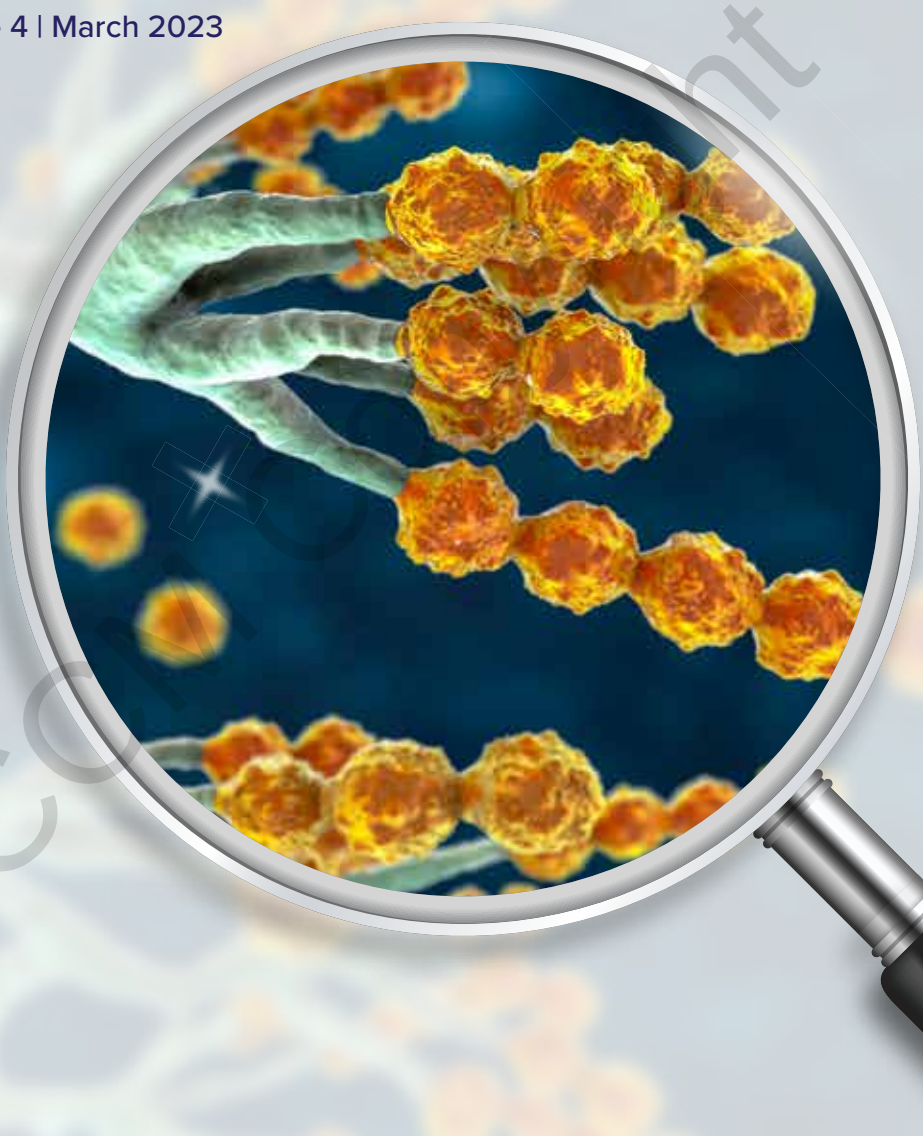
UPDATE IN INVASIVE FUNGAL INFECTIONS

Vol. 1 | issue 4 | March 2023



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UPDATE IN INVASIVE FUNGAL INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

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MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

UPDATE IN INVASIVE FUNGAL INFECTIONS

Welcome

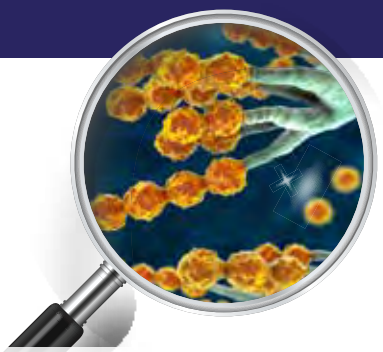
This is the fourth issue of the first volume of our series of newsletters intended to appear at timely intervals to take advantage of important developments.

Update in Invasive Fungal Infections presents seasoned observations, opinions, and judgment on drug interactions, and the recognition and management of infectious diseases.

The aim of this Newsletter is to bring to the physician's doorstep **Update in Invasive Fungal Infections** in a concise and friendly manner. We have made every effort to search the local and international literature to present the most current, interesting and cutting-edge literature, in order to make this newsletter a respected as well as a useful tool for the everyday practice of physicians, with one aim: To provide good service to their patients.

The information stated and presented is the result of search in various search engines and others, including Medline searches.

UPDATE IN
INVASIVE FUNGAL INFECTIONS



MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS

Vol. 1 | issue 4 | March 2023

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MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

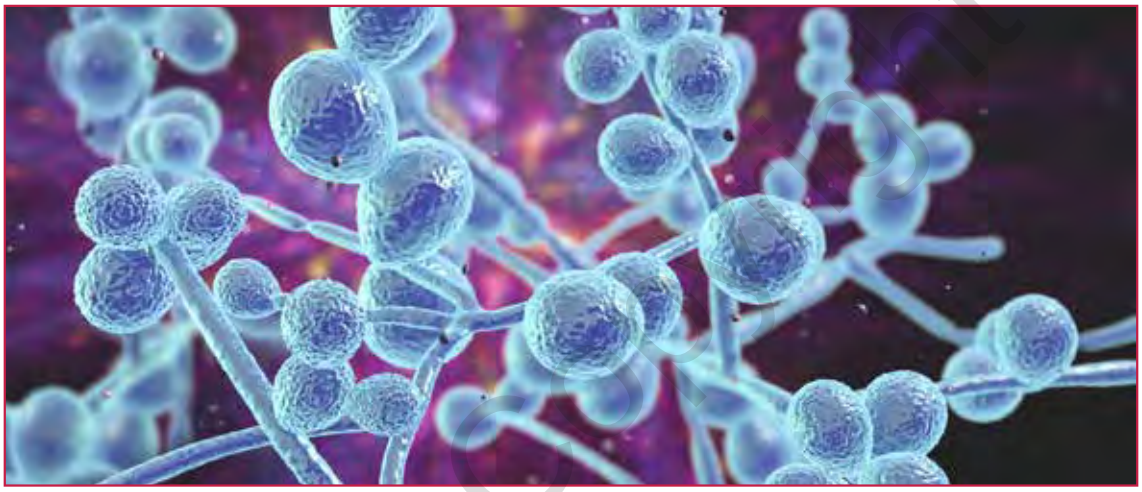
UPDATE IN INVASIVE FUNGAL INFECTIONS

Table of Contents

UPDATE IN
INVASIVE FUNGAL INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

Fungal Priority Pathogens



Introduction

On October 25 2022, WHO published for the first time a list of 19 fungal priority pathogens. The focus was on fungi that cause invasive disease and threaten public health. Each pathogen has been classified as critical, high, or medium priority using criteria that take into account incidence, mortality, drug-resistance, and treatment options. The stated aim of the list was: "to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance". It is an urgent task. A reasonable estimate as to the population affected by long-term disease caused by fungal infections would number in the hundreds of millions, with at least 1.6 million deaths every year.[1,2]

Yet, less than 1.5% of all research spending on infectious diseases is directed at fungal pathogens. As a result, only four classes of antifungals are used in clinical practice and there are few new drugs in the pipeline. In many countries, the recommended treatments for *Cryptococcus neoformans* and *Candida auris* are unavailable. Both pathogens have been classed as critical priorities. WHO stressed the importance of developing novel antifungals, but there are similar challenges to those associated with antibiotics. Pharmaceutical companies are put off by the return on investment offered by antifungals, especially given the lengthy de-

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

velopment process and the scientific obstacles around identifying new targets.[1,2]

WHO Critical Priority Group

The WHO critical priority group currently includes *Aspergillus fumigatus, Candida albicans, Candida auris,* and *Cryptococcus neoformans. Candida albican* and *Candida auris* are invasive fungal pathogens that can cause outbreaks with high mortality in healthcare facilities and are resistant to major classes of antifungal drugs. Invasive *Aspergillus fumigatus* is a deadly infection with a 50% mortality rate. *Cryptococcus neoformans* and *Cryptococcus gattii* are invasive spore-forming yeasts with a high mortality rate following infection.[1,3]

In 2020, following reports of the first cases of COVID-19-associated azole-resistant pulmonary aspergillosis, a consensus diagnosis and management statement was developed by experts, and supported by international mycology societies. The 2020 European Confederation for Medical Mycology and International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria recommended that first-line therapy be either voriconazole or the triazole antifungal, isavuconazole. If azole resistance is identified, liposomal amphotericin B is recommended.[3]

Pathogenic Drug Resistant Fungi

Aspergillus, Cryptococcus, and Candida spp. are the main fungal species associated with invasive fungal infections of the lungs, brain, and bloodstream, respectively. Disseminated infections are typically caused by Blastomyces, Coccidioides, Paracoccidioides, Histoplasma, and Cryptococcus spp. The pulmonary system is the most common site of invasive fungal infections (IFIs). Triazole-resistant *A. fumigatus* and MDR yeast including *Candida glabrata* and *Candida auris* are of particular concern. IFIs are separated from superficial mycoses due to the involvement of blood and other sterile body tissues or organs, and they are categorized as serious, deep, deep-seated, disseminated, and systemic fungal infections.[4] To cause an IFI in a patient, the fungi must have the ability to grow at or above 37°C to reach internal tissues, the ability to lyse tissues and absorb their components, and they must be able to evade the host's immune system. Clinically invasive fungal diseases affect many organs and deep tissues, causing endocarditis, meningitis, and respiratory infections, and they are often not detected in blood cultures.[4] Furthermore, the insertion of venous catheters and intravascular devices, as well as medical interventions allow for infections with nosocomial invasive fungal diseases (IFDs). Cryptococcal meningitis caused by *Cryptococcus neoformans* or *Cryptococcus gattii* is common in HIV patients, where both of the species possess an innate resistance to fluconazole, where a combination therapy with flucytosine is implemented to improve the fungal clearance. Additionally, ca. 7% of systemic

UPDATE IN
INVASIVE
FUNGAL
INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

