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Short Communication

Rare mould infections caused by Mucorales, *Lomentospora prolificans* and *Fusarium*, in San Diego, CA: the role of antifungal combination therapy

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ABSTRACT

Non-*Aspergillus* invasive mould infections (IMIs) are associated with devastating morbidity and mortality rates and are increasingly diagnosed in immunocompromised hosts. The aim of this study was to describe the epidemiology and outcomes of non-*Aspergillus* IMIs at a university hospital in San Diego, California, USA. A retrospective chart review of the medical records of all patients with cultures growing non-*Aspergillus* moulds at the microbiology laboratory in the Center for Academic Laboratory Medicine, Department of Pathology, University of California, San Diego (UCSD) Health between mid-2014 and mid-2017 (3-year period) was performed. A total of 23 cases of non-*Aspergillus* IMI were identified, including 10 cases of mucormycosis, 8 cases of lomentosporiosis and 5 cases of fusariosis. Antifungal susceptibility testing was performed for 14 isolates, and 10/11 *Fusarium* and *Lomentospora* isolates had minimum inhibitory concentrations (MICs) of >16 μg/mL for voriconazole and/or posaconazole. Overall 180-day mortality was significantly lower among those who received combination antifungal therapy than among those who received single-agent therapy [3/13 (23%) vs. 9/10 (90%); $P = 0.003$]. In conclusion, *Lomentospora prolificans* (35% of non-*Aspergillus* IMIs) and *Fusarium* spp. (22%) accounted for high proportions of non-*Aspergillus* IMIs during the study period. Non-*Aspergillus* IMIs were detected in patients with various underlying diseases and were associated with high mortality rates, which was significantly lower in those who received antifungal combination therapy.

1. Introduction

Despite recent advances in diagnosis and treatment, invasive mould infections (IMIs) are an important cause of morbidity and mortality globally, particularly in immunocompromised individuals [1]. The incidence of invasive aspergillosis (IA), the most common IMI, is 10–20 cases per 1 million population overall, with an incidence of 0.2–0.6% in intensive care units (ICUs), 0.5–3.9% following haematopoietic stem cell transplant (HSCT) and 0.1–2.4% following solid-organ transplantation (SOT) [2]. Reported mortality rates from IA range from 30% to 60% at 12 weeks in patients with an underlying haematological malignancy, HSCT, SOT or solid tumour and 41% at 12 months in SOT patients [1–3]. Prophylaxis against IA with newer triazoles such as posaconazole and voriconazole, particularly with induction chemotherapy for acute myeloid leukaemia and in patients with graft-versus-host disease, is now widely recommended and has helped decrease the morbidity and mortality from IA and increase overall survival [4–6].

However, the selective pressure of antifungal prophylaxis may be contributing to the emergence of less common IMIs [7]. Mucormycosis, the second most common IMI, is caused by widely prevalent fungi found in decaying organic matter and accounts for 8% of invasive fungal infections (IFIs) following HSCT [3] and 2% following SOT [8], with an incidence rate of 1.7 cases per 1 million

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population and mortality rates averaging 54%. Other filamentous fungi such as *Scedosporium* spp., *Lomentospora* spp. and *Fusarium* spp. are also emerging opportunistic pathogens in immunocompromised individuals, with incidence rates 3–8 times lower than the Mucorales. *Scedosporium* and *Lomentospora* spp. are commonly found in soil and polluted waters and account for 1.6% of infections following HSCT and 0.9% of IFIs following SOT [8]. *Fusarium* spp. are major plant pathogens and account for 3.2% of IFIs following HSCT and 0.5% of IFIs following SOT [8]. All can cause serious invasive infections and are associated with mortality rates between 30% and 77% for *Scedosporium* and *Lomentospora* infections [8]. Invasive fusariosis has also been associated with very high mortality rates of 79% at 90 days in patients with underlying haematological malignancies and 87% in HSCT recipients [9] when treated with amphotericin B deoxycholate. Survival rates for invasive fusariosis have increased since the introduction of lipid formulation of amphotericin B (53% survival) and voriconazole (60% survival) [9].

The aim of this study was to investigate the risk factors, clinical manifestations, treatment modalities and outcomes in patients with rare IMIs at our institution in San Diego, California, USA.

