HHS Public Access

Author manuscript

*Int J Antimicrob Agents*. Author manuscript; available in PMC 2019 November 01.

Published in final edited form as:

*Int J Antimicrob Agents*. 2018 November ; 52(5): 706–712. doi:10.1016/j.ijantimicag.2018.08.005.

# Rare Mold Infections Caused by *Mucorales, Lomentospora Prolificans* and *Fusarium*, San Diego: The Role of Antifungal Combination Therapy

**Jeffrey D. Jenks, MD, MPH**[1,#], **Sharon L. Reed, MD, ABMM**[1,2], **Danila Seidel, PhD**[3], **Philipp Koehler, MD**[3], **Oliver A. Cornely, MD, FECMM, FACP, FIDSA, FAAM**[3,4], **Sanjay R. Mehta, MD, ABMM**[1,*], and **Martin Hoenigl, MD, FECMM**[1,5,*,#]

[1]Department of Medicine, University of California San Diego, San Diego, CA, United States

[2]Department of Pathology, University of California San Diego, San Diego, CA, United States

[3]Department of Internal Medicine, Excellence Center for Medical Mycology (ECMM), University Hospital Cologne, and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

[4]Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany

[5]Department of Medicine, Medical University of Graz, Graz, Austria

## Abstract

Non-*Aspergillus* invasive mold infections (IMIs) are associated with devastating morbidity and mortality rates, and are increasingly diagnosed in immunocompromised hosts. The objective of this study was to describe the epidemiology and outcomes of non-*Aspergillus* IMIs at our university hospital in San Diego, California, United States. We performed a retrospective chart review of medical records of all patients with cultures growing non-*Aspergillus* molds 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). A total of 23 cases of non-*Aspergillus* IMIs were identified, including 10 cases of mucormycosis, 8 cases of lomentosporiosis, and 5 cases of fusariosis. Antifungal susceptibility

[#]Corresponding authors: Jeffrey D Jenks, M.D., M.P.H, Division of General Internal Medicine, Department of Medicine, University of California San Diego, San Diego, CA 92103, USA, Phone: +16194719250, jjenks@ucsd.edu, AND, Martin Hoenigl, M.D., FECMM, Division of Infectious Diseases, Department of Medicine, University of California San Diego, San Diego, CA 92103, USA, Phone: +16195435605, mhoenigl@ucsd.edu. [*]Sanjay R Mehta and Martin Hoenigl are shared Senior Authors.



**Competing Interests:** OAC is supported by the German Federal Ministry of Research and Education and the European Commission, and has received research grants from, is an advisor to, or received lecture honoraria from Actelion, Amplyx, Arsanis, Astellas, AstraZeneca, Basilea, Cidara, Da Volterra, Duke University (NIH UM1AI104681), F2G, Gilead, GSK, Janssen, Leeds University, Matinas, Medicines Company, MedPace, Menarini, Merck/MSD, Miltenyi, Paratek, Pfizer, PSI, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres, Summit, Tetraphase, and Vical. PK reports non-financial support from Merck, non-financial support from MedImmune and lecture honoraria from Astellas. MH received research funding from Gilead and reports lecture honoraria from the Research Practitioner Network, Gilead, Basilea and Merck. All other authors have none to declare.

**Ethical Approval:** The Human Research Protections Program at the University of California, San Diego approved the study protocol and all study-related procedures (Project #171104).

testing was performed in 14 isolates and 10/11 *Fusarium* and *Lomentospora* isolates had MICs >16 μg/mL for voriconazole and/orposaconazole. 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 time period. Non-*Aspergillus* IMIs were detected in patients with various underlying diseases and associated with high mortality rates, which was significantly lower in those who received antifungal combination therapy.

