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Editorial

Update on invasive fungal infections: emerging trends in the incidence of fungal infections in immunosuppressed patients and associated conditions

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Introduction

Haematological malignancies are known to be significant risk factors for invasive fungal infections (IFIs),[1] particularly in high-income countries. Multiple myeloma, a common haematological cancer,[2] makes patients highly susceptible to infections, mostly bacterial and viral, and, to a lesser extent, fungal.[3] However, there is a growing concern about the increase in IFI in these patients. This rise is linked to the use of newer drug combinations and prolonged treatments that lead to severe, long-term neutropenia. Moreover, innovative immunotherapies like bispecific antibodies and chimeric antigen receptor T cell therapy, though effective for treating relapsing and refractory myeloma, also heighten the risk of infections, including fungal ones.[3] In light of this, Valković et al.[4] have highlighted the urgent need for vigilance. They foresee a notable rise in IFI among myeloma patients in the near future. They stress the importance of closely monitoring these trends, both in clinical trials and real-world settings. Their review aimed to emphasize the need to thoroughly document the epidemiological characteristics of these infections, identify risk factors and explore treatment and prevention strategies for myeloma patients.

Epidemiology

Recent publications have identified aspergillosis not only as the most common IFI,[5] but also as one of the most concerning ones for the mycological community.[6–16] Unfortunately, studies have historically overlooked data from regions outside Europe and the United States. To address this gap, Khan et al.[17] show the current distribution of *Aspergillus* species and risk factors for aspergillosis in mainland China. The authors analysed data from various published articles to assess the prevalence of *Aspergillus* infection, as well as the associated risk factors, mortality rates and underlying conditions. Their findings indicate that, similar to other regions, *Aspergillus fumigatus* is the most common species in mainland China, followed by *A. flavus*, *A. niger* and *A. terreus*. The review also covers cases of chronic pulmonary aspergillosis and allergic bronchopulmonary aspergillosis, which have also been frequently underrepresented in the literature. The authors emphasize the importance of improved surveillance to better control and treat aspergillosis, highlighting the need for future research to address these gaps.

Reflecting the increasing growing global concern on rare fungi, Khalid et al.[18] have detailed the clinical characteristics, outcomes and mortality factors of pulmonary mucormycosis in a retrospective single-centre study from Pakistan. Diabetes mellitus emerged as the most common comorbidity, in line with previous regional data,[19] with chronic lung diseases and concurrent COVID-19 pneumonia also identified as significant predisposing conditions.[20] The study found *Rhizopus* spp. and *Mucor* spp. to be the most

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prevalent. Despite global guidelines advising against it,[21] over 70% of patients were treated with amphotericin B deoxycholate, a limitation also noted in the literature from other low- and middle-income countries (LMIC). In fact, this appropriate antifungal access limitation has yielded the creation of specific guidelines from LMIC.[22] In some cases, treatment involved a combination of medical and surgical approaches. Multivariable analysis revealed that immunosuppression, thrombocytopenia and mechanical ventilation were significant risk factors for mortality.

Epidemiology in transition

The epidemiology and risk factors associated with IFI are continually evolving, necessitating regular updates. Iqbal et al.[23] provide a recent update on the local epidemiology of these infections in Pakistan, highlighting thoracic empyema as an emerging risk factor in the country. This issue is particularly relevant due to the underreporting of cases from LMIC. In their retrospective study, the authors examined the risk factors, clinical features, treatments, and outcomes of fungal empyema. They reviewed 26 patients with a mean age of 43.6 ± 20.3 years, of whom 61.5% were male, and found diabetes mellitus to be the most common comorbidity. *Candida* spp. were isolated in 80.8% of the cases and *Aspergillus* spp. in 26.9%. Over half of the patients (53.8%) underwent video-assisted thoracoscopy surgery, 80.8% received antifungal agents, and the overall in-hospital mortality rate was 38.5%. The authors stress that early diagnosis and intervention are crucial for improving outcomes.