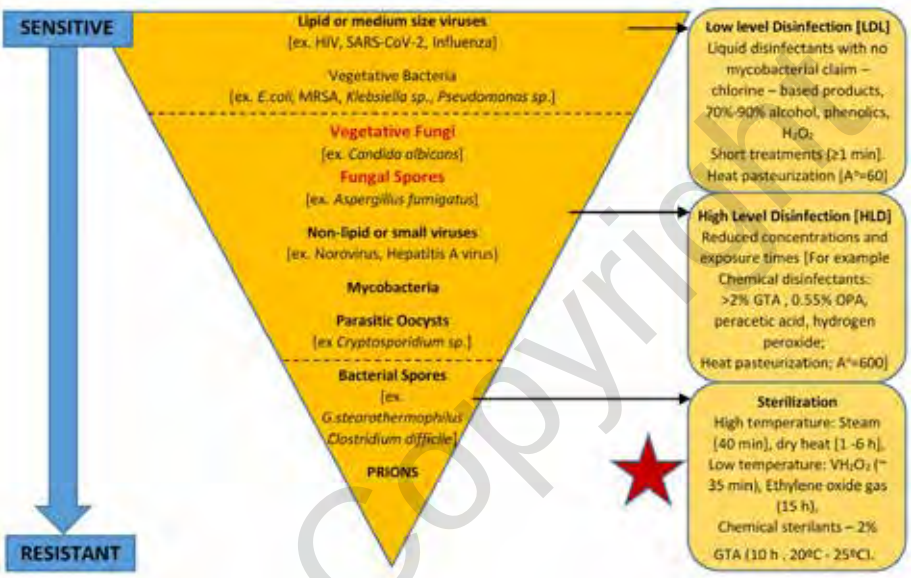


Figure 1. Pyramid of increasing microbial resistance to medical device processing and sterilization stressors. The microbial resistance profile to applied disinfection and sterilization modalities. It should be noted that the overall pattern of resistance to applied lethal technologies may vary depending on the modality. Microorganisms with higher resistance are widely used to challenge and test the effectiveness of disinfection and sterilization methods. Mycobacterial cells and Bacillus endospores have been used as indicators of HLD and sterilization, respectively. Fungi exhibit greater biocidal resistance to enveloped viruses (such as HIV and SARS-COV-2) and to Gram-positive and -negative vegetative bacterial cells. Fungi present in vegetative- and spore-forming morphologies can be further differentiated based upon these morphologies with increasing exposure to these applied lethal stresses. For example, Aspergillus spores are more tolerant to higher doses of UV-irradiation due to the protective peak absorption of pigments at a similar UV-C wavelength to that of DNA (ca. from 250 to 260 nm). However, fungi are considered to be more susceptible to high-level disinfection (HLD) compared to similarly treated non-enveloped viruses (such as norovirus), mycobacterial cells, and parasitic oocysts (Cryptosporidium species), or cysts (Giardia species) (from Garvey M, et al. Int J Mol Sci. 2023).

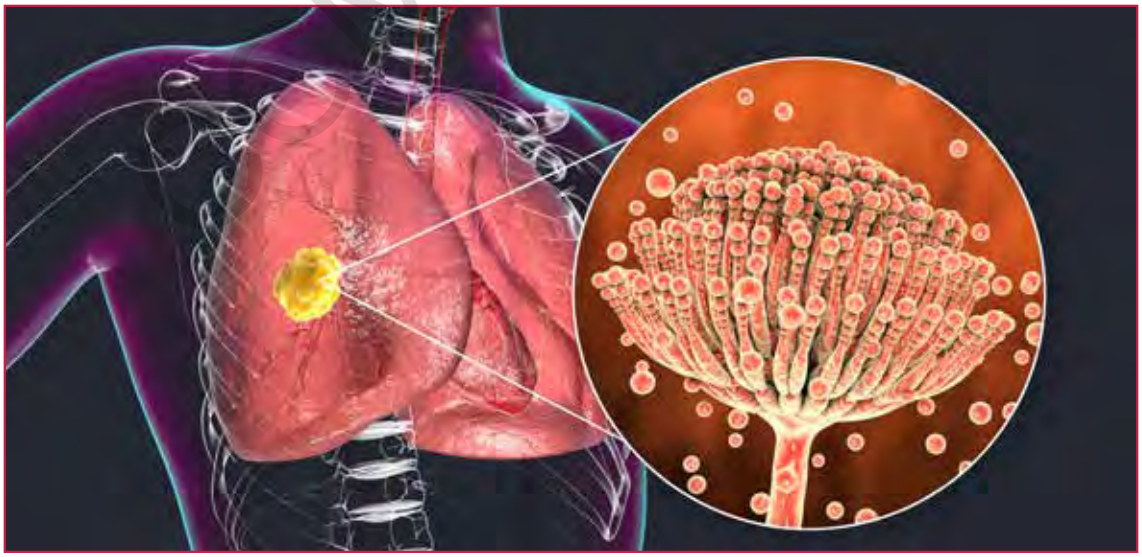
Candida infections display reduced azole susceptibility. For invasive aspergillosis, voriconazole is typically administered, and amphotericin B (AMPB) and the echinocandins also show anti-aspergillus activity, whereas the Aspergillus species possess a resistance to fluconazole. The effective treatment of IFIs is also impacted by the lack of an accurate diagnosis. The diagnosis of IFIs is challenging, as the tests are slow, with limited sensitivity and specificity, and they are typically quite expensive. IFI diagnosis consists of three elements: clinical symptoms (fever, a cough, dyspnea, chest pain, and hemoptysis), which are not always present, imaging results, and the detection of the causative agent. The diagnosis of pulmonary invasive aspergillosis, for example, is achieved via

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

a computed tomography (CT) scan of the chest in a patient with the appropriate risk factors to observe the nodules that are surrounded by a halo, which is a radiological feature. Many *A. fumigatus* isolates are resistant to triazoles and possess pan-azole resistance. *A. niger,* for example, has resistance to oral itraconazole and isovuconazole drugs, with *Aspergillus terreus* and *Asperguillus nidulans* possessing a resistance to AMPB. The FDA suggests that AMPB is the safest antifungal agent for the treatment of systemic fungal infections, irrespective of its side effects, long half-life, and liver and kidney toxicity.[4]

Conclusions

Fungal pathogens represent a serious public health risk, where antimicrobial resistance (AMR)-incorporating biocidal resistance has complicated the issue. The WHO has announced a fungal priority pathogen list, further highlighting the seriousness of the disease risk of these potentially life-threatening organisms. Antifungal resistance is further augmented by a lack of novel antifungal therapeutic options and associated biocompatibility issues, thereby limiting the medical applications. Without efficient control measures, the critically important WHO listed pathogens such as *C. auris* and *C. neoformans* will continue to result in unacceptably high rates of mortality. Additionally, the emergence of new species such as the non-*Candida albicans* bloodstream Infections (BSIs) will increase, leading to the proliferation of AMR and increasing the death rates, particularly in immunocompromised persons. As with



MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

all of the infectious diseases, prevention is the optimal way to mitigate disease outbreak and transmission. The application of effective disinfection and sterilization regimes, particularly in hospital settings, is vitally important, where a focus on fungal biofilm formation on indwelling medical devices is important. Currently, there is an ongoing drug resistance crisis globally, where fungal AMR is often overlooked in terms of diagnosis and pathogen monitoring. In order to more accurately monitor and respond to the actual number of fungal-mediated infections that is underestimated, there is a need to improve fungal diagnostic and detection methods along with effective communication to clinicians. The widespread application of antimicrobial therapeutics without having conducted more investigative studies should not be applied. There is a pressing need to understand the cellular and molecular mechanistic relationship between device reprocessing and the inactivation of biofilm-forming fungi in order to mitigate device-related transmission. Semi-critical devices should be reviewed to reduce the risk to the patient, where there is an unreasonable number of cleaning and processing steps to satisfy the margin of safety in the healthcare setting. Preventing the growth of mycotoxin-producing fungi on foods through the performance of appropriate end-to-end processes is advisable, as mycotoxins are recalcitrant and challenging to eliminate once they have been formed. Adopting the OneHealth approach will support and enable solutions to address this complex societal challenge.[4]

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1 WHO. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. © World Health Organization 2022.

2 Burki T. WHO publish fungal priority pathogens list. Lancet Microbe. 2023 Jan 9:S2666-5247(23)00003-4. doi: 10.1016/S2666-5247(23)00003-4. Epub ahead of print. PMID: 36634695.

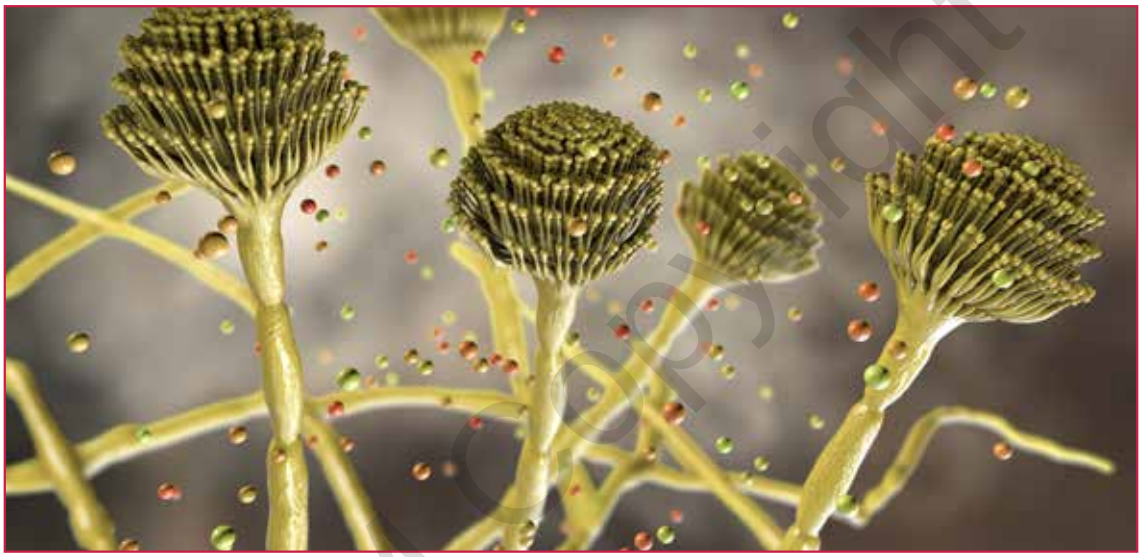
3 Parums DV. Editorial: The World Health Organization (WHO) Fungal Priority Pathogens List in Response to Emerging Fungal Pathogens During the COVID-19 Pandemic. Med Sci Monit. 2022 Dec 1;28:e939088.

4 Garvey M, Rowan NJ. Pathogenic Drug Resistant Fungi: A Review of Mitigation Strategies. Int J Mol Sci. 2023 Jan 13;24(2):1584.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

UPDATE IN
INVASIVE
FUNGAL
INFECTIONS

Invasive Fungal Infections



Invasive Fungal Pneumonia in Immunocompromised Patients[1]

Fungal pneumonia is the most frequent presentation of invasive fungal infections (IFIs) in patients with hematologic malignancies (HM) and hematopoietic stem cell transplantation (HSCT) recipients. The most common causes include Aspergillus, Mucor, Fusarium, and Candida species. The high incidence and high morbidity and mortality rate of fungal pneumonias in HM/HSCT populations arise from severe immune dysfunction that may be caused by both the underlying disease and/or its treatment. Computed tomography (CT) is routinely used when pulmonary complications are suspected after HSCT. Appropriate image interpretation of the posttransplant patient requires a combination of pattern recognition and knowledge of the clinical setting. In this article, Codoy et al provided an overview of the clinical manifestations and CT imaging features of the most common invasive fungal pneumonias (IFPs) seen in severely immunosuppressed hosts:

- In the setting of HSCT most invasive fungal infections occur in the neutropenic or pre-engraftment phase (up to 2–3 weeks after HSCT) and are most commonly caused

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

by Aspergillus, Mucor, Fusarium, and Candida species.