2. Methods

All patients with a non-*Aspergillus* mould isolated in any sample/material in the microbiology laboratory at University of California, San Diego (UCSD) Health (San Diego, CA) between 1 July 2014 and 1 July 2017 were included in this study. A retrospective chart review of medical records of all of these potential cases with non-*Aspergillus* mould isolates was then performed to determine whether the positive cultures represented true invasive infection or colonisation. Isolates were determined to represent colonisation if there was either a lack of compatible findings of invasive disease on imaging, the treating physician documented that the isolate represented colonisation rather than true infection, and/or no antifungal therapy was initiated in response to these positive microbiological findings. Conversely, isolates were determined to represent true infection if there were compatible findings on imaging and clinical findings consistent with invasive infection, and the treating physician determined that the microbiological findings represented true infection and antifungal therapy was initiated. Only cases in adult patients (age >18 years) were included in the analysis. Cases were classified according to revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria, which have been established for classifying proven IMIs in all types of cases, and as probable and possible IMIs only in the subset of individuals with underlying haematological malignancies or who received SOT. Cases without proven infection and without underlying haematological malignancies and who were not recipients of a SOT were classified as 'not classifiable'. Clinical data were compiled using the web-based registry FungiScope™ [1].

In vitro susceptibilities were determined for a total of 14 strains by a broth microdilution technique following the guidelines of the Clinical and Laboratory Standards Institute (CLSI) M38A document. Antifungal susceptibility testing was performed at the University of Texas at San Antonio Pathology, Fungus Testing Laboratory (San Antonio, TX) in 2014 and at the Associated Regional and University Pathologists, Inc. (ARUP) Laboratories, (Salt Lake City, UT) in 2015–2017. Results were read after 48 h. All azoles were tested at concentrations ranging from 0.016–16 μg/mL, all echinocandins and amphotericin B were tested at concentrations ranging from 0.0625–8 μg/mL and terbinafine was tested at concentrations ranging from 0.0625–2 μg/mL.

Statistical analyses were performed using IBM SPSS Statistics v.23 (IBM Corp., Armonk, NY). Proportions were compared using Fisher's exact test for two groups and using χ^2 test for three groups. A two-sided *P*-value of <0.05 was considered statistically significant. The Human Research Protections Program at the UCSD approved the study protocol and all study-related procedures.

3. Results

A total of 62 adult cases with non-*Aspergillus* mould isolates were identified over the 3-year study period, of which 23 cases had sufficient clinical data available and were determined to represent invasive infection (60% of cases with *Mucor* isolates, 40% of cases with *Rhizopus* isolates, 57% of cases with *Lomentospora prolificans* isolates and 18% of cases with *Fusarium* isolates).

The analysis was focused on the 23 cases of invasive non-*Aspergillus* IMI (Tables 1 and 2), including 10 (43%) caused by Mucorales spp. (6 by *Mucor* and 4 by *Rhizopus*; case 7 also had later detection of *Trichosporon asahii*; 8 proven cases, 2 probable cases), 8 (35%) by *L. prolificans* (case 16 had also detection of *Scedosporium apiospermum* in a later sputum culture and case 18 also had later detection of *Mucor* sp.; 6 proven cases, 1 probable case and 1 not classifiable) and 5 (22%) by *Fusarium* spp. (4 proven cases and 1 probable case). Overall, 35% of infections (8/23) occurred in patients with underlying haematological malignancy or following SOT, whilst 26% (6/23) occurred in burn patients, 17% (4/23) in patients with diabetes mellitus and 13% (3/23) following trauma or in patients in the ICU.

Table 1 shows the demographic characteristics, underlying diseases, source of isolates and survival for each group of IMI. No significant differences were observed in underlying diseases between the three groups ($P = 0.142$), whilst significant differences were observed regarding the source of the fungal isolate ($P = 0.017$), with Mucorales being more frequently isolated from sinuses and *L. prolificans* being more frequently isolated from eyes.

Table 2 shows patient and disease characteristics as well as treatment and outcome for all 23 cases. Overall 180-day mortality was 52% (12/23) and was significantly lower among those who received combination antifungal therapy than among those who received single-agent therapy [3/13 (23%) mortality among those with combination therapy vs. 9/10 (90%) mortality among those with single agent therapy; $P = 0.003$].

Of 10 cases of mucormycosis (4 caused by *Rhizopus* spp. and 6 by *Mucor* spp.), 6 died within 30 days of detection of Mucorales; all 4 survivors received combination therapy with liposomal amphotericin B and posaconazole, whilst only 2/6 non-survivors received combination therapy ($P = 0.076$).

Table 3 shows the results of antifungal susceptibility testing and minimum inhibitory concentration (MIC) determination. Antifungal susceptibility testing revealed that 10/11 *L. prolificans* and *Fusarium* spp. isolates had MICs > 16 μg/mL against voriconazole and/or posaconazole. Among cases with *L. prolificans* infection, all four survivors received combination therapy with either voriconazole plus terbinafine ($n = 3$) or voriconazole plus micafungin ($n = 1$), whilst 1/4 non-survivors received also combination therapy ($P = 0.143$). In patients with invasive fusariosis, treatment with voriconazole alone or in combination showed a trend to being associated with survival (3/3 survived, whilst both patients who did not receive voriconazole did not survive; $P = 0.100$).

4. Discussion

Invasive infection due to non-*Aspergillus* moulds is an important cause of morbidity and mortality, particularly in immunocompromised individuals. In this study, infections occurred in patients with a variety of underlying diseases and at diverse sites, with mucormycosis most likely isolated from the sinuses, *L. prolificans* from the eye and *Fusarium* from soft tissue. Thus, invasive infection from

Table 1
Demographic characteristics, underlying diseases and survival for each group of invasive mould infection.

	Mucormycosis ($n = 10$)	Lomentosporiosis ($n = 8$)	Fusariosis ($n = 5$)
Female sex (n)	4	5	2
Age (years) [median (range)]	47 (18–81)	53 (18–69)	45 (23–63)
Underlying diseases/main risk factors (n)			
Haematological malignancy	3	2	1
Burn	3	–	3
Uncontrolled diabetes mellitus	3	1	–
Lung transplant/cystic fibrosis	–	2	–
ICU/polytrauma	1	2	–
Liver disease	–	–	1
Chronic granulomatous disease	–	1	–
Source of isolate (n)			
Blood culture	–	2	–
Lung/BALF	3	2	–
Deep soft tissue/biopsy	2	1	3
Eye	–	3	–
Sinuses	5	–	1
Peritoneal fluid	–	–	1
Survival at Day 180 (n)	4	4	3

ICU, intensive care unit; BALF, bronchoalveolar lavage fluid.

Table 2
Cases of non-*Aspergillus* invasive mould infection (IMI): underlying diseases, IMI characteristics, treatment and outcome.

Case no.	Primary underlying disease	Antifungals within 14 days of diagnosis (Day 0) (duration)	Source of isolate	IMI classification	Antifungal treatment (day of initiation)	Surgery	Outcome (final assessment)	Survival at Day 180
Mucormycosis								
1	Trauma ICU	L-AmB (Day –8 to Day 0), MFG (Day –10 to Day –3) and FLU (Day –15 to Day –11)	Soft tissue, biopsies from stomach, omentum, abdominal wall, colon/splenic flexure	Proven	L-AmB (Day –8) and PSC (Day 4; combination)	Stomach, sleeve resection, colon/splenic flexure resection	Progression/ uncontrolled disease (Day 13)	No
2	Acute myeloid leukaemia	L-AmB and PSC (combination; Day –7 to Day 0)	Sinuses, intraoperative tissue (2 ×)	Proven	L-AmB (Day –7), PSC (Day –7) and MFG (Day 2; combination)	Debridement	Complete response (Day 330)	Yes
3	Uncontrolled diabetes mellitus	L-AmB and MFG (combination; Day –3 to Day 0)	Sinuses	Proven	L-AmB (Day –3) and PSC (Day 6; combination)	–	Partial response (Day 56)	Yes
4	Burn	L-AmB (Day –10 to Day –7) and MFG (Day –10 to Day 0)	Soft tissue	Proven	L-AmB and PSC (Day 0; combination)	Debridement	Complete response (Day 42)	Yes
5	Uncontrolled diabetes mellitus (ICU)	FLU (Day –4 to Day 0)	BALF, sputum, lung tissue	Proven	MFG (Day –2)	–	Progression/ uncontrolled disease (Day 2)	No
6	Uncontrolled diabetes mellitus	–	Sinuses, hard palate biopsy	Proven	L-AmB and PSC (Day 0; combination)	Debridement	Progression/ uncontrolled disease (Day 22)	No
7	Acute lymphatic leukaemia	PSC (Day –44 to Day 0)	BALF	Probable	L-AmB (Day 0)	–	Progression/ uncontrolled disease (Day 15)	No
8	Burn	VRC (Day –30 to Day 0)	Sinuses (6 ×)	Proven	L-AmB (Day 0)	Debridement	Progression/ uncontrolled disease (Day 26)	No
9	Acute lymphocytic leukaemia	PSC (Day –17 to Day 0)	BALF	Probable	L-AmB (Day 0)	–	Progression/ uncontrolled disease (Day 17)	No
10	Burn	VRC (Day –3 to Day 10) and FLU (Day –12 to Day 0)	Sinuses (5 ×)	Proven	L-AmB (Day 0) and PSC (Day 10; combination)	Debridement	Complete response (Day 104)	Yes

(*continued on next page*)

Table 2 (*continued*)

Case no.	Primary underlying disease	Antifungals within 14 days of diagnosis (Day 0) (duration)	Source of isolate	IMI classification	Antifungal treatment (day of initiation)	Surgery	Outcome (final assessment)	Survival at Day 180
Lomentosporiosis								
11	Uncontrolled diabetes mellitus	N/A	Eye	Proven	VRC systemic and intravitreal (Day 0)	Right eye enucleation	Progression/ uncontrolled disease (Day 3)	No
12	Chronic cardiovascular disease (ICU)	FLU (Day −4 to Day −2)	Eye (2 ×)	Proven	VRC (Day −1) and TRB (Day 0; combination) ± MFG (Day 2 to Day 9)	Left eye enucleation	Partial response (Day 75)	Yes
13	Non-Hodgkin's lymphoma	MFG (Day −11 to Day 0) and FLU (Day −11 to Day −9)	Blood culture (2 ×)	Proven	MFG (Day −11) and L-AmB (Day 5)	–	Progression/ uncontrolled disease (Day 6)	No
14	Multiple myeloma	L-AmB intravitreal (Day −5)	Eye (2 ×)	Proven	L-AmB systemic and intravitreal (Day 0)	Left eye vitrectomy	Progression/ uncontrolled disease (Day 7)	No
15	Lung transplant recipient (4 years ago); cystic fibrosis	PSC (Day −31 to Day 0)	BALF	Probable	VRC, MFG and TRB (Day 2; combination)	–	Stable disease (Day 84)	Yes
16	Cystic fibrosis	N/A	Sputum (2 ×)	Not classifiable	VRC and MFG (Day 0; combination)	–	Stable disease (Day 84)	Yes
17	Chronic granulomatous disease	MFG (Day −12 to Day −8) and FLU (Day −31 to Day 0)	Blood culture	Proven	VRC (Day 0) and TRB (Day 2; combination)	–	Complete response (Day 42)	Yes
18	Major surgery (ICU)	MFG and L-AmB (Day −15 to Day 0; combination)	Deep soft tissue (7 ×)	Proven	VRC and L-AmB (Day 0; combination), then PSC and TRB (Day 21; combination)	Debridement	Stable disease (Day 115)	No
Fusariosis								
19	Chronic lymphocytic leukaemia	N/A	Sinuses (5 ×)	Proven	VRC (Day 0) and TRB (Day 4; combination)	Debridement of sinuses	Stable disease (Day 230)	Yes
20	Burn	MFG (Day −3 to Day 0) and FLU (Day −12 to Day −5)	Skin/soft tissue (2 ×)	Proven	L-AmB (Day −3) and VRC (Day 0; combination)	Debridement	Complete response (Day 42)	Yes
21	Alcoholic liver disease	MFG (Day −20 to Day 0) and FLU (Day −6 to Day −3)	Peritoneal fluid	Proven	L-AmB (Day 0)	–	Progression/ uncontrolled disease (Day 2)	No
22	Burn	FLU (Day −16 to Day 0)	Skin/soft tissue (2 ×)	Proven	L-AmB (Day 0)	Debridement	Stable disease (Day 54)	No
23	Burn	N/A	Skin/soft tissue (8 ×); sterile fluid (2 ×)	Proven	VRC (Day 0)	Debridement	Complete response (Day 183)	Yes

ICU, intensive care unit; L-AmB, liposomal amphotericin B; MFG, micafungin; FLU, fluconazole; PSC, posaconazole; BALF, bronchoalveolar lavage fluid; VRC, voriconazole; N/A, not applicable; TRB, terbinafine.

these moulds can occur in individuals without classically-defined immunocompromising drugs and conditions (e.g. HSCT or SOT) and can occur in a variety of sites. Clinicians should be observant for signs of these infections in the right clinical context. Overall, non-*Aspergillus* IMIs were associated with high mortality rates, particularly in cases with single-agent antifungal therapy [9/10 (90%) died], whilst mortality was significantly lower in those who received combination antifungal therapy [3/13 (23%)].

High mortality rates from non-*Aspergillus* moulds were noted in this study, similar to previous studies [3,8,9]. Mortality at 180 days ranged from 40% with invasive fusariosis to 50% with *Lomentospora* infection and 60% with mucormycosis. There was an association between survival and the use of combination therapy, driven in particular by patients with mucormycosis and *Lomentospora* infections, with a trend towards improved survival in both. Of the 10 patients with mucormycosis, 6 received combination therapy with liposomal amphotericin B plus posaconazole, with 1 patient receiving treatment with micafungin as well. Of those who received combination therapy, 4/6 survived, with none surviving in those who received monotherapy. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) / European Confederation for Medical Mycology (ECMM) and the European Conference on Infections in Leukemia (ECIL-6) guidelines recommend liposomal amphotericin B as first-line therapy (AII and BII recommendations, respectively) for the management of invasive mucormycosis [10], although posaconazole has shown good efficacy for salvage treatment of mucormycosis [11].

There are some data supporting combination therapy for the treatment of mucormycosis. In vitro studies with combination of amphotericin B and posaconazole have demon-

Table 3
Results of antifungal susceptibility testing performed in 14 of the 23 invasive mould infection isolates.

Case no.	Isolate	Antifungal before isolation	MICs (μg/mL)
2	*Rhizopus* sp.	L-AmB and posaconazole (combination)	L-AmB, 1 Itraconazole, 1 Posaconazole, 0.5 Voriconazole, 8
3	*Rhizopus* sp.	L-AmB and micafungin (combination)	L-AmB, 2 Itraconazole, 2 Posaconazole, 1 Voriconazole, >16
10	*Mucor* sp.	Voriconazole, fluconazole	L-AmB, 0.5 Itraconazole, >16 Voriconazole, >16
11	*Lomentospora prolificans*	N/A	L-AmB, >8 Itraconazole, >16 Posaconazole, >16 Voriconazole, >16 Anidulafungin, 4 Caspofungin, >8 Micafungin, >8
12	*L. prolificans*	Fluconazole	Posaconazole, >16 Anidulafungin, 1
14	*L. prolificans*	L-AmB systemic and intravitreal	Posaconazole, >16 Terbinafine, >2
15	*L. prolificans*	Posaconazole	L-AmB, >8 Itraconazole, >16 Posaconazole, >16 Voriconazole, >16 Anidulafungin, >8 Caspofungin, >8 Micafungin, 1
16	*L. prolificans*	N/A	Itraconazole, >16 Posaconazole, 1 Anidulafungin, 2 Caspofungin, 1 Micafungin, 0.25
17	*L. prolificans*	Micafungin, fluconazole	L-AmB, >8 Posaconazole, >16 Voriconazole, >16 Anidulafungin, <0.0625 Caspofungin, <0.0625 Micafungin, <0.0625 Terbinafine, 2
18	*L. prolificans*	Micafungin and L-AmB (combination)	Posaconazole, >16 Anidulafungin, >8 Caspofungin, >8 Micafungin, >8
19	*Fusarium solani*	N/A	L-AmB, 2 Posaconazole, >16 Voriconazole, 16 Caspofungin, >8 Isavuconazole, >16 Terbinafine, 0.25
20	*Fusarium* sp.	Micafungin, fluconazole	L-AmB, 2 Itraconazole, >16 Posaconazole, >16 Voriconazole, >16
21	*Fusarium* sp.	Micafungin, fluconazole	L-AmB, 2 Itraconazole, >16 Voriconazole, >16
22	*Fusarium* sp.	Fluconazole	L-AmB, >8 Itraconazole, >16 Voriconazole, >16

MIC, minimum inhibitory concentration; L-AmB, liposomal amphotericin B; N/A, not applicable.

strated synergy against *Rhizopus* isolates [12]. Combination therapy with amphotericin B and posaconazole in animal models has yielded mixed results. In one study investigating combination therapy with amphotericin B plus posaconazole versus monotherapy with amphotericin B in diabetic ketoacidotic or neutropenic mice with disseminated mucormycosis, combination therapy did not result in improved survival [13]. However, in another study in immunosuppressed mice, amphotericin B plus posaconazole improved survival and reduced fungal tissue burden compared with monotherapy with either drug in mice with disseminated mucormycosis [14].

In terms of clinical data, a retrospective study of diabetic patients with rhino-orbital or rhino-orbital-cerebral mucormycosis showed that combination therapy with amphotericin B and caspofungin was associated with greater 30-day survival compared with monotherapy with amphotericin B (100% vs. 45%), although the

sample size was small [15]. Another retrospective study examined combination therapy with amphotericin B and posaconazole to treat invasive mucormycosis in 32 patients with haematological malignancy or aplastic anaemia [16]. Most patients initially received monotherapy with amphotericin B, with posaconazole added as salvage therapy due to lack of response with amphotericin B alone. At 3 months, those patients who received both antifungal agents did not have worse survival, although posaconazole was used as salvage rather than combination therapy [16]. Another large retrospective study of 106 patients with underlying haematological malignancy or HSCT recipients with mucormycosis investigated outcomes between patients treated with monotherapy and combination therapy at a single medical centre from 1994–2014. This study did not find an overall mortality benefit between those treated with monotherapy and combination therapy at 6-weeks (43% vs. 41%, respectively), although those receiving combination therapy with amphotericin B plus posaconazole had a higher rate of survival compared with those receiving monotherapy (24/32 survived vs. 27/47, respectively) [17]. Thus, combination therapy with liposomal amphotericin B with posaconazole may be more efficacious than monotherapy with amphotericin B, although further investigation is warranted.

In line with previous studies, high MICs against most antifungals were observed for *L. prolificans* isolates, with some isolates displaying lower MICs for echinocandins and one isolate displaying a low MIC for posaconazole. Of the eight patients with *Lomentospora* infection, 5 received combination therapy with voriconazole plus at least one other agent (in 4/5 patients the combination included voriconazole and terbinafine). Of those receiving combination therapy, 80% (4/5) survived, whilst no patients who received monotherapy survived. Combination treatment (primarily broad-spectrum azole plus terbinafine) is also the recommended treatment (BII recommendation) for the treatment of *L. prolificans* infections by the ESCMID and the European Confederation of Medical Mycology (ECMM) [18]. This recommendation is mostly based on case reports demonstrating clinical efficacy with combination voriconazole and terbinafine, whilst data from large-scale studies to support this approach are lacking given the rareness of these infections.

Notably, the majority of *Fusarium* isolates were resistant both to first-line and salvage therapy. Of the five patients with *Fusarium* infection, 4 had antifungal susceptibility testing; of these, all 4 had an MIC $\geq$ 16 μg/mL to voriconazole, and of those tested against posaconazole (2/4) both had a MIC $>$ 16 μg/mL. In other studies, the MIC of voriconazole and posaconazole against *Fusarium* ranged from 1.0–16.0 μg/mL and 0.25–32 μg/mL, respectively [19]. Nevertheless, studies have shown the benefit of voriconazole-based treatment regimens for survival of invasive fusariosis [9] and a similar trend was also observed in the current study (all patients with voriconazole-based treatment regimens survived, whilst both patients who did not receive voriconazole did not survive). However, this difference may also be explained by the fact that all survivors received surgery, which plays a major adjuvant role in the treatment of these infections, particularly when high MICs are noted, as in this study.

This non-randomised study does have several limitations and the main finding that combination therapy was strongly associated with a better outcome should therefore be interpreted with caution. This is a retrospective cohort study at a single medical institution in San Diego, so these findings may not be representative of other patient populations. Still, the patients in this study had a wide variety of predisposing factors increasing their risk for IMI, resulting in a diverse cohort. In addition, the sample size was low, although this is a natural limitation of studies looking at rare diseases such as those documented here. This study was mostly descriptive in character and was underpowered to assess for clear associations, such as antifungal treatment and survival, for example. Finally, none of the cases received isavuconazole, which has recently been shown to be a promising therapeutic option for non-*Aspergillus* IMIs as well as IMIs caused by more than one fungal species [20]. Nevertheless, this study adds to the current body of literature investigating rare IMIs.

5. Conclusions

In conclusion, this study describes non-*Aspergillus* IMIs in patients with various underlying diseases that resulted in high mortality rates. Notably, of these IMIs, *L. prolificans* (35%) and *Fusarium* spp. (22%) were emerging pathogens, with the vast majority of isolates resistant to both voriconazole and posaconazole, the two agents preferred for the treatment of these infections. Overall, mortality rates were significantly lower in patients who received antifungal combination therapy. Further investigation is needed to determine the optimal treatment for these infections, including whether combination antifungal therapy offers a survival benefit over monotherapy.

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Competing Interests

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Ethical Approval

The Human Research Protections Program at the University of California, San Diego (San Diego, CA) approved the study protocol and all study-related procedures [project #171104].

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