Respiratory viral infections have increasingly been recognized as triggers for IFI, a trend seen mainly with both influenza[24,25] and coronavirus disease 2019 (COVID-19).[26,27] Different authors explored not only COVID-19-associated infections,[28] with a particular focus on cryptococcosis in adults, but also post-COVID-19 IFI. Quincho-López et al.[29] reviewed 58 studies, including 51 that provided individual patient data for 65 cases and 8 that reported on the prevalence of cryptococcosis in COVID-19 patients. Common comorbidities were arterial hypertension and diabetes mellitus, with human immunodeficiency virus status documented in nearly two-thirds of cases. Over half of the patients required intensive care unit (ICU) admission and mechanical ventilation, and many developed disseminated cryptococcosis. Secondary bacterial infections were also noted, contributing to an overall high mortality rate of 47.7%. The studies on cryptococcosis in COVID-19 patients were primarily descriptive and often presented in conference abstracts, in contrast to the extensive literature available on other COVID-19-associated IFI like aspergillosis and mucormycosis. The authors identified male sex, older age, ICU admission, mechanical ventilation, secondary infections, and lymphopenia as factors associated with increased mortality. In a second review featured, Ulloque-Badaracco et al.[30] focus on post-COVID-19 IFI, occurring after patients have recovered from the viral illness. Despite limited literature, they compiled data on 774 patients, of whom 746 developed an IFI. Mucorales were identified as the main mycosis in 19 studies, *Pneumocystis jirovecii* in 10 studies, and *Aspergillus* spp. in 7 studies. The authors noted that the clinical presentation and prognosis of patients with IFI after recovering from COVID-19 differed from those with acute COVID-19 or those without COVID-19 infection.

Diagnosis and treatment paradigms

In a noteworthy case, Giacinta et al.[31] detail the successful treatment of femoral osteomyelitis caused by *A. granulosus* in a heart transplant recipient. The patient had been experiencing left knee pain for three months, and imaging studies, including X-ray and MRI, revealed an aggressive lesion in the distal third of the left femur. An excisional surgery was performed to remove the affected area, and *A. granulosus* was cultured from the excised material. Following the surgery, the patient was treated with oral isavuconazole, in line with recommendations.[32] Chest imaging ruled out pulmonary aspergillosis, and a positron emission tomography (PET)/computed tomography (CT) scan, which currently attracts great interest from the scientific community for its potential to monitor and achieve better diagnosis and treatment,[33,34] revealed a remnant of a prosthetic vascular graft, which had been implanted previously as part of a left ventricular assist device used as a bridge to transplantation. The patient showed rapid clinical improvement, achieving complete functional recovery. The residual vascular graft was later surgically removed. This case is particularly significant as it represents the first reported instance of long bone osteomyelitis due to *A. granulosus* in a heart transplant recipient without concurrent pulmonary infection, and

it was effectively managed with isavuconazole. The authors emphasize the value of PET/CT in diagnosing and monitoring such cases and the importance of molecular methods for accurate fungal identification.

Moreover, Cipolat et al.[35] explored the use of urine tests for IFI in asymptomatic patients who were about to begin treatment with tumour necrosis factor (TNF)-α inhibitors, medications used for autoimmune diseases. The researchers aimed to assess the prevalence of histoplasmosis, an endemic IFI in Brazil,[36] in these patients. In the study conducted in southern Brazil, 54 patients were tested for *Histoplasma* antigen in their urine before starting TNF-α inhibitor therapy. They were then monitored for 180 days to check for any symptoms of histoplasmosis. The results revealed that 14.8% of the patients tested positive for the *Histoplasma* antigen before starting treatment. Despite this, none of the patients, including those who tested positive, developed histoplasmosis during the 6-month follow-up period. The researchers concluded that histoplasmosis may be more common in this patient group than previously recognized. However, it remains uncertain whether asymptomatic patients with a positive antigen test are at risk of developing histoplasmosis once they start TNF-α inhibitor treatment. The study did not identify specific risk factors for developing histoplasmosis in these patients and did not recommend routine screening or preventive therapy for histoplasmosis before starting TNF-α inhibitors based on their findings.

Treatment approaches

In this special edition, the latest recommendations and therapeutic strategies for managing IFI in adults have been also reviewed. Boutin et al.[37] have compiled and summarized recent literature and guidelines on treating invasive mould and yeast infections to provide evidence-based recommendations. Their review highlights new data on the use of antifungal agents, noting updates in the efficacy of various triazoles compared to older treatments. The authors cover the management of infections caused by emerging moulds like *Scedosporium* spp. and *Fusarium* spp., as well as yeasts such as *Trichosporon asahii* and *Candida auris*. The article also discusses newer antifungal agents and formulations currently under investigation, including olorofim, rezafungin, fosmanogepix and encochleated amphotericin B. These novel treatments aim to address existing therapeutic challenges. Additionally, the review covers the role of surgical resection or debridement, the appropriate duration of antifungal therapy, follow-up strategies and the need for secondary prophylaxis, particularly for immunocompromised patients. Furthermore, Farina et al.[38] raised awareness about using isavuconazole and sirolimus together in allogeneic hematopoietic stem cell transplantation. Over a 5.5-year period, 51 out of 377 patients received continuous isavuconazole for more than 2 weeks. Among these, 17 patients were on isavuconazole for IFI at the time of transplant, while another 34 patients started isavuconazole post-transplant for newly diagnosed IFIs. Of these, 16 had breakthrough IFIs despite mould-active prophylaxis, and 38% of these patients died, often due to lower isavuconazole levels. Six weeks after diagnosis, 63% of the patients were alive, with 50% resolving their infections. Eighteen patients received isavuconazole as a pre-emptive therapy for fever and pulmonary infiltrates, showing a 68% clinical response rate at 90 days. Isavuconazole was more effective for pulmonary IFIs than for extra-pulmonary ones. Isavuconazole was safely used alongside sirolimus and, in 23 cases, letermovir, without any reported overdosing or toxicities. The 1-year survival rate was 78% for isavuconazole responders compared to just 18% for non-responders. The study concluded that coadministering isavuconazole and sirolimus is both safe and effective, showing favourable clinical outcomes in patients receiving multiple drugs.

Capacity mapping

Understanding how to best manage our patients is not always enough. Thus, this edition also addresses this issue through two publications by Kovács et al.[7] and Sigera et al.[39] Kovács et al.[7] explore the Hungarian experience as part of a series of global awareness initiatives that began in the Caribbean and Latin America[16] in 2019 and have since expanded to other continents, including Africa,[15] Asia/Pacific,[10] and Europe,[11] and specific countries like Austria,[12] Argentina,[9] the Balkans,[8] Italy,[14] Germany,[13] or Portugal.[6] The primary goal of these initiatives is to assess the current status of access to fungal diagnostic and treatment tools. Their study involved 17 institutions (about two per million inhabitants) and found that all had access to microscopy and culture. However, access to antigen detection was

available in 71% of institutions, and molecular assays in 59%. Regarding antifungal treatment, all institutions used at least one triazole, with voriconazole being the most commonly used (77%). Additionally, 71% used amphotericin B, 65% used echinocandins, while only 18% used 5-flucytosine. The Hungarian experience underscores concerns about the variability in resources for diagnosing and treating IFI across different hospitals. This variability highlights the need for public health authorities to address these disparities and encourage regional cooperation within Hungary to improve access and treatment options. In a related review, Sigera et al.[39] examine the issue of limited access to and underuse of flucytosine, an antifungal agent that has been available since the 1970s but remains underutilized and globally scarce.[40] Their review underscores the clinical and pharmacological significance of flucytosine, drawing from clinical studies and in vitro susceptibility data. They highlight its effectiveness against *Cryptococcus* spp., *Candida* spp., and dematiaceous fungi, despite its limited availability. Flucytosine's water solubility is a key factor in its effectiveness, allowing it to penetrate various body regions, including cardiac vegetations, the central nervous system, the eyes, and the urinary tract, as well as fungal biofilms. The review warns that the lack of access to flucytosine, particularly in low-income countries, severely impacts the management of severe IFI. Improving access to flucytosine could potentially reduce mortality from IFI, especially when used in combination therapy for yeast and dematiaceous infections. It might also serve as a monotherapy for urinary candidiasis, although there is a modest risk of resistance. The authors stress the need to address these access issues to enhance treatment outcomes for IFI.

Conclusion

Overall, this edition illuminates the persistent challenges and recent advancements in the management of IFI (Table 1). It highlights the urgent need for sustained vigilance, ongoing research and

Table 1. Summary of manuscript part of this special issue.

Author	Reference	Country	Pathogens involved	Topic	Target population	Focus
Cipolat et al.	35	Brazil	*Histoplasma* spp.	Timely testing-clinic interaction	Immunosuppressed	Antifungal diagnosis/ treatment
Boutin and Luong	37	Canada	*Aspergillus* spp. *Candida auris* *Candida* spp. *Cryptococcus* spp. *Fusarium* spp. *Lomentospora prolificans* Mucorales *Scedosporium* spp. *Trichosporon asahii*	Clinical management of IFI	Any	Antifungal treatment
Khan et al.	17	China	*Aspergillus* spp.	*Aspergillus* spp. epidemiology	Any	Conventional epidemiology
Valković et al.	4	Croatia	Multipathogen	IFI in hematological malignancies	Multiple myeloma	Conventional epidemiology
Kovács et al.	7	Hungary	Multipathogen	IFI diagnostic and treatment capacity	Any	Access to diagnosis and treatment
Farina et al.	38	Italy	*Aspergillus flavus* *Aspergillus* spp. *Candida glabrata*	Drug-drug interactions	alloHSCT	Antifungal treatment

(Continued)

Table 1. (Continued)

Author	Reference	Country	Pathogens involved	Topic	Target population	Focus
Khalid et al.	18	Pakistan	Mucorales	Mucorales epidemiology	Any	Conventional epidemiology
Igbal et al.	23	Pakistan	*Aspergillus* spp. *Candida* spp. *Fusarium* spp.	Emerging IFI forms	Any	Evolving epidemiology
Quincho-López et al.	29	Peru	*Cryptococcus* spp.	COVID-19 associated IFI	Respiratory viral infection	Evolving epidemiology
Ulloque-Badaracco et al.	30	Peru	*Aspergillus* spp. *Pneumocystis jirovecii* Mucorales	Post-COVID-19 IFI	Respiratory viral infection	Evolving epidemiology
Giacinta et al.	31	Spain	*Aspergillus granulosus*	IFI in SOT	SOT	Evolving epidemiology
Sigera and Denning	39	United Kingdom	Multipathogen	Access to antifungals	Any	Access to diagnosis and treatment

alloHSCT, allogeneic stem-cell transplantation; IFI, invasive fungal infection; SOT, solid organ transplantation; spp., species.

significant improvements in diagnostic and therapeutic resources worldwide. The contributions underscore the importance of enhancing surveillance systems, particularly in underrepresented regions and low- and middle-income countries LMIC, to better understand and address the evolving epidemiology of IFI. They also call for increased access to advanced diagnostic tools and effective treatments, emphasizing the necessity of integrating novel therapeutic options into clinical practice. By addressing these critical areas, we can mitigate the global burden of IFI, improve patient outcomes and advance the overall management of these complex infections.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution
Jon Salmanton-García: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; Writing – review & editing.

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