- The typical CT findings of angioinvasive aspergillosis include nodules (>1 cm) or masses surrounded by a halo of ground-glass attenuation ("CT halo sign") and pleural-based, wedge-shaped areas of consolidation, the latter representing hemorrhagic infarction.
- The reversed halo sign (RHS) on CT is characterized by a central ground-glass opacity surrounded by a complete or incomplete ring of consolidation and is suspicious for pulmonary mucormycosis in immunosuppressed patients, especially in the context of concomitant sinusitis and prior voriconazole prophylaxis.
- The noninfectious complications seen in the neutropenic phase of HSCT (pulmonary edema, diffuse alveolar hemorrhage, drug toxicity, idiopathic pneumonia syndrome, and engraftment syndrome), in contrast to fungal infection, tend to present with a diffuse pattern of disease.

In conclusion, pulmonary complications, including infectious and non-infectious conditions, are common in HSCT recipients. IFIs remain a leading cause of morbidity in HM/HSCT patients, associated with a high mortality rate, despite widespread use of antifungal prophylaxis in the last 30 years. Fungal infections occur in up to 10% of patients undergoing HSCT and have a reported mortality rate of 80 to 90%. It has been shown that survival can be improved with early administration of antifungal therapy.

Source: Godoy MCB, Ferreira Dalla Pria HR, Truong MT, Shroff GS, Marom EM. Invasive Fungal Pneumonia in Immunocompromised Patients. Radiol Clin North Am. 2022 May;60(3):497-506. doi: 10.1016/j.rcl.2022.01.006.

Incidence and Mortality of COVID-19-associated Pulmonary Aspergillosis[2]

COVID-19-associated pulmonary aspergillosis (CAPA) has been reported worldwide. However, basic epidemiological characteristics have not been well established.

In this systematic review and meta-analysis, Mitaka et al estimated the incidence and mortality of CAPA in critically ill patients with COVID-19 in the ICU, aiming to improve guidance on surveillance and prognostication.

CAPA occurred in 10.2% of cases in these studies and was associated with high mortality. Since the start of the COVID-19 pandemic, CAPA has been reported as a complication of mechanically ventilated patients with COVID-19 from across the world. However, epidemiological data on incidence and mortality were variable, as the reports were mainly based on case series and small observational studies, especially in the early stages of the pandemic.

Observational studies reporting COVID-19-associated pulmonary aspergillosis were searched with PubMed and Embase databases, followed by an additional manual search in April 2021. The authors performed a one-group meta-analy-

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

sis on the incidence and mortality of CAPA using a random-effect model. The authors identified 28 observational studies with a total of 3148 patients to be included in the meta-analysis. Among the 28 studies, 23 were conducted in Europe, two in Mexico and one each in China, Pakistan and the United States. Routine screening for secondary fungal infection was employed in 13 studies. The modified AspICU algorithm was utilized in 15 studies and was the most commonly used case definition and diagnostic algorithm for pulmonary aspergillosis. The incidence and mortality of CAPA in the intensive care unit (ICU) were estimated to be 10.2% (95% CI, 8.0-12.5; I^2 = 82.0%) and 54.9% (95% CI, 45.6-64.2; I^2 = 62.7%), respectively.

In conclusion, this meta-analysis provides integrated and refined estimates for the incidence and mortality of CAPA. These findings can be utilized as a basis for surveillance of CAPA and prognostication in the ICU. Large, prospective cohort studies based on the new case definitions of CAPA are warranted to validate these estimates of incidence and mortality in this important complication of COVID-19.

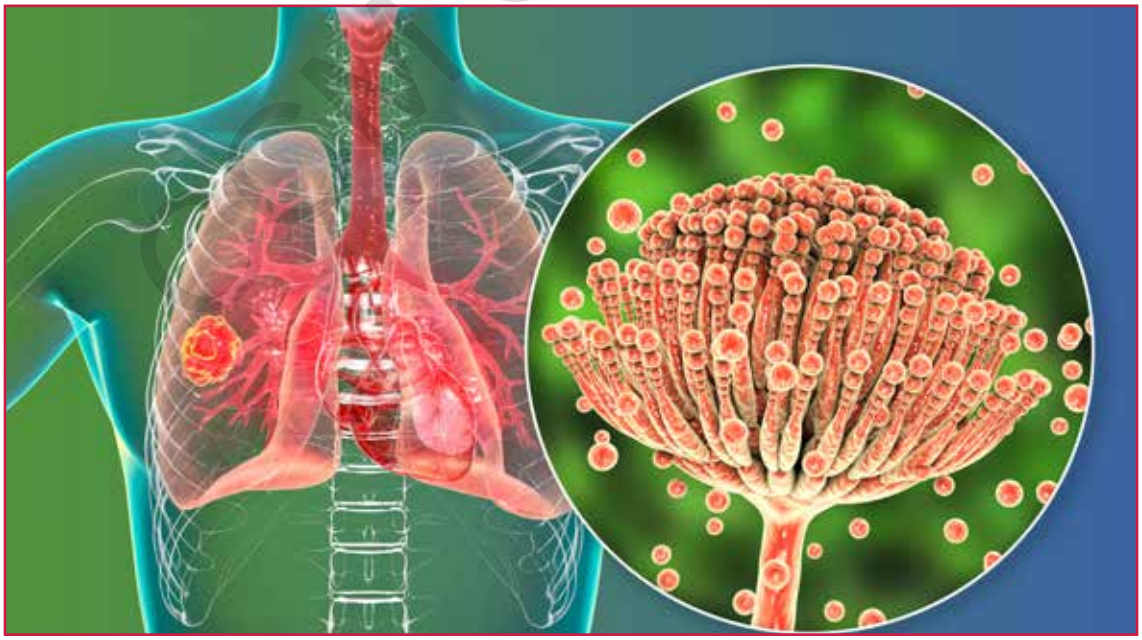
Source: Mitaka H, Kuno T, Takagi H, Patrawalla P. Incidence and mortality of COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis. Mycoses. 2021 Sep;64(9):993-1001. doi: 10.1111/myc.13292.

UPDATE IN
INVASIVE
FUNGAL
INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

A Prospective Multicenter Cohort Surveillance Study of Invasive Aspergillosis in Patients with Hematologic Malignancies in Greece[3]

Data concerning the incidence of invasive aspergillosis (IA) in high-risk patients in Greece are scarce, while the impact of the revised 2020 EORTC/MSGERC consensus criteria definitions on the reported incidence rate of IA remains unknown. A total of 93 adult hematology patients were screened for IA for six months in four tertiary care Greek hospitals. Serial serum specimens (n = 240) in which the sample was considered negative by PCR were collected twice-weekly and tested for galactomannan (GM) and *Aspergillus* DNA (PCR) detection. IA was defined according to both the 2008 EORTC/MSG and the 2020 EORTC/MSGERC consensus criteria. Based on the 2008 EORTC/MSG criteria, the incidence rates of probable and possible IA was 9/93 (10%) and 24/93 (26%), respectively, while no proven IA was documented. Acute myeloid leukemia was the most common underlying disease (67%) with most patients (82%) being on antifungal prophylaxis/treatment. Based on the new 2020 EORTC/MSGERC criteria, 2/9 (22%) of probable and 1/24 (4%) of possible cases should be reclassified as possible and prob-



MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

able, respectively. The episodes of probable IA were reduced by 33% when GM alone and 11% when GM + PCR were used as mycological criterion. The incidence rate of IA in hematology patients was 10%. Application of the 2020 EORTC/MSGERC updated criteria results in a reduction in the classification of probable IA particularly when PCR is not available.

An infection with an evolving epidemiology, such as IA, necessitates a local surveillance system given the inter-center variability in incidence rates and treatment modalities. The incidence of probable IA in the present study was 10% although a significant inter-center variation was observed and most patients were on antifungal prophylaxis/treatment. In-depth knowledge of the problem will help design appropriate treatment strategies as shown in the present study, where the employment of antifungal prophylaxis in a center with high incidence rate of IA had an impact on mortality. Clearly, the making of a definitive diagnosis of IA remains a major challenge in hematology patients. The implementation of the 2020 EORTC/MSGERC revised criteria resulted in reduction of the reported incidence of probable IA by 33% when the GM alone and 11% when the combination of GM and PCR were used as mycological evidence. The EORTC/MSGERC definitions were not designed to be used in routine clinical practice and there is certainly a need for new accurate assays to enable the diagnosis of the infection, ideally at an early stage.

Source: Siopi M, Karakatsanis S, Roumpakis C, Korantanis K, Sambatakou H, Sipsas NV, Tsirigotis P, Pagoni M, Meletiadis J. A Prospective Multicenter Cohort Surveillance Study of Invasive Aspergillosis in Patients with Hematologic Malignancies in Greece: Impact of the Revised EORTC/MSGERC 2020 Criteria. J Fungi (Basel). 2021 Jan 5;7(1):27. doi: 10.3390/jof7010027.

The Role of Diagnostics-Driven Antifungal Stewardship in the Management of Invasive Fungal Infections[4]

Antifungal stewardship (AFS) programs are key to optimizing antifungal use and improving outcomes in patients with invasive fungal infections. This systematic literature review evaluated the impact of diagnostics in AFS programs by assessing performance and clinical measures. Most eligible studies were from Europe and the United States (n=12/17).

Diagnostic approaches included:

- serum β-1–3-D-glucan test (n/N studies, 7/17)
- galactomannan test (4/17)
- computed tomography scan (3/17)
- magnetic resonance (2/17)
- matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS; 2/17)
- polymerase chain reaction (1/17)
- peptide nucleic acid fluorescent in situ hybridization (PNA-FISH) assay (1/17)
- other routine methods (9/17)

Diagnostics-driven interventions can poten-

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

Key findings
Reduction in antifungal consumption: 10/17 studies (11.6%-59.0% in 7 studies)
Reduction in Antifungal cost: 10/17 studies (13.5%-50.6% in 5 studies)
Improvement in mortality related outcomes: 13/17 studies
Other findings
Improved time to species identification (n=2) and time to targeted therapy (n=3) using MALDI-TOF and PNA-FISH
Decreased length of empiric therapy (n=3)
Reduced length of stay (LOS) (n=6)
No negative impact was reported on patient outcomes

tially improve AFS measures (antifungal consumption, cost, mortality, and length of stay); therefore, AFS implementation should be encouraged.

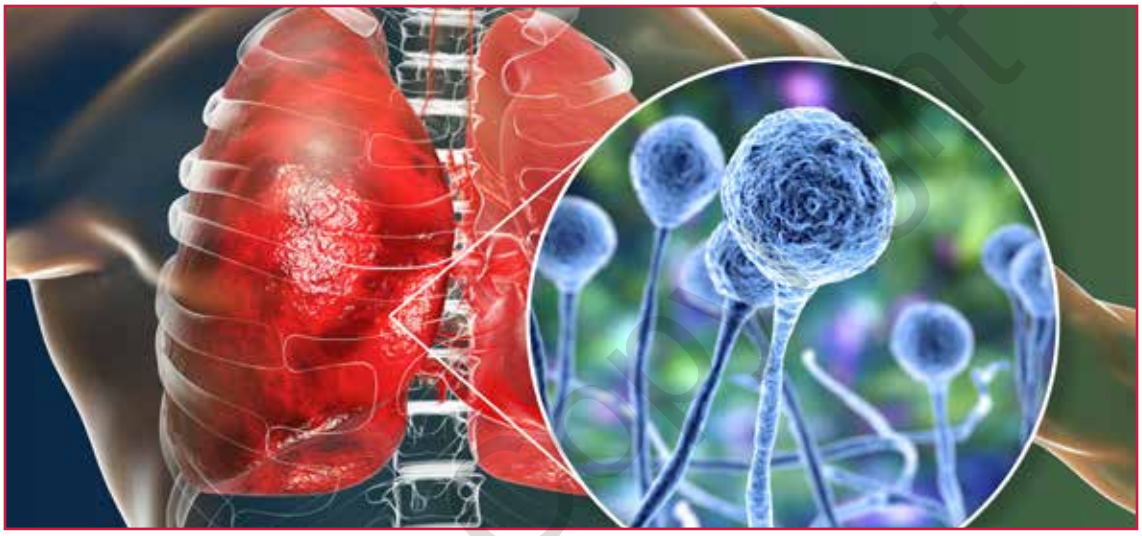
This systematic literature review provides crucial evidence on the potential of AFS initiatives to implement diagnostic approaches that improve clinical and economic outcomes for patients. Implementation of appropriate diagnostic tests yielding results 24 hours every day should be fostered to support timely and appropriate antifungal therapy (AFT). Additionally, AFS programs must focus on clinical indicators to show improvement in patient outcomes, in addition to achieving the cost-savings associated with decreased antifungal consumption. The current review also identified a gap in implementing and reporting AFS in developing countries. Of note, access to advanced diagnostic techniques is a major challenge in developing countries and remains a potential issue to be addressed. Considering that AFS studies did not demonstrate any negative impact on patient outcomes, AFS initiatives should be encouraged across countries.

Source: Chakrabarti A, Mohamed N, Capparella MR, Townsend A, Sung AH, Yura R, Muñoz P. The Role of Diagnostics-Driven Antifungal Stewardship in the Management of Invasive Fungal Infections: A Systematic Literature Review. Open Forum Infect Dis. 2022 May 11;9(7):ofac234.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

UPDATE IN INVASIVE FUNGAL INFECTIONS

Mucormycosis



Evaluation of Serum Mucorales Polymerase Chain Reaction (PCR) for the Diagnosis of Mucormycoses[5]

Early diagnosis and prompt initiation of specific antifungal treatment are essential for improving the prognosis of mucormycosis. Millon et al aimed to assess the performance of serum Mucorales quantitative polymerase chain reaction (qPCR) for the early diagnosis and follow-up of mucormycosis.

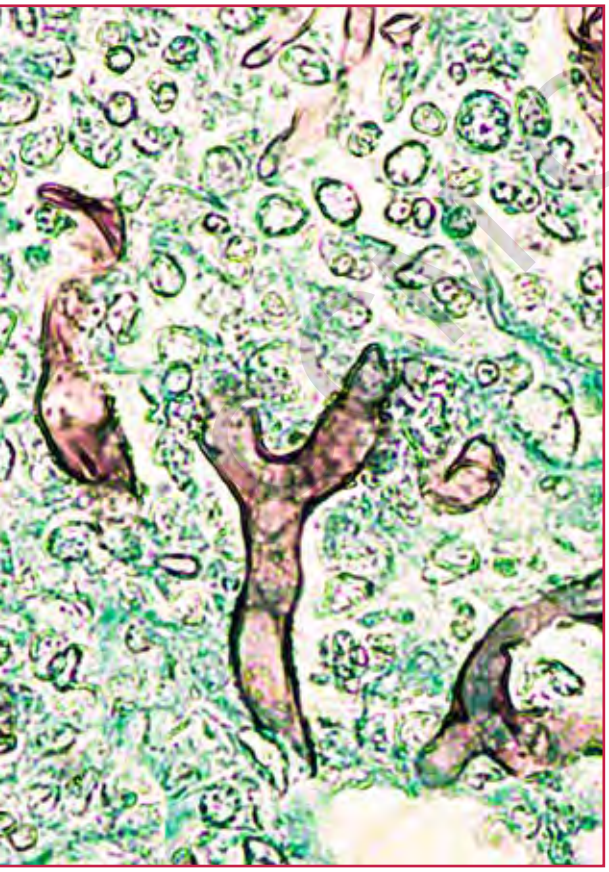
To this end, they performed the MODIMUCOR study (Projet Hospitalier de Recherche Clinique national-PHRC 2013-0397) to confirm their previous results. This prospective multicenter study aimed to assess the performance of serum Mucorales qPCR for the diagnosis of mucormycosis. Patients with a suspicion of IMD were prospectively enrolled in nine teaching hospitals. Mucorales qPCR was performed at the time of serum sampling in each center using the combination of genera-specific qPCR assays targeting *Lichtheimia*, *Rhizomucor*, and *Mucor/Rhizopus* the authors had previously described.

The authors prospectively enrolled 232 patients with suspicion of invasive mold disease, evaluated using standard imaging and mycological procedures. Thirteen additional patients with proven or probable mucormycosis were included to analyze DNA load kinetics. Serum samples were collected twice-a-week

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

for Mucorales qPCR tests targeting the Mucorales genera *Lichtheimia*, *Rhizomucor*, and *Mucor/Rhizopus*.

Results showed that sensitivity was 85.2%, specificity was 89.8%, and positive and negative likelihood ratios were 8.3 and 0.17, respectively in this prospective study. The first Mucorales qPCR-positive serum was observed at a median of 4 days (interquartile range [IQR], 0-9) before sampling of the first mycological or histological positive specimen and a median of one day (IQR, -2 to 6) before the first imaging was performed. Negativity of Mucorales qPCR within seven days after liposomal-amphotericin B initiation was associated with an 85% lower 30-day mortality rate (adjusted hazard ratio = 0.15, 95% confidence interval [0.03-0.73], *p*=0.02).



In conclusion, serum Mucorales qPCR is a non-invasive technique that can help anticipate the diagnosis of mucormycosis and trigger early targeted antifungal treatment. Follow-up of the Mucorales DNA load in serum could also be helpful for therapeutic management. The possible standardization of the test and very good performance now demonstrated in a prospective multicenter study, argue for the addition of Mucorales qPCR in clinical settings and EORTC/MSGERC consensual definitions to improve the management of mucormycosis. There is still the issue of the diagnostic strategy, as regards the prospective screening or part of the diagnostic work-up for suspicion of a mold disease. The second strategy is likely more realistic because of the low frequency of mucormycosis in hematology patients.

Source: Millon L, Caillot D, Berceanu A, Bretagne S, Lanternier F, Morio F, Letscher-Bru V, Dalle F, Denis B, Alanio A, Boutoille D, Bougnoux ME, Botterel F, Chouaki T, Charbonnier A, Ader F, Dupont D, Bellanger AP, Rocchi S, Scherer E, Gbaguidi-Haore H, Herbrecht R. Evaluation of Serum Mucorales Polymerase Chain Reaction (PCR) for the Diagnosis of Mucormycoses: The MODIMUCOR Prospective Trial. Clin Infect Dis. 2022 Sep 14;75(5):777-785.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

UPDATE IN
INVASIVE
FUNGAL
INFECTIONS

Candida Infections

Species Distribution, Azole Resistance and Related Molecular Mechanisms in Invasive *Candida Parapsilosis* Complex Isolates[6]

Candida parapsilosis complex is a common cause of nosocomial candidemia with increasing prevalence worldwide. However, identification to species level was not available in routine clinical microbiology laboratories before the introduction of matrix-assisted laser desorption-time-of-flight mass spectrometry (MALDI-TOF MS). Surveillance studies revealed that *C. parapsilosis* sensu stricto was the most prevalent cause of fungemia. *C. orthopsilosis* was less common, and *C. metapsilosis* was rare. The frequency of different species varied in different geographical regions. *C. orthopsilosis* prevalence was 8.5% in Brazil, 8.2% in Spain and was as high as 23.4% in Malaysia, among candidemia isolates. The studies from Turkey revealing species-level distribution of *C. parapsilosis* complex isolates are scarce, yet similar results were reported. Studies from different time periods identified most of the *C. parapsilosis* complex isolates as *C. parapsilosis* sensu stricto. In this study, all of the 181 candidemia episodes investigated through 21 years was caused by *C. parapsilo-*

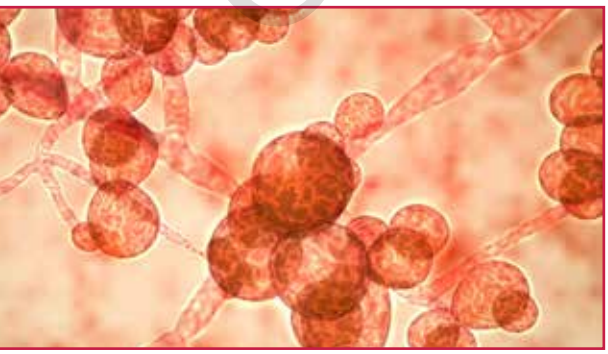
MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

sis sensu stricto (99.4%), except one episode caused by *C. orthopsilosis* (0.4%).

In this study, Demirci-Duarte et al aimed to determine the species distribution in *C. parapsilosis* complex strains isolated from blood cultures, detect azole resistance rates and investigate molecular mechanisms of resistance in their hospital, which is a major regional center for patients predisposed to invasive mycoses.

To this end, isolates from blood cultures from 1997 to 2017 were included. Species were identified using restriction fragment length polymorphisms (RFLP) of the secondary alcohol dehydrogenase (SADH) gene and confirmed with internal transcribed spacer (ITS) sequencing when needed. In vitro susceptibility to fluconazole, voriconazole and posaconazole was tested and evaluated using EUCAST guidelines. Sequences of ERG11 and MRR1 genes were analyzed for fluconazole non-susceptible isolates.

A total of 283 isolates from 181 patients were tested for azole susceptibility. All were *C. parapsilosis* sensu stricto, except one *C. orthopsilosis.* All three azoles were effective against 213 of the isolates from 135 patients, including one *C. orthopsilosis.* Fluconazole resistance was 13.3% (24/181 patients). While the first fluconazole-resistant isolates were detected in 2004, increase was evident after 2011. In ERG11, Y132F mutation was the most common among fluconazole non-susceptible isolates (71.7%), followed by G458S (10.9%) and D421N (4.3%). In MRR1, R405K (56.5%) and G927C (8.7%) were detected. However, association of these mutations to azole resistance is yet to be investigated.



In conclusion, *C. parapsilosis* sensu stricto was the dominant species and increasing fluconazole resistance rates raised concerns for candidemia caused by *C. parapsilosis* complex in this retrospective study. The most common azole resistance mechanism was Y132F mutation in the ERG11 gene. Except for limited evidence on G458S that was detected in azole-resistant isolates previously, effects of single nucleotide polymorphisms (SNPs) detected in both ERG11 and MRR1 genes are yet to be explained. In addition, different minimum inhibitory concentration (MIC) values detected in the isolates with the same SNPs suggest that other mechanisms should be evaluated for full recognition of azole resistance in *C. parapsilosis* complex.

Source: Demirci-Duarte S, Arikan-Akdagli S, Gülmez D. Species distribution, azole resistance and related molecular mechanisms in invasive Candida parapsilosis complex isolates: Increase in fluconazole resistance in 21 years. Mycoses. 2021 Aug;64(8):823-830.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

Rare Yeasts and Molds

Factors Associated with Breakthrough Fungemia Caused by *Candida*, *Trichosporon*, or *Fusarium* Species in Patients with Hematological Disorders[7]

Limited data are available on breakthrough fungemia, defined as fungemia that develops on administration of antifungal agents, in patients with hematological disorders. Kimura et al reviewed the medical and microbiological records of adult patients with hematological diseases who had breakthrough fungemia between January 2008 and July 2019 at Toranomon Hospital and Toranomon Hospital Kajigaya in Japan. A total of 121 cases of breakthrough fungemia were identified. Of the 121 involved patients, 83, 11, 5, and 22 were receiving micafungin, voriconazole, itraconazole, and liposomal amphotericin B, respectively, when the breakthrough occurred. Of the 121 causative breakthrough fungal strains, 96 were *Candida* species, and the rest were 13 cases of *Trichosporon* species, 7 of *Fusarium* species, 2 of *Rhodotorula mucilaginosa*, and 1 each of *Cryptococcus neoformans*, *Exophiala dermatitidis*, and *Magnusiomyces capitatus*. The crude 14-day mortality rate of breakthrough fungemia was 36%. Significant independent factors associated with the crude 14-day mortality rate were age of ≥60 years (p=0.011), chronic renal failure (p=0.0087), septic shock (p<0.0001), steroid administration (p=0.0085), and liposomal amphotericin B breakthrough fungemia (p=0.0011). An absolute neutrophil count of >500/μL was significantly more common in candidemia in the multivariate analysis (p=0.0065), neutropenia and nonallogeneic hematopoietic stem cell transplants were significantly more common in *Trichosporon* fungemia (p=0.036 and p=0.033, respectively), and voriconazole breakthrough fungemia and neutropenia were significantly more common in *Fusarium* fungemia (p=0.016 and p=0.016, respectively).

Results showed that three novel insights were obtained from this study:

- the epidemiology of the breakthrough fungemia, including distribution of causative fungal species, was shown
- the significant factors associated with the mortality of the cases with breakthrough fungemia were documented
- significant practical predictors of candidemia, Trichosporon fungemia, and Fusarium fungemia were identified from the cohort of all the 121 cases with breakthrough fungemia

In conclusion, epidemiological and clinical

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

characteristics of breakthrough fungemia in patients with hematological disorders were demonstrated. Some useful significant predictors of candidemia, *Trichosporon* fungemia, and *Fusarium* fungemia were identified. These factors probably will help in the immediate initiation of an appropriate antifungal agent when breakthrough fungemia occurs.

Source: Kimura M, Asano-Mori Y, Sakoh T, Abe M, Ueno K, Hoshino Y, Nakamura S, Umeyama T, Yamagoe S, Miyazaki Y, Baba M, Okada C, Ogura S, Mitsuki T, Yamaguchi K, Yuasa M, Kaji D, Kageyama K, Nishida A, Taya Y, Ishiwata K, Takagi S, Yamamoto H, Yamamoto G, Uchida N, Wake A, Taniguchi S, Araoka H. Factors Associated with Breakthrough Fungemia Caused by Candida, Trichosporon, or Fusarium Species in Patients with Hematological Disorders. Antimicrob Agents Chemother. 2022 Mar 15;66(3):e0208121.

Treatment of Cryptococcal Meningitis: How Have We Got Here and Where Are We Going?[8]

This Therapy in Practice review is an update of a talk first given by JN Day (JND) at the European Congress on Clinical Microbiology and Infectious Diseases in 2019 in the Netherlands. The review contextualized the most recently published World Health Organization (WHO) guidelines for the treatment of HIV-associated cryptococcal meningitis in terms of the data from large, randomized, controlled trials published between 1997 and 2022. Ngan et al discussed the rationale for induction and maintenance therapy and the efficacy and undesirable effects of the current therapeutic armamentarium of amphotericin, flucytosine and fluconazole. The authors addressed recent research into repurposed drugs such as sertraline and tamoxifen, and potential future treatment options, including the novel antifungals fosmanogepix, efungumab and oteseconazole, and non-pharmaceutical solutions such as neurapheresis cerebrospinal fluid filtration.

There has been a "renaissance" in the number of large, randomized, controlled trials in cryptococcal meningitis over the past 10 years, and the evidence base for prescribing has never been stronger. However, the studies have primarily been focused on the best use of current therapy, particularly in low-incomes settings, or drug repurposing. There has been little impact on the headline survival rates, which have changed little over the past 30 years, and there is a pressing need to develop new, more effective drugs. Moreover, HIV-uninfected patients with cryptococcal disease have been a particularly neglected group. Given that the vast majority of cases of cryptococcal disease are in low-income settings, which are unlikely to be lucrative and offer significant financial returns, we need new models for funding innovation to encourage industry and academia to work together to identify and develop novel anticryptococcal drugs. It is unsatisfactory to hope that new antifungal drugs developed for other diseases in high-income countries may also have effects that can then be applied in cryptococcal disease—we need specific efforts. While recent

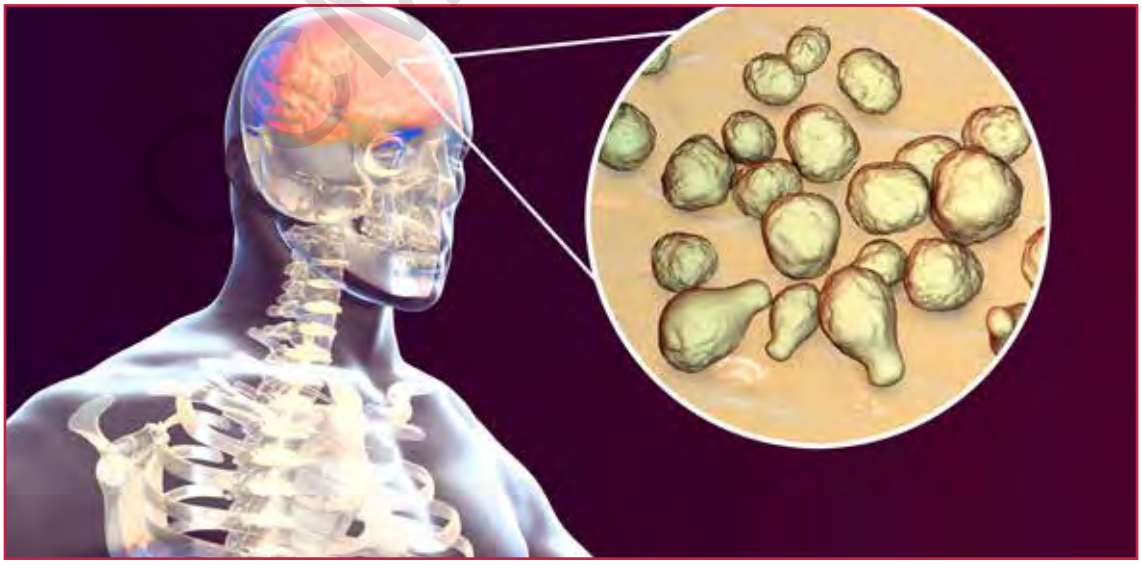
MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

experience with repurposing for cryptococcal meningitis has been disappointing, such small, randomized trials, looking at the effect on the rate of clearance of yeast from cerebrospinal fluid (CSF), should continue with the remaining candidates. As the COVID-19 pandemic has demonstrated, there is no substitute for randomized, controlled trials when trying to identify best treatments.

Significant numbers of patients have been enrolled into clinical trials of treatment for human immunodeficiency virus HIV-associated cryptococcal meningitis over the past 3 decades, delivering a robust foundation of data on which to base treatment guidelines. However, mortality with optimized current treatment remains high—there is a pressing need to develop novel drugs.

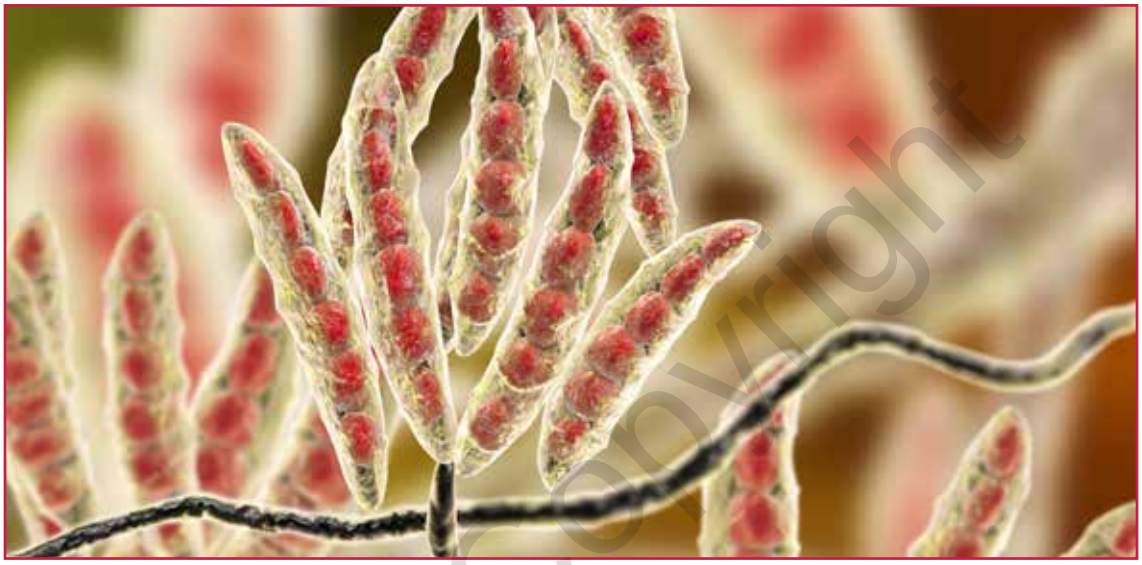
In conclusion, the optimal induction therapy is a single high-dose of liposomal amphotericin B (10 mg/kg) plus flucytosine (100 mg/kg/day) and high-dose fluconazole (1200 mg/day) each for 14 days. This is followed by consolidation with fluconazole (800 mg/day) for 8 weeks and then long-term maintenance. However, the availability of both liposomal amphotericin B and flucytosine is limited in many high-burden settings, meaning alternative inferior regimens have to be used. Alternative, currently available antifungals and attempts at drug repurposing have so far shown disappointing efficacy, but novel antifungal agents are in development and show promise.

Source: Ngan NTT, Flower B, Day JN. Treatment of Cryptococcal Meningitis: How Have We Got Here and Where are We Going? Drugs. 2022 Aug;82(12):1237-1249.



UPDATE IN
INVASIVE FUNGAL INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023



Frequency and Causes of Antifungal Treatment Changes in Allogeneic Hematopoïetic Cell Transplant Recipients with Invasive Mould Infections[9]

Antifungal treatment duration and changes for invasive mould infections (IMI) have been poorly described. Roth et al performed a 10-year cohort study of adult (≥18-year-old) allogeneic hematopoietic cell transplant recipients with proven/probable IMI to describe the duration and changes of antifungal treatment. All-cause-12-week mortality was described.

Sixty-one patients with 66 IMI were identified. Overall treatment duration was 157 days (IQR: 14–675) and 213 (IQR: 90–675) days for patients still alive by Day 84 post-IMI diagnosis. There was at least one treatment change in 57/66 (86.4%) cases: median 2, (IQR: 0–6, range: 0–8). There were 179 antifungal treatment changes for 193 reasons: clinical efficacy (104/193, 53.9%), toxicity (55/193, 28.5%), toxicity or drug interactions resolution (15/193, 7.8%) and logistical reasons (11/193, 5.7%) and 15/193 (7.8%) changes due to unknown reasons. Clinical efficacy reasons included lack of improvement (34/104, 32.7%), targeted treatment (30/104, 28.8%), subtherapeutic drug levels (14/104, 13.5%) and other (26/104, 25%). Toxicity reasons included hepatotoxicity, nephrotoxicity, drug interactions, neurotoxicity and other in 24 (43.6%), 12 (21.8%), 12 (21.8%), 4 (7.4%) and 3 (5.5%) cases respectively. All-cause 12-week

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

mortality was 31% (19/61), higher in patients whose antifungal treatment (logrank 0.04) or appropriate antifungal treatment (logrank 0.01) was started >7 days post-IMI diagnosis. All-cause 1-year mortality was higher in patients with ≥2 changes of treatment during the first 6 weeks post-IMI diagnosis (logrank 0.008) with an OR: 4.00 (p =0.04).

This single-center retrospective cohort study provided important information on the treatment of IMI in allogeneic HCT recipients, showing long treatment courses requiring multiple changes, prompted by a large variety of reasons. In contrast to current guidelines recommending a predefined duration of 12 weeks for the treatment of invasive aspergillosis (IA) and up to 3–6 months for mucormycosis. The data suggest that antifungal treatment for IMI in high-risk hematology patients is administered for much longer. When focusing on patients still alive by 12 weeks, treatment duration was at an average of 30 weeks: 28 for IA and 1.3 years for mucormycosis. It is likely that in a number of patients antifungal treatment could have been continued as secondary prophylaxis in the setting of continuous high-grade immunosuppression. The latter could explain, in part, the long treatment courses reported in this study.

In conclusion, this study reported long treatment courses for the management of IMI, requiring multiple treatment changes due to variable reasons and potential effects on clinical outcomes. These findings further point to the limitations of the current antifungal therapy landscape and the urgent need for effective and safer treatment options. Early initiation of appropriate antifungal treatment is associated with improved outcomes.

Source: Roth RS, Masouridi-Levrat S, Giannotti F, Mamez AC, Glambedakis E, Lamoth F, Bochud PY, Erard V, Emonet S, Van Delden C, Kaiser L, Chalandon Y, Neofytos D. Frequency and causes of antifungal treatment changes in allogeneic haematopoïetic cell transplant recipients with invasive mould infections. Mycoses. 2022 Feb;65(2):199-210.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

Antifungal Prophylaxis

Antifungal Prophylaxis in Acute Myeloblastic Leukemia Patients Receiving Intensive Induction Chemotherapy[10]

Although recommended in patients with acute myeloblastic leukemia (AML) after induction chemotherapy, the real-life use of antifungal prophylaxis (AFP) varies between centers.

The main objectives of the ancillary study were to:

1. Describe the different AFP strategies used.
2. Evaluate the consistency between invasive fungal infection (IFI) assessment by the centers and that of independent experts.
3. Describe the rate of IFIs and their cumulative incidence according to AFP strategies.
4. Evaluate the place of AFP in AML patients receiving intensive chemotherapy and to assess the relationship between the hematological disease state, the success of AFP and its impact on the overall survival and the IFI-related death rate.

This was an ancillary study to a randomized trial on intensive induction chemotherapy in AML patients, where AFP with posaconazole was recommended. IFIs were graded by investigators and by central reviewers according to the revised European Organization for Research and Treatment of Cancer (EORTC) definitions. Experts' conclusions were compared to the investigators' ones.

A total of 677 patients were included. Four AFP strategies were reported: Group-1: no AFP (n = 203, 30%), Group-2: posaconazole (n = 241, 36%), Group-3: posaconazole with other AFP (n = 142, 21%), Group-4: other AFP (n = 91, 13%). Experts graded more IFI than investigators: proven/probable IFI, 9.0% (n = 61) versus 6.2% (n = 42). The cumulative incidence at day 60 of probable/proven IFI was 13.9% (Group-1); 7.9% (Group-2); 5.6% (Group-3); and 6.6% (Group-4). IFI onset was 26 (19-31) days after induction in Groups 2-3, versus 16 (9-25) days in Group 1 and 20 (12-24) days in Group 4 (p<0.001). After a median follow-up of 27.5 months (0.4-73.4), the mortality rate was 38.3%, with 5.4% attributed to IFI. In multivariate analysis, IFI occurrence was an independent risk of death (HR 5.63, 95%-CI 2.62-12.08, p<0.001). EORTC recommendations were applied in only 57% of patients. In patients without IFI, the rate of AML complete remission was higher.

This observational study provided a unique picture of the AFP strategy used by French hematological centers to prevent the occurrence of IFI in AML patients who underwent an intensive induction chemotherapy. The AFP was administered according to the physician's judgement and in patients with posaconazole-based

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

AFP, the rate of proven/probable IFI was reduced by almost half and the IFI onset was delayed by 10 days versus patients without AFP.

In conclusion, this ancillary study associated to a large randomized study on AML patients receiving intensive chemotherapy confirmed in real world practice that AFP allowed a statistically significant decrease of the IFI cumulative incidence, and delayed IFI onset. In this study, the review of the clinical data by hematological experts based on 2008 EORTC guidelines led to revision of the grading for almost half of the patients. In addition, it was shown that the rate of AML complete remission was significantly higher among patients who did not have any IFI than among those who had an IFI, even among patients with AFP, raising the hypothesis that the AFP was not efficient for patients with uncontrolled disease.

Source: Michallet M, Sobh M, Morisset S, Deloire A, Raffoux E, de Botton S, Caillot D, Chantepie S, Girault S, Berthon C, Bertoli S, Lepretre S, Leguay T, Castaigne S, Marolleau JP, Pautas C, Malfuson JV, Veyn N, Braun T, Gastaud L, Suarez F, Schmidt A, Gressin R, Bonmati C, Celli-Lebras K, El-Hamri M, Ribaud P, Dombret H, Thomas X, Bergeron A. Antifungal Prophylaxis in AML Patients Receiving Intensive Induction Chemotherapy: A Prospective Observational Study From the Acute Leukaemia French Association (ALFA) Group. Clin Lymphoma Myeloma Leuk. 2022 May;22(5):311-318.

UPDATE IN
INVASIVE
FUNGAL
INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

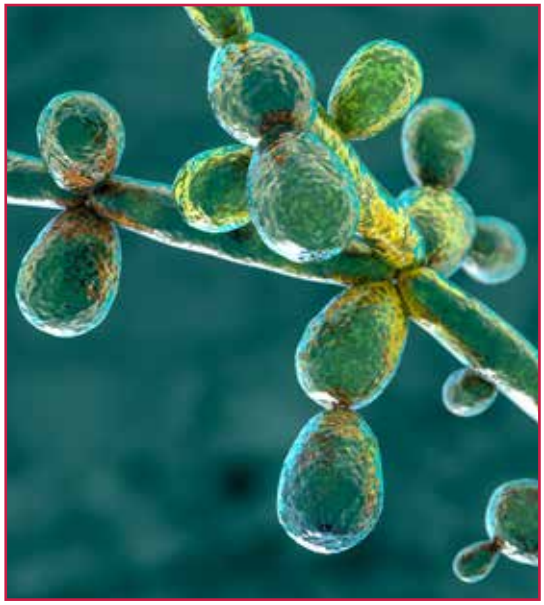
Importance of Early Empirical Antifungal Treatment

Results of an Innovative Program for Surveillance, Prophylaxis, and Treatment of Infectious Complications Following Allogeneic Stem Cell Transplantation in Hematological Malignancies[11]

Infectious complications are a significant cause of morbidity and mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (Allo-SCT).

The long-term outcome of patients submitted to allo-SCT is strongly influenced by two events: disease recurrence and non-relapse mortality (NRM). These events are responsible for the failure of the transplant procedure, which happens in approximately 50% of all transplants. One way to reduce NRM is to reduce the incidence and the mortality of infectious complications, which are recorded in more than two-thirds of patients submitted to allo-SCT. The management of infections is complex, and involves hematologists as well as specialists in infectious diseases, and microbiologists. This management includes prophylaxis and treatment programs that need to be frequently revised and updated, according to the monitoring of local epidemiology and changes in transplant platforms.

The BATMO (Best-Antimicrobial-Therapy-TMO) is an innovative program for infection prevention and management and has been used in the authors' centre since 2019. The specific features of the BATMO protocol regard both prophylaxis during neutropenia (abandonment of fluoroquinolone, posaconazole use in high-risk patients, aerosolized liposomal amphotericin B use until engraftment or a need for antifungal treatment, and letermovir use



MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

in CMV-positive recipients from day 0 to day +100) and therapy (empirical antibiotics based on patient clinical history and colonization, new antibiotics used in second-line according to antibiogram with the exception of carbapenemase-producing *K pneumoniae* for which the use in first-line therapy is chosen).

Data on the infectious complications of 116 transplant patients before BATMO protocol (Cohort A; 2016 - 2018) were compared to those of 84 transplant patients following the introduction of the BATMO protocol (Cohort B; 2019 - 2021). The clinical and transplant characteristics of the 2 Cohorts were comparable, even though patients in Cohort B were at a higher risk of developing bacterial, fungal, and CMV infections, due to a significantly higher proportion of myeloablative regimens and haploidentical donors.

No change in the incidence of infections with organ localization was observed between the two Cohorts. A significant reduction in *Clostridioides difficile* infections by day +100 was observed in Cohort B (47% vs. 15%; $p = 0.04$). At day +30, a higher incidence of Gram-negative bloodstream infections (BSIs) was observed in Cohort B (12% vs. 23%; $p = 0.05$). By day +100 and between days +100 and +180, the incidence of BSIs and of the various etiological agents, the mortality from Gram-negative bacteria, and the incidence of invasive fungal infections were not different in the two Cohorts. The incidence of CMV reactivations by day +100 dropped drastically in patients of Cohort B, following letermovir registration (51% vs. 15%; $p = 0.00001$).

Nearly 2 years after the adoption of the BATMO protocol, the authors concluded that:

- **Fluoroquinolone prophylaxis during the neutropenic phase can be safely abolished.**
- **The intensification of fungal prophylaxis in high-risk patients with a highly anti-mould drug such as posaconazole is a good choice, particularly in the era of haploidentical Transplants.**
- **Letermovir significantly reduced the clinical impact of CMV reactivations by day +100.**

In summary, the BATMO protocol is an example of a specific antimicrobial therapy that was developed at the authors' centre to improve infection treatments for patients submitted to allo-SCT. The authors are aware of the fact that the efficacy and safety of this protocol are strictly dependent on the ecology of their transplant center and that similar results may not be observed in other centers with different microbiological epidemiology. Overall, it is considered that the BATMO protocol of an active antimicrobial stewardship will be modified in the future and adapted to local epidemiology, new anti-infectious drugs, and new conditioning platforms for allo-SCT.

Source: Malagola M, Turra A, Signorini L, Corbellini S, Polverelli N, Masina L, Del Fabro G, Lorenzotti S, Fumarola B, Farina M, Morello E, Radici V, Buttini EA, Colnaghi F, Bernardi S, Re F, Caruso A, Castelli F, Russo D. Results of an Innovative Program for Surveillance, Prophylaxis, and Treatment of Infectious Complications Following Allogeneic Stem Cell Transplantation in Hematological Malignancies (BATMO Protocol). Front Oncol. 2022 Jun 17;12:874117.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

Diagnosis and Management of Invasive Candida Infections in Critically Ill Patients[12]

Invasive candidiasis (IC) has become a serious problem in the intensive care unit patients with an attributable mortality rate that can reach up to 51%. Multiple global surveillance studies have shown an increasing incidence of candidemia. Despite their limited sensitivity (21-71%), cultures remain the gold standard for the diagnosis of IC associated with candidemia. Many adjunct laboratory tests exist to support or rule out the diagnosis, each with its indications and limitations, including procalcitonin, 1,3-β-D-glucan, mannan and anti-mannan antibodies, and *Candida albicans* germ tube antibody. In addition, polymerase chain reaction-based methods could expedite species identification in positive blood cultures, helping in guiding early empirical antifungal therapy. The management of IC in critically ill patients can be classified into prophylactic, preemptive, empiric, and directed/targeted therapy of a documented infection. There is no consensus concerning the benefit of prophylactic therapy in critically ill patients. While early initiation of appropriate therapy in confirmed IC is an important determinant of survival, the selection of candidates and drug of choice for empirical systemic antifungal therapy is more controversial. The choice of antifungal agents is determined by many factors, including the host, the site of infection, the species of the isolated *Candida*, and its susceptibility profile. Echinocandins are considered initial first-line therapy agents. Due to the conflicting results of the various studies on the benefit of preemptive therapy for critically ill patients and the lack of robust evidence, the Infectious Diseases Society of America (IDSA) omitted this category from its updated guidelines and the European Society of Intensive Care Medicine (ESICM) and the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) do not recommend it.

In conclusion, this review article addresses the epidemiology, diagnosis, and treatment of invasive *Candida* infections in patients in the intensive care unit. The authors showed that host characteristics and the species of *Candida* determine the likelihood of invasive infection. Timely diagnosis is key, yet can be challenging. Several risk calculators have been created and validated in order to aid in diagnosis. Treatment can be prophylactic, empiric, or targeted and should be determined by host risk factors. This review provides an overview of the diagnosis and treatment of invasive *Candida* infections in ICU patients. Early identification and treatment can reduce the significant morbidity and mortality caused by the increasing number ot these infections.

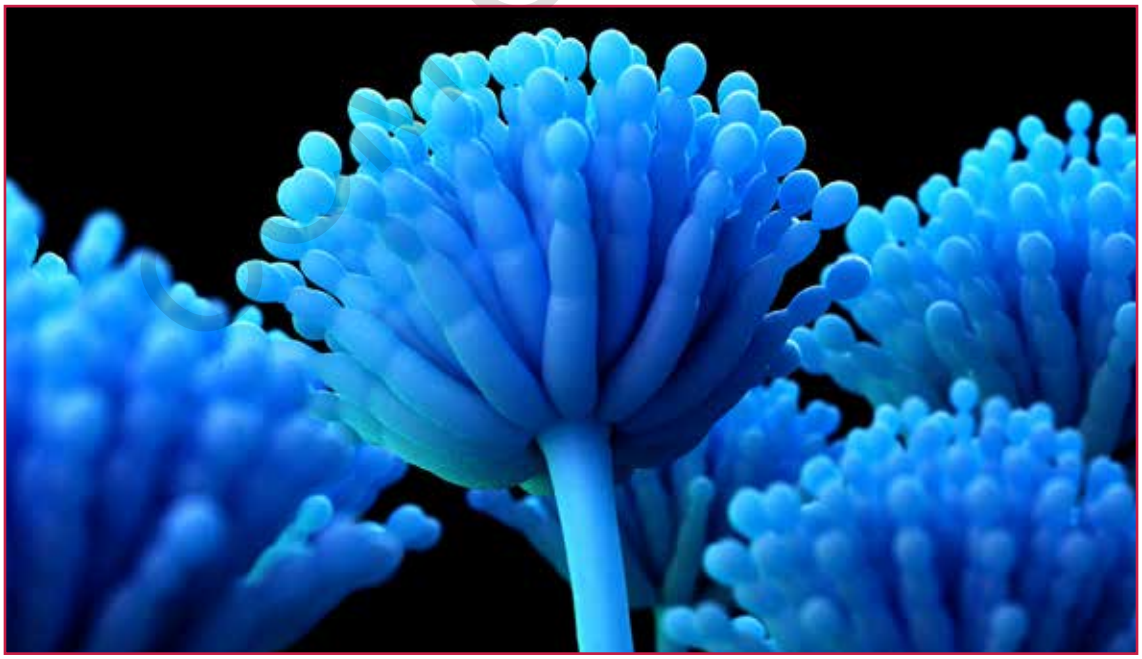
Source: Zakhem AE, Istambouli R, Jabbour JF, Hindy JR, Gharamti A, Kanj SS. Diagnosis and Management of Invasive Candida Infections in Critically Ill Patients. Semin Respir Crit Care Med. 2022 Feb;43(1):46-59. doi: 10.1055/s-0041-1741009.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

Epidemiology, Drug Susceptibility, and Clinical Risk Factors in Patients with Invasive Aspergillosis[13]

Invasive aspergillosis (IA) is clinically one of the most serious invasive fungal infections, with high morbidity, mortality, and cost of care. Over 200,000 cases are reported to be infected with *Aspergillus* species each year. *Aspergillus fumigatus* is the most frequently encountered *Aspergillus* species that causes IA and allergic diseases, although other species, such as *Aspergillus flavus, Aspergillus niger, Aspergillus terreus, Aspergillus versicolor*, and *Aspergillus nidulans*, can also induce diseases. Immunocompromised patients and those with underlying lung diseases are susceptible to IA, ranging from acute IA to chronic pulmonary aspergillosis (CPA). However, early diagnosis of IA is difficult and its misdiagnosis happens readily since *Aspergillus* infections seldom have characteristic manifestations and the specific pathogenic agents regularly take a long time to be detected.

Currently, more than 30 *Aspergillus* species have been confirmed to correlate with IA, the most common ones are *A. fumigatus, A. flavus, A. niger, A. terreus*, and *A. nidulans*. The prevalence of IA and its associated fungal spectrum



UPDATE IN
INVASIVE
FUNGAL
INFECTIONS

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

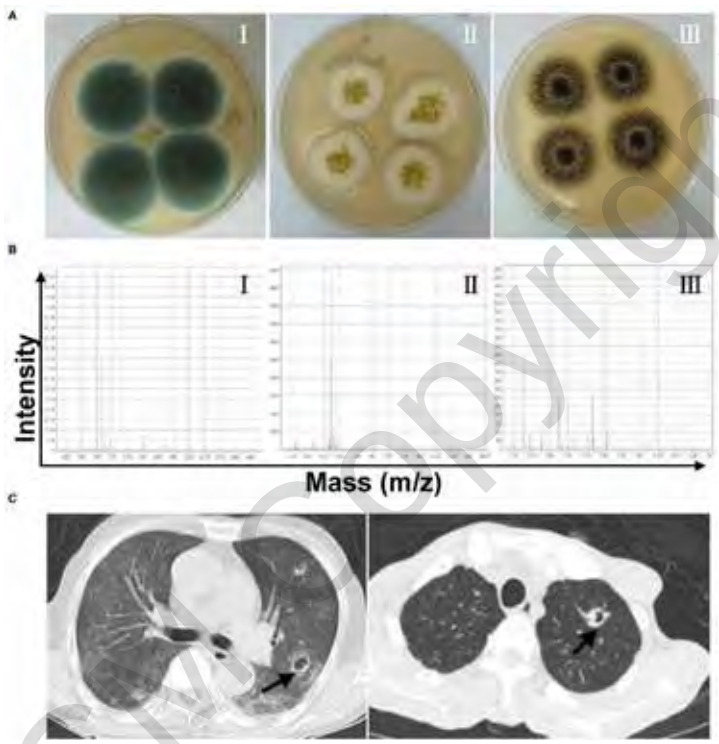


Figure 1. (A) Representative culturing macroscopic results of Aspergillus spp. (Sabouraud Dextrose agar medium). I–III: Aspergillus fumigatus, Aspergillus flavus, and Aspergillus niger. (B) Representative identification information of Aspergillus spp. by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). I–III: A. fumigatus, A. flavus, and A. niger. (C) Chest CT imaging features of patients with invasive pulmonary aspergillosis. (From: Wang Y, et al. Front Public Health. 2022)

widely vary from country to country and even among different regions within a country, due to infection sites, age, climate, geographic conditions, agricultural activities, and other factors.

In this study, Wang et al investigated the species distribution and drug sensitivities of *Aspergillus* spp. from patients with IA and their clinical characteristics and risk factors in combination with corresponding clinical data in the local Anhui Province of China. Notably, the gene encoding CYP51A in azole-resistant *A. fumigatus* was sequenced to potentially explore a possible molecular reason for the antifungal resistance.

In this study, 156 *Aspergillus* isolates were collected from patients admitted to a 2,800-bed comprehensive hospital between January

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

2019 and April 2021. The epidemiology of *Aspergillus* species was well-examined, and its antifungal susceptibility was specifically measured by the microbroth dilution method. The risk factors of patients with IA were documented and analyzed intensively. In addition, gene sequencing was employed to determine gene mutations of cytochrome P450 14-α sterol demethylase-*Aspergillus* (cyp51A) associated with azole resistance among *Aspergillus fumigatus*.

The *Aspergillus* species distribution was dominated by *A. fumigatus* (56.41%), *Aspergillus flavus* (20.51%), and *Aspergillus niger* (15.38%) locally. In particular, all *Aspergillus* species showed very low minimum inhibitory concentrations (MICs ≤ 0.5 μg/ml) for azoles and echinocandins, slightly higher MICs (1.66–2.91 μg/ml) for amphotericin B, and exceptionally high MICs (>64 μg/ml) for flucytosine. Azole-resistant rate of *Aspergillus* species in this local region reached up to 5.79%. Correlation analyses of multiple antifungals

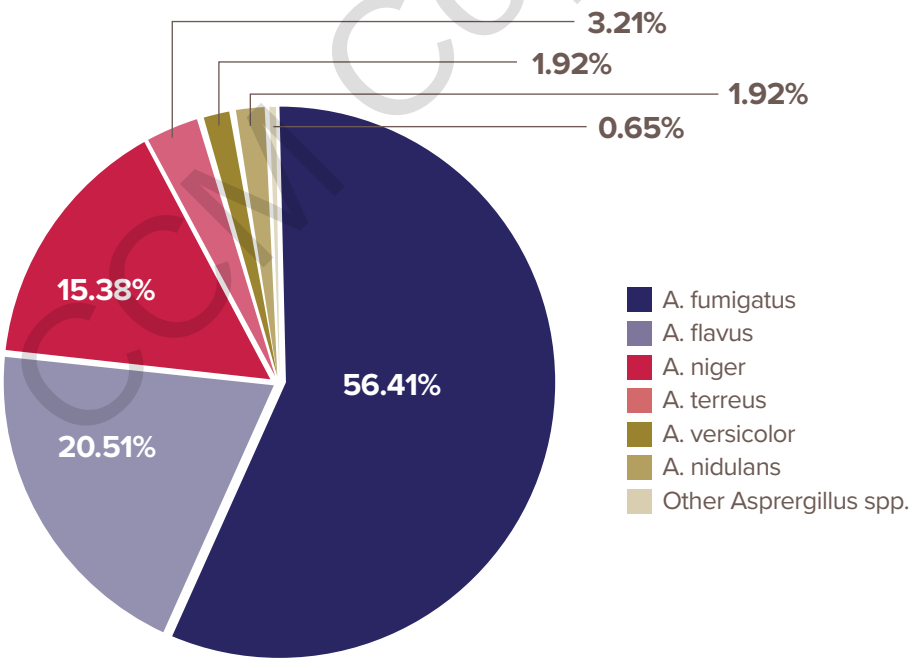


Figure 2. The species distribution of 156 *Aspergillus* isolates in this study. (From: Wang Y, et al. Front Public Health. 2022)

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

indicate a significant MIC relevance between isavuconazole and voriconazole (Pearson correlation coefficient was 0.81, $p<0.0001$). The clinical risk factors for patients with IA were found primarily to be pulmonary diseases ($p=0.007$) and patients' age ($p<0.001$). Notably, three mutant loci (TR46/Y121F/T289A) of the *cyp51A* gene were identified in azole-resistant *A. fumigatus*.

In summary, this study reported the Aspergillus species distribution and antifungal sensitivities, and clinical characteristics and risk factors of patients with IA of a local region in central China. The *A. fumigatus* and *A. flavus* were still the major pathogens for invasive *Aspergillus* infections here. The vast majority of *Aspergillus* spp. exhibited good susceptibility to almost all the antifungals commonly used in clinics. The findings implied that pulmonary diseases and age are likely considered as the main risk factors for such infections. The polymorphism of the cyp51A gene in *A. fumigatus* may be closely associated with azole resistance, contributing to treatment failures in patients with IA. Their important clinical implications emphasize the need for antifungal susceptibility surveillance and screening out mutations in resistance-linked genes.

Source: Wang Y, Zhang L, Zhou L, Zhang M, Xu Y. Epidemiology, Drug Susceptibility, and Clinical Risk Factors in Patients With Invasive Aspergillosis. Front Public Health. 2022 Apr 15;10:835092.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

UPDATE IN
INVASIVE
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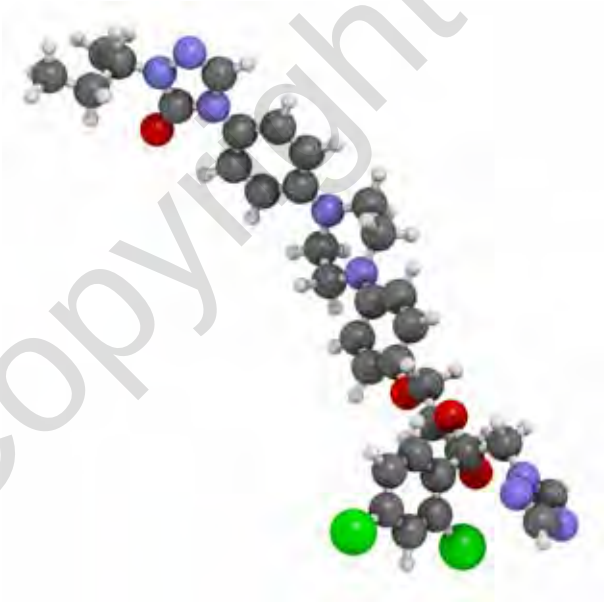
Antifungal Treatment Drug-Drug Interactions

The Overview on the Pharmacokinetic and Pharmacodynamic Interactions of Triazoles[14]



Second generation triazoles are widely used as first-line drugs for the treatment of invasive fungal infections, including aspergillosis and candidiasis. This class, along with itraconazole, voriconazole, posaconazole, and isavuconazole, is characterized by a broad range of activity, however, individual drugs vary considerably in safety, tolerability, pharmacokinetics profiles, and interactions with concomitant medications. The interaction may be encountered in the absorption, distribution, metabolism, and elimination (ADME) step. All triazoles as inhibitors or substrates of CYP isoenzymes can often interact with many drugs, which may result in the change of the activity of the drug and cause serious side effects. Drugs of this class should be used with caution with other agents, and an understanding of their pharmacokinetic profile, safety and drug-drug interaction profiles is important to provide effective antifungal therapy. The manuscript reviews significant drug interactions of azoles with other medications, as well as with food. The PubMed and Google Scholar bases were searched to collect the literature data. The interactions with anticonvulsants, antibiotics, statins, kinase inhibitors, proton pump inhibitors, non-nucleoside reverse transcriptase inhibitors, opioid analgesics, benzodiazepines, cardiac glycosides, nonsteroidal anti-inflammatory drugs, immunosuppressants, antipsychotics, corticosteroids, biguanides, and anticoagulants are presented. Possible interactions with drugs during experimental therapies for the treatment of COVID-19 were also taken into consideration.

The effectiveness of the treatment of fungal infections with azoles is influenced by factors such as the type of food, the pH of the gastroin-

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

testnal tract, and the concomitant use of other drugs. In the case of the second generation of azoles, the impact of food might vary between the drugs. For itraconazole it is unpredictable. However, taken with a meal or shortly after, it may improve bioavailability. Posaconazole is a drug for which bioavailability is increased when taken with meals (especially the high fat meals) and dietary supplements. The absorption of isavuconazole is not influenced by food intake. It can be administered regardless of the meal. On the other hand, voriconazole should not be taken with a meal.

The other factor that can modify the absorption is taking a proton pump inhibitor (PPI). An acidic pH is required for the absorption of itraconazole. A similar situation is observed for posaconazole. An elevation in pH reduces bioavailability. In the case of isavuconazole, absorption is not affected by PPI. The co-administration did not lead to statistically significant changes.

The other interaction that may have an impact on therapy is the interaction with CYP enzymes. The most significant is the interaction with CYP3A4, observed for itraconazole, voriconazole, and posaconazole. They are inhibitors of this enzyme. The antifungal drugs can interact with other enzymes such as CYP2B6 (isavuconazole) and CYP2C9 (voriconazole). Itraconazole is metabolized mainly by CYP3A4, whereas voriconazole by CYP2C19. Posaconazole is not metabolized by cytochromes to a significant extent. It might be considered as a potentially safer drug.

P-glycoprotein (P-gp) is a transporter that removes xenobiotics from the body. Clinical trials and in vitro studies have proven that itraconazole, posaconazole, and isavuconazole are inhibitors of P-gp. Voriconazole has not an affinity to that transporter. This is a significant issue when the other drugs that are substrates for P-gp are co-administered. The complexity of interactions may lead to a lack of fungicidal effect and failure of the treatment, therefore the therapy of the patients with use of azoles should be supported with therapeutic drug monitoring.

Source: Czyrski A, Resztak M, Świderski P, Brylak J, Główka FK. The Overview on the Pharmacokinetic and Pharmacodynamic Interactions of Triazoles. Pharmaceutics. 2021 Nov 19;13(11):1961.

MiFi
MIDDLE EAST INVASIVE FUNGAL INFECTIONS
Vol. 1 | issue 4 | March 2023

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Antifungal In Vitro Susceptibility of Fungal Species

Ampho B formulations are showing the broadest spectrum with over 50 years minimal acquired resistance.

In vitro susceptibility of fungal species to antifungal agents, by the EUCAST methodology

	Yeast (MIC range µg/ml)								Moulds (MIC range µg/ml)										
	Candida species					Other yeasts			Aspergillus species				Other moulds						
	C. albicans	*C. glabrata*	*C. tropicalis*	*C. krusei*	*C. parapsilosis*	*Saccharomyces cerevisiae*	*Trichosporon inkin*	*Trichosporon ashahii*	*A. fumigatus*	*A. terreus*	*A. flavus*	*A. niger*	*Fusarium oxysporum*	*Fusarium solani*	*Mucor Sp.*	*Penicillium Sp.*	*Rhizomucor Sp.*	*Rhizopus Sp.*	*Scedosporium apiospermum*
LAmB																			
amphotericin B																			
caspofungin													N/A	N/A	N/A	N/A	N/A	N/A	N/A
itraconazole																	N/A	N/A	
voriconazole														N/A	N/A		N/A	N/A	
posaconazole																			

Adapted from Lass-Flörl et al. Antimicrob Agents Chemother 2008;52(10):3637-3641.

MIC range ≤ 2 µg/ml

MIC range >2 – ≤ 4 µg/ml

MIC range >4 – > 8 µg/ml

MIC = minimal inhibitory concentration NA = no activity

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if your patient has symptoms that don't get better with treatment.

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