**Keywords**

Zygomycosis; Scedosporium; Scedosporiosis; Mucormycosis; Fusarium solanii; Epidemiology; burn

## 1. Background

Despite recent advances in diagnosis and treatment, invasive mold 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 the intensive care unit (ICU), 0.5–3.9% after hematopoietic stem cell transplant (HSCT), and 0.1–2.4% after solid organ transplant (SOT) [2]. Reported mortality rates from IA range from 30% to 60% at 12 weeks in patients with an underlying hematologic malignancy, HSCT, SOT or solid tumor and 41% at 12 months in SOT patients [1,2,3]. Prophylaxis against IA with newer triazoles such as posaconazole and voriconazole, particularly with induction chemotherapy for acute myeloid leukemia (AML) and in patients with graft versus host disease (GVHD), 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 after HSCT [3] and 2% after SOT [8], with an incidence rate of 1.7 cases per 1 million 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 after HSCT and 0.9% of IFIs after SOT [8]. *Fusarium* spp are major plant pathogens and account for 3.2% of IFIs after HSCT, and 0.5% of IFIs after 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 hematologic malignancies and 87% in HSCT recipients [9] when treated with deoxycholate amphotericin B. Survival rates for invasive fusariosis have

increased since the introduction of lipid formulation of amphotericin B (53% survival) and voriconazole (60% survival) [9].

The goal 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.

## 2. Methods

All patients who had a non-*Aspergillus* mold isolated in any sample/material in the Microbiology Laboratory at University of California San Diego (UCSD) Health (San Diego, CA, USA) between July 1, 2014 and July 1, 2017 were included in the study. We then performed a retrospective chart review of medical records of all of these potential cases with non-*Aspergillus* mold isolates to determine if the positive cultures represented true invasive infection or colonization. Isolates were determined to represent colonization if there was either a lack of compatible findings of invasive disease on imaging, the treating physicians documented that the isolates represented colonization rather than true infection, and/or no antifungal therapy was initiated in response to these positive microbiologic 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 physicians determined that the microbiologic findings represented true infection and antifungal therapy was initiated. Only cases in adult patients over the age of 18 were included in the analysis. Cases were classified according to revised EORTC/MSG criteria, which have been established for classifying proven IMIs in all types of cases, and probable and possible IMIs only in the subset of individuals with underlying hematologic malignancies or who received a SOT. Cases without proven infection and without underlying hematological malignancies and who were not recipients of solid organ transplantation were classified as “not classifiable”. Clinical data were compiled using the web-based registry FungiScope™ [1].

In vitro susceptibilities were determined in 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 San Antonio, Pathology, Fungus Testing Laboratory, San Antonio, Texas in 2014 and at the Associated Regional and University Pathologists, Inc. (ARUP) Laboratories, Salt Lake City, Utah, United States (2015–2017). Results were read after 48h. All azoles were tested in concentrations ranging from 0.016 to 16 μg/ml, all echinocandins and amphotericinB were tested in concentrations ranging from 0.0625 to 8 μg/ml, while terbinafine was tested in concentrations from 0.0625 to 2 μg/ml.

Statistical analyses were performed using SPSS 23 (SPSS Inc., Chicago, IL, USA). Proportions were compared using Fishers Exact test for 2 groups, and Chi-squared testing for 3 groups. A two-sided P-value of less than 0.05 was considered statistically significant. The Human Research Protections Program at the University of California, San Diego approved the study protocol and all study-related procedures (Project #171104).

## 3. Results

A total of 62 adult cases with non-*Aspergillus* mold 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).

We focused our analysis on the 23 cases of invasive non-*Aspergillus* IMI (Table 1 and Table 2), including the 10 (43%) caused by Mucorales spp (6 by *Mucor* and 4 by *Rhizopus*; case 7 had later also detection of *Trichosporon asahii*; 8 proven cases, 2 probable cases), 8 (35%) by *Lomentospora prolificans* (case 16 had also detection of *Scedosporium apiospermum* in a later sputum culture, case 18 had later also 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 hematologic malignancy or after SOT, while 26% (6/23) occurred in burn patients, 17% (4/23) in patients with diabetes mellitus, and 13% (3/23) after trauma or in patients in the ICU.

Table 1 shows demographic characteristics, underlying diseases, source of isolates and survival for each group of IMI. No significant difference was observed in underlying diseases between the three groups (p=0.142), while significant differences were observed regarding the source of the fungal isolate (p=0.017), with Mucorales being more frequently isolated from sinuses and *Lomentospora 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 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].

Out 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, while only 2/6 non-survivors received combination therapy (p=0.076).

Table 3 shows results of antifungal susceptibility testing and minimum inhibitory concentrations (MIC). Antifungal susceptibility testing revealed that 10/11 *Lomentospora prolificans* and *Fusarium* spp isolates had MICs >16 μg/mL against voriconazole and/or posaconazole. Among cases with *Lomentospora prolificans* infections, all four survivors received combination therapy with either voriconazole plus terbinafine (n=3) or voriconazole plus micafungin (n=1), while 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, while both patients who did not receive voriconazole did not survive; p=0.100).

## 4. Discussion

Invasive infection due to non-*Aspergillus* molds 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 diverse sites, with mucormycosis most likely isolated from the sinuses, *Lomentospora prolificans* from the eye, and *Fusarium* from soft tissue. Thus, invasive infection from these molds 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 died, 90%), while mortality was significantly lower in those who received combination antifungal therapy (2/13 died, 23%).

High mortality rates from non-*Aspergillus* molds were noted in this study, similar to previous studies [3, 8, 9]. Mortality at 180 days ranged from 40% with invasive fusariosis, 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 one patient receiving treatment with micafungin as well. Of those who received combination therapy, 4/6 survived, with none surviving in those that received monotherapy. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 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 is some data supporting combination therapy for the treatment of infections from mucormycosis. In-vitro studies with combination of amphotericin B and posaconazole has demonstrated 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 to 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 to monotherapy with amphotericin B (100% versus 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 hematologic malignancy or aplastic anemia

[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 hematologic malignancy or HSCT recipients with mucormycosis investigated outcomes between patients treated with monotherapy and combination therapy at a single medical center from 1994 to 2014. This study did not find an overall mortality benefit between those treated with monotherapy and combination therapy at 6-weeks (43% versus 41%, respectively), although those receiving combination therapy with amphotericin B plus posaconazole had a higher rate of survival compared to those receiving monotherapy (24/32 survived versus 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 *Lomentospora prolificans* isolates, with some isolates displaying lower MICs for echinocandins and one isolate displaying a low MIC for posaconazole. Of the 8 patients with *Lomentospora* infections, 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, while 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 *Lomentospora 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, while data from large scale studies to support this approach is lacking given the rareness of these infections.

Notably, the majority of *Fusarium* isolates were resistant to both first-line and salvage therapy. Of the 5 patients with *Fusarium* infection, 4 had antifungal susceptibility testing; of these, all 4 had an MIC ≥16 to voriconazole, and of those tested against posaconazole (2/4), both had a MIC >16 mg/L. In other studies the MIC of voriconazole and posaconazole against *Fusarium* ranged from 1.0 – 16.0 mg/L and 0.25 – 32 mg/L [19], respectively. 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 our study (all patients with voriconazole based treatment regimens survived, while 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-randomized study does have several limitations and our main finding that combination therapy was strongly associated with a better outcome should therefore be interpreted with caution. This is a retrospective cohort study done 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 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 and also 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 *Lomentospora 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 if combination antifungal therapy offers a survival benefit over monotherapy.

## Acknowledgments

Declarations

**Funding:** This work was supported by Grants from the National Institutes of Health (AI036214, MH113477, and AI106039). The Fungiscope database, which was used for data collection, is supported by unrestricted grants from Astellas Pharma, Gilead Sciences, MSD/Merck, and Pfizer Pharma GmbH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The funders had no role in study design, data collection, analysis, interpretation, decision to publish, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

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## Highlights

- Retrospective analysis of patients diagnosed with non-*Aspergillus* invasive mold infections at the University of California San Diego Medical Center, San Diego, California, United States.
- IMIs occurred in patients with a variety of underlying diseases and diverse sites, not just those with classically-defined immunocompromising drugs and conditions
- Most *Fusarium* and *Lomentospora* isolates had MICs >16 μg/mL for voriconazole and/or posaconazole
- Overall 180-day mortality was significantly lower among those who received combination antifungal therapy [3/13 (23%)] than among those who received single agent therapy [9/10 (90%); p=0.003]

**Table 1:**

Demographic Characteristics, Underlying Diseases and Survival.

| | **Mucormycosis (n=10)** | **Lomentosporiosis (n=8)** | **Fusariosis (n=5)** |
|---|---|---|---|
| **Female Sex** | 4 | 5 | 2 |
| **Age (median, range)** | 47 (18–81) | 53 (18–69) | 45 (23–63) |
| **Underlying Diseases/Main Risk Factors** | | | |
| *Hematological Malignancies* | 3 | 2 | 1 |
| *Burn* | 3 | - | 3 |
| *Uncontrolled Diabetes* | 3 | 1 | - |
| *Lung Transplant/Cystic Fibrosis* | - | 2 | - |
| *ICU/Polytrauma* | 1 | 2 | - |
| Liver Disease | - | - | 1 |
| Chronic Granulomatous Disease | - | 1 | - |
| **Source of Isolate** | | | |
| *Blood Culture* | - | 2 | - |
| *Lung / BALF* | 3 | 2 | - |
| *Deep Soft Tissue / Biopsies* | 2 | 1 | 3 |
| *Eye* | - | 3 | - |
| Sinuses | 5 | - | 1 |
| Peritoneal Fluid | - | - | 1 |
| **Survival day 180** | 4 | 4 | 3 |

ICU, intensive care unit; BALF, bronchoalveolar lavage fluid

**Table 2:**

Cases of non-*Aspergillus* Invasive Mold infections (IMI): Underlying Diseases, IMI Characteristics, Treatment and Outcome.

| Case number | Primary Underlying Disease | Antifungals within 14 Days before Diagnosis = Day 0 (Duration in Days) | Source of Isolate | IMI Classification | Antifungal Treatment (Day of Initiation) | Surgery | Outcome (final assessment) | Survival day 180 |
|---|---|---|---|---|---|---|---|---|
| **Mucormycosis** | | | | | | | | |
| 1 | Trauma ICU | LipAmphB (Day -8 – Day 0), Micafungin (Day -10 – Day -3), Fluconazole (Day -15 – Day -11) | Soft Tissue, Biopsies from: stomach, omentum, abdominal wall, Colon/Splenic flexion | Proven | LipAmphB (Day -8) & Posaconazole (Day 4; combination) | Stomach, sleeve resection, Colon/Splenic flexion resection | Progression/uncontrolled disease (day 13) | No |
| 2 | Acute Myeloid Leukemia | LipAmphB & Posaconazole (combination; Day -7 – Day 0) | Sinuses, Intraoperative Tissue (2×) | Proven | LipAmphB (Day -7) & Posaconazole (Day -7) & Micafungin (Day 2; combination) | Debridement | Complete response (day 330) | Yes |
| 3 | Uncontrolled Diabetes mellitus | LipAmphB & Micafungin (combination; Day -3 – Day 0) | Sinuses | Proven | LipAmphB (Day -3) & Posaconazole (Day 6; combination) | - | Partial response (day 56) | Yes |
| 4 | Burn | LipAmphB (Day -10 – Day -7), Micafungin (Day -10 – Day 0) | Soft Tissue | Proven | LipAmphB & Posaconazole (Day 0; combination) | Debridement | Complete response (day 42) | Yes |
| 5 | Uncontrolled Diabetes mellitus (ICU) | Fluconazole (Day -4 – Day 0) | BALF, Sputum, Lung Tissue | Proven | Micafungin (Day -2) | - | Progression/uncontrolled disease (day 2) | No |

| Case number | Primary Underlying Disease | Antifungals within 14 Days before Diagnosis = Day 0 (Duration in Days) | Source of Isolate | IMI Classification | Antifungal Treatment (Day of Initiation) | Surgery | Outcome (final assessment) | Survival day 180 |
|---|---|---|---|---|---|---|---|---|
| 6 | Uncontrolled Diabetes mellitus | - | Sinuses, Hard palate biopsy | Proven | LipAmphB & Posaconazole (Day 0; combination) | Debridement | Progression/uncontrolled disease (day 22) | No |
| 7 | Acute Lymphatic Leukemia | Posaconazole (Day -44 – Day 0) | BALF | Probable | LipAmphB (Day 0) | - | Progression/uncontrolled disease (day 15) | No |
| 8 | Burn | Voriconazole (Day -30 – Day 0) | Sinuses (6×) | Proven | LipAmphB (Day 0) | Debridement | Progression/uncontrolled disease (day 26) | No |
| 9 | Acute Lymphatic Leukemia | Posaconazole (Day -17 – Day 0) | BALF | Probable | LipAmphB (Day 0) | - | Progression/uncontrolled disease (day 17) | No |
| 10 | Burn | Voriconazole (Day -3 – Day 10), Fluconazole (Day -12 – Day 0) | Sinuses (5×) | Proven | LipAmphB (Day 0) & Posaconazole (Day 10; combination) | Debridement | Complete response (day 104) | Yes |
| **Lomentosporiosis** | | | | | | | | |
| 11 | Uncontrolled Diabetes Mellitus | NA | Eye | Proven | Voriconazole systemic & intravitreal (Day 0) | Right Eye Enucleation | Progression/uncontrolled disease (day 3) | No |
| 12 | Chronic Cardio-vascular Disease (ICU) | Fluconazole (Day -4 – Day -2) | Eye (2×) | Proven | Voriconazole (Day -1) & Terbinafine (Day 0; combination) +/− Micafungin (Day 2 – Day 9) | Left Eye Enucleation | Partial Response (day 75) | Yes |
| 13 | Non Hodgkin Lymphoma | Micafungin (Day -11 – Day 0), Fluconazole | Blood Culture (2×) | Proven | Micafungin (Day -11), LipAmphB (Day 5) | - | Progression/uncontrolled disease (day 6) | No |

| Case number | Primary Underlying Disease | Antifungals within 14 Days before Diagnosis = Day 0 (Duration in Days) | Source of Isolate | IMI Classification | Antifungal Treatment (Day of Initiation) | Surgery | Outcome (final assessment) | Survival day 180 |
|---|---|---|---|---|---|---|---|---|
| | | (Day -11 – Day -9) | | | | | | |
| 14 | Multiple Myeloma | Lip AmphB intravitreal (Day -5) | Eye (twice) | Proven | Lip AmphB systemic and intravitreal (Day 0) | Left Eye Vitrectomy | Progression/uncontrolled disease (day 7) | No |
| 15 | Lung Transplant Recipient (4 years ago); Cystic Fibrosis | Posaconazole (Day -31 – Day 0) | BALF | Probable | Voriconazole & Micafungin & Terbinafine (Day 2; combination) | - | Stable disease (day 84) | Yes |
| 16 | Cystic Fibrosis | NA | Sputum 2× | Not classifiable | Voriconazole & Micafungin (Day 0; combination) | - | Stable disease (day 84) | Yes |
| 17 | Chronic granulo-matous disease | Micafungin (Day -12 – Day -8), Fluconazole (Day -31 – Day 0) | Blood culture | Proven | Voriconazole (Day 0) & Terbinafine (Day 2; combination) | - | Complete response (day 42) | Yes |
| 18 | Major Surgery (ICU) | Micafungin & LipAmphB (Day -15 – Day 0; combination) | Deep soft tissue (7×) | Proven | Voriconazole & LipAmphB (Day 0; combination), then Posaconazole & Terbinafine (Day 21; combination) | Debridement | Stable Disease (day 115) | No |
| **Fusariosis** | | | | | | | | |

| Case number | Primary Underlying Disease | Antifungals within 14 Days before Diagnosis = Day 0 (Duration in Days) | Source of Isolate | IMI Classification | Antifungal Treatment (Day of Initiation) | Surgery | Outcome (final assessment) | Survival day 180 |
|---|---|---|---|---|---|---|---|---|
| 19 | Chronic lymphocytic leukemia | NA | Sinuses (5×) | Proven | Voriconazole (Day 0) & Terbinafine (Day 4; combination) | Debridement of sinuses | Stable disease (day 230) | Yes |
| 20 | Burn | Micafungin (Day -3 – Day 0), Fluconazole (Day -12 – Day -5) | Skin/soft tissue (2×) | Proven | LipAmphB (Day -3) & Voriconazole (Day 0; combination) | Debridement | Complete response (day 42) | Yes |
| 21 | Alcoholic liver disease | Micafungin (Day -20 – Day 0), Fluconazole (Day -6 - Day -3) | Peritoneal fluid | Proven | LipAmphB (Day 0) | - | Progression/uncontrolled disease (day 2) | No |
| 22 | Burn | Fluconazole (Day -16 – Day 0) | Skin/soft tissue (2×) | Proven | LipAmphB (Day 0) | Debridement | Stable disease (day 54) | No |
| 23 | Burn | NA | Skin/soft tissue (8×) Sterile fluid (×) | Proven | Voriconazole (Day 0) | Debridement | Complete response (day 183) | Yes |

Abbreviations: BALF, bronchoalveolar lavage fluid; ICU, intensive care unit; LipAmphB, liposomal Amphotericin B

**Table 3.**

Results of Antifungal Susceptibility Testing (performed in 14/23 isolates). Minimum inhibitory concentrations (MIC) displayed.

| Case number | Isolate | AF Before Isolation | MIC (mg/L) |
|---|---|---|---|
| 2 | *Rhizopus* sp. | LipAmphB & Posaconazole (combination) | LipAmphB: 1<br>Itraconazole: 1<br>Posaconazole: 0.5<br>Voriconazole: 8 |
| 3 | *Rhizopus* sp. | LipAmphB, Micafungin (combination) | LipAmphB: 2<br>Itraconazole: 2<br>Posaconazole: 1<br>Voriconazole: >16 |
| 10 | *Mucor* sp. | Voriconazole, Fluconazole | LipAmphB: 0.5<br>Itraconazole: >16<br>Voriconazole: >16 |
| 11 | *Lomentospora prolificans* | NA | LipAmphB: >8<br>Itraconazole: >16<br>Posaconazole: >16<br>Voriconazole: >16<br>Anidulafungin: 4<br>Caspofungin: >8<br>Micafungin: >8 |
| 12 | *Lomentospora prolificans* | Fluconazole | Posaconazole: >16<br>Anidulafungin: 1 |
| 14 | *Lomentospora prolificans* | Lip AmphB systemic and intravitreal | Posaconazole: >16<br>Terbinafine: >2 |
| 15 | *Lomentospora prolificans* | Posaconazole | LipAmphB: >8<br>Itraconazole: >16<br>Posaconazole: >16<br>Voriconazole: >16<br>Anidulafungin: >8<br>Caspofungin: >8<br>Micafungin: 1 |
| 16 | *Lomentospora prolificans* | NA | Itraconazole: >16<br>Posaconazole: 1<br>Anidulafungin: 2<br>Caspofungin: 1<br>Micafungin: 0.25 |
| 17 | *Lomentospora prolificans* | Micafungin, Fluconazole | LipAmphB: >8<br>Posaconazole: >16<br>Voriconazole: >16<br>Anidulafungin: <0.0625<br>Caspofungin: <0.0625<br>Micafungin: <0.0625<br>Terbinafine: 2 |
| 18 | *Lomentospora prolificans* | Micafungin & LipAmphB (combination) | Posaconazole: >16<br>Anidulafungin: >8<br>Caspofungin: >8<br>Micafungin: >8 |
| 19 | *Fusarium solanii* | NA | LipAmphB: 2<br>Posaconazole: >16<br>Voriconazole: 16<br>Caspofungin: >8<br>Isavuconazole: >16<br>Terbinafine: 0.25 |
| 20 | *Fusarium* sp. | Micafungin, Fluconazole | LipAmphB: 2<br>Itraconazole: >16<br>Posaconazole: >16<br>Voriconazole: >16 |

| Case number | Isolate | AF Before Isolation | MIC (mg/L) |
|---|---|---|---|
| 21 | *Fusarium* sp. | Micafungin, Fluconazole | LipAmphB: 2<br>Itraconazole: >16<br>Voriconazole: >16 |
| 22 | *Fusarium* sp. | Fluconazole | LipAmphB: >8<br>Itraconazole: >16<br>Voriconazole: >16 |

Abbreviations: AF, antifungals; LipAmphB, liposomal Amphotericin B; NA, not applicable