialised)	Commonly resistant to all available antifungals; AST is recommended; consider performing cranial MRI; perform surgery whenever feasible; strategies to restore immunity
Other hyaline moulds [94]	<i>Paecilomyces</i> spp., <i>Acremonium</i> spp., <i>Rasamsonia</i> spp., <i>Penicillium</i> spp., <i>Trichoderma</i> spp.	Narrow, septate hyphae with acute angle branching (like <i>Aspergillus</i> spp.); some differences between species; molecular diagnosis	Optimal antifungal therapy not established and depends on the isolated species	Importance of molecular diagnosis and AST; perform surgery whenever feasible; strategies to restore immunity
Phaeohiphomyces [94]	<i>Alternaria</i> spp., <i>Exophiala</i> spp., <i>Curvularia</i> spp., <i>Cladosporium</i> spp., <i>Ochroconis</i> spp., <i>Bipolaris</i> spp.	Septate hyphae with dark-pigmented colonies (melanin production); some differences between species; 1,3-β-D-glucan may be positive; molecular diagnosis	Optimal antifungal therapy not established and depends on the isolated species	AST is recommended; perform surgery whenever feasible; strategies to restore immunity

CT: computed tomography; AST: antifungal susceptibility testing; MRI: magnetic resonance imaging. [#]: microscopic morphology description is based on direct examination; [¶]: due to the very low quality of evidence available, some of these recommendations are based on the personal experience of the authors.

amphotericin B formulations [72]. Posaconazole is another first-line treatment option, especially since the development of intravenous formulations and delayed-release tablets. Importantly, Mucorales exhibit a wide range of intraspecies minimum inhibitory concentration distribution for both posaconazole and isavuconazole [4]. In this setting, antifungal susceptibility testing should be conducted whenever possible. While echinocandins display no antifungal activity against Mucorales, they may act synergistically with amphotericin B due to both the unmasking of β -D-glucan and neutrophil activation [73]. Combined therapy with liposomal amphotericin B plus posaconazole has also been proposed. However, drug combination studies have failed to show any benefit [74, 75]. Further multicentre clinical trials are needed to define the best treatment options.

Fusariosis

Fusarium spp. are ubiquitous environmental moulds and major plant pathogens that cause infections especially among patients with haematological malignancies and HSCT [76, 77]. Around 80% of human infections are caused by *Fusarium solani* species complex and *Fusarium oxysporum* species complex [78, 79]. Profound neutropenia and T-cell impairment have been identified as the main associated risk factors [80, 81]. Invasive fusariosis commonly presents as sinus, pulmonary or disseminated infections, characteristically producing multiple skin lesions in the setting of haematogenous spread [77, 80, 82, 83]. In the setting of disseminated infections, there have been reports of mortality reaching as high as 80% [80, 84]. As already presented, both β -D-glucan and galactomannan may be useful in diagnosing and monitoring fusariosis.

Amphotericin B-based formulations or voriconazole comprise the two treatments of choice for invasive fusariosis, with no clear superiority of one over the other. Some *in vitro* and murine models have displayed potential synergism between different antifungals for fusariosis [85–90]. Considering the high treatment failure, intrinsic resistance to most antifungals and devastating mortality rates [80, 84, 91–93], combination therapies are commonly undertaken [94]. However, clinical results of such an approach have been controversial to date [92, 95]. In fact, in the setting of invasive fusariosis, immune reconstitution endeavours, such as neutropenia recovery and withdrawal of immunosuppressant therapy, are the only factors commonly associated with improved survival [4, 82, 96]. Nonetheless, primary combination therapy, with a potential early step down to monotherapy later (once antifungal susceptibility testing results are available), is recommended by international guidelines [94].

Scedosporiosis

Scedosporium spp. and *Lomentospora* (formerly *Scedosporium*) *prolificans* are ubiquitous filamentous fungi frequently found in soil, sewage and polluted waters. These moulds cause infection mainly among immunosuppressed patients presenting with subcutaneous infections, pneumonia, fungaemia and brain abscesses [97, 98]. *Scedosporium* spp., mainly represented by *S. apiospermum*, *S. boydii* and *S. aurantiacum*, are commonly resistant to amphotericin B, while susceptible to voriconazole and posaconazole [98]. The activity of isavuconazole or itraconazole seems marginal [99]. Voriconazole-based regimens are recommended [94].

In turn, *L. prolificans* is usually resistant to all available antifungals [100–102], with voriconazole being the most active agent *in vitro* once again [103]. Both moulds show a particular neurotropism, making low permeability of the blood–brain barrier an additional difficulty when facing treatment. For all of these reasons, it is not unexpected that mortality rates up to 90% are reported [104, 105]. In this scenario, combination therapies are often considered, with *in vitro* synergism found for combinations of echinocandins and triazoles, and voriconazole or itraconazole and terbinafine [106–108]. However, a recent study analysing all published studies of scedosporiosis showed no benefits in terms of mortality when comparing the combination of voriconazole and terbinafine against voriconazole alone [98]. Despite this, current European Confederation of Medical Mycology (ECMM) guidelines for rare moulds support voriconazole-based combination antifungal therapy for infections caused by *L. prolificans*, particularly voriconazole plus terbinafine, even considering the addition of other antifungal agents [94].

Olorofim is a novel antifungal agent. It belongs to a new class of drugs, the orotomides, which target dihydroorotate dehydrogenase, an important enzyme for pyrimidine biosynthesis [109, 110]. This new antifungal has shown potent *in vitro* activity against both *Scedosporium* spp. and *L. prolificans* strains [111–113]; however, clinical experience is still lacking.

Others

There are several other non-*Aspergillus* moulds that cause lung infections. The hyalohyphomycetes or hyaline moulds (including *Fusarium* spp. and *Scedosporium* spp.) are filamentous fungi characterised by a

lack of pigmentation, with branching septate hyphae similar to *Aspergillus*. Some examples of other hyaline moulds include *Paecilomyces* spp., *Acremonium* spp., *Rasamsonia* spp., *Penicillium* spp. and *Trichoderma* spp. Hyaline moulds are ubiquitous in the environment, and may cause pulmonary and/or disseminated infection, especially in immunosuppressed patients [3, 114]. Other moulds that cause lung infections include the phaeohyphomycetes or dematiaceous fungi, which produce melanin that results in the dark pigmentation of their colonies. These moulds are also ubiquitous and may cause superficial infection in immunocompetent hosts, but pulmonary or disseminated infections in the immunosuppressed [3, 114]. Information on clinical characteristics or the best antifungal treatment for both groups of moulds is scarce. In this sense, the recent ECMM guidelines provided recommendations on the treatment of some of these fungi [94], although the quality of evidence is very low. Molecular techniques for species identification as well as antifungal susceptibility testing are recommended.

Other treatment strategies

Surgery

Surgery may prove useful in pulmonary IMIs for source control, to prevent massive haemoptysis when infection affects pulmonary arteries, and to reduce fungal burden and decrease the risk of later relapse. Some case series reported a possible benefit conferred by surgery on patients with IMIs, even with decreased mortality [67, 115, 116]. However, most studies focused on aspergillosis, were conducted before the introduction of new antifungals and were subject to significant publication bias. Additionally, surgery is commonly not feasible in many patients who are clinically unstable and/or display multiple pulmonary lesions or disseminated infections [68]. Despite the lack of scientific evidence, aggressive and prompt surgery is still recommended, especially in cases of mucormycosis [71], whenever feasible.

Restoration and/or enhancement of the host immune response

As already presented, immunosuppression is commonly the main risk factor underlying a lung IFD due to non-*Aspergillus* moulds. For this reason, strategies to restore the host immune response could be appealing.

Administering granulocyte–macrophage or granulocyte colony-stimulating factor is used in some cases to promote neutropenia recovery. Additionally, granulocyte–macrophage colony-stimulating factor alone or in combination with interferon- γ has been shown to enhance the fungicidal activity of innate phagocytic cells [117–119]. However, benefits in patients with non-*Aspergillus* IMIs have not been demonstrated.

Some studies have evaluated the use of white blood cell (granulocyte) transfusions in neutropenic patients. Two recent Cochrane reviews concluded that there was low quality of evidence to support the use of granulocyte transfusion in prophylaxis [120] and not enough evidence to make a recommendation on treatment [121]. In this scenario, granulocyte transfusion may still be considered on a case-by-case basis.

Some pre-clinical studies showed that vaccination could improve the response to fungal infection [122]. Its use might be applicable prophylactically in some high-risk patients such as those receiving lung transplants. However, there is concern about the efficacy of this strategy in highly immunocompromised patients.

Adoptive T-cell therapy is a promising new discipline wherein immune cells (usually T-lymphocytes) are isolated and expanded *ex vivo* in an antigen-specific manner, and later infused into the patient. This can be done *via* either the adoptive transfer of antimould T-cells or the engineering of immune cells (natural killer or T-cells) with chimeric antigen receptors (CARs). Both approaches have shown some encouraging results in murine models [123–126]. Moreover, freezing and thawing protocols are being established so that these therapies could conceptually be used together with antifungals as an “off-the-shelf” option when a severe IMI is documented. Figure 1 displays the simplified process and mechanism of action of a potential antifungal CAR therapy.

Other therapeutic strategies

Iron overload has been related to an increased risk of IMIs, as this element is essential for fungal survival and growth. The iron chelator deferasirox demonstrated direct fungicidal activity against Mucorales *in vitro* and in animal models *via* iron starvation [127]. Additionally, it was even shown to be synergistic with liposomal amphotericin B. The role of deferasirox was evaluated against placebo (with both arms receiving liposomal amphotericin B) in 20 proven or probable cases of mucormycosis [128]. Patients in the deferasirox arm had higher mortality; however, they also randomly had an overrepresentation of some poor prognostic factors such as active malignancy, neutropenia and corticosteroid therapy. Regardless, deferasirox may play a role in diabetic ketoacidosis, in which there is an excess of free iron in tissues [4].

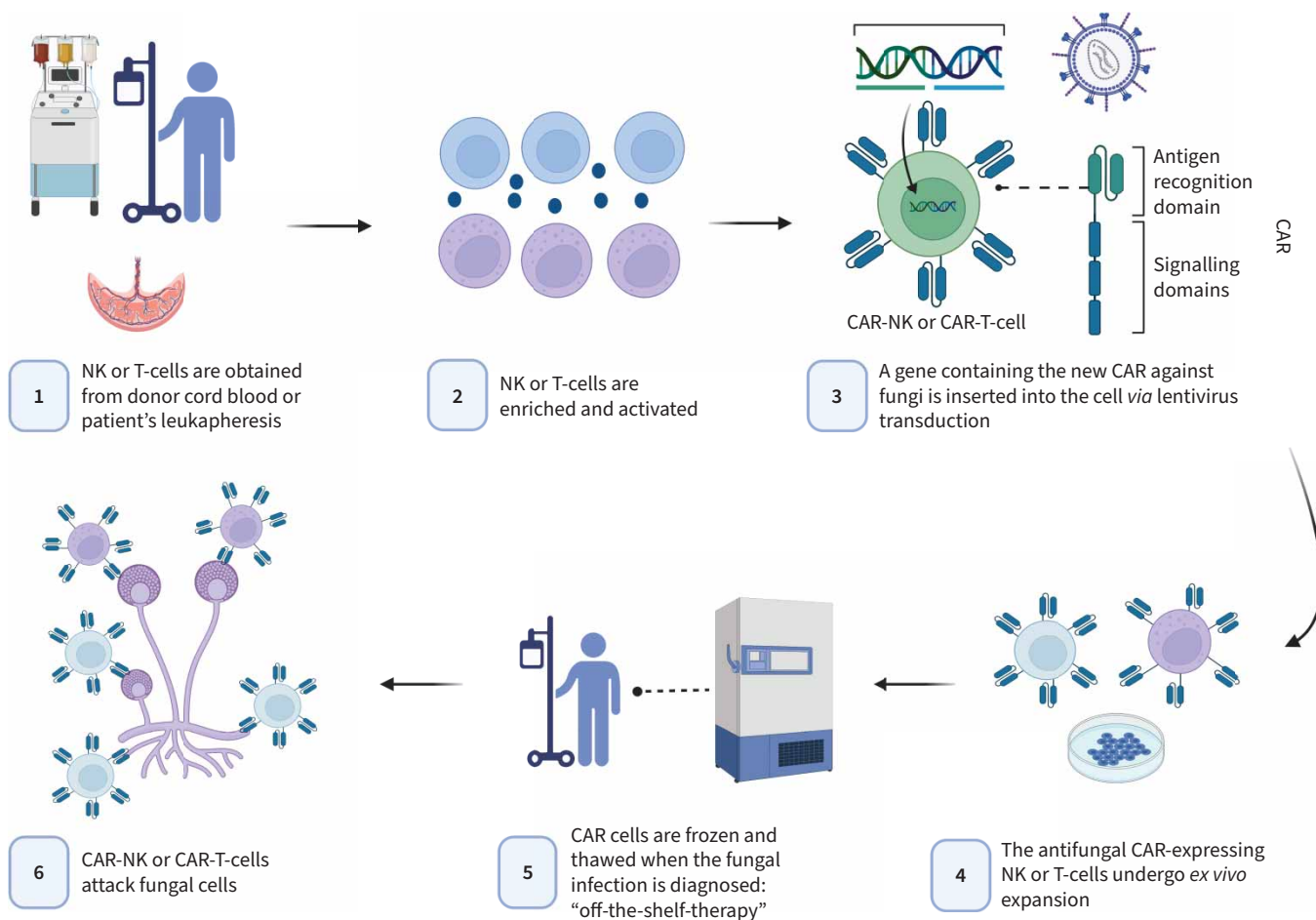


FIGURE 1 A simplified production process and mechanism of action of a potential antifungal chimeric antigen receptor (CAR) therapy. NK: natural killer. Figure created with BioRender.com.

The use of hyperbaric oxygen has been suggested as an adjunctive therapeutic modality in IMIs due to its capacity to revert hypoxia in necrotic tissues. Some studies suggest that adjunctive hyperbaric oxygen may be useful in patients with diabetes, but its benefit in immunosuppressed patients is unclear [129]. Moreover, its use has been tested primarily in patients with rhino-sinus infections and not in those with lung infections.

Future research

- Large prospective studies evaluating the current epidemiology of non-*Aspergillus* IMIs are needed.
- Improvement in microbiological techniques is needed. There is a need for the development of new fungal biomarkers. Species-specific molecular diagnosis might be helpful.
- Novel antifungal treatments are under development and could improve the prognosis of these entities.
- Various promising strategies to enhance immune response against fungi are being investigated, with special interest in the use of antifungal CAR cells.

Conclusions

Non-*Aspergillus* filamentous fungi causing IMIs have increased over recent years, especially in patients with haematological malignancies, and in HSCT and SOT recipients. Although the overall incidence appears low, these infections are probably underrecognised. At the same time, however, they are associated with exceedingly high mortality. Diagnosing non-*Aspergillus* IMIs is extremely challenging due to a lack of definitive symptoms, radiological findings and specific biomarkers, together with the low yield of cultures. A high degree of suspicion in conjunction with thorough knowledge of local epidemiology and

different mould characteristics is essential. The future scenario of this currently devastating entity may improve, nonetheless, due to the advent of molecular diagnostic techniques, revolutionary strategies to restore or even enhance the immune response and novel antifungal drugs.

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