International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

An Overview on Invasive Fungal Infection

Marwa Nashat Shahin[1], Mohamed Anwer Refky[1], Sahar Mohamed Saad Eldeen[1], Essamedin M. Negm[1], Haitham Gouda Moayed[2] and Eslam Ahmed Hassan Naser[1]

[1]Anesthesia , Intensive Care and pain management Department, Faculty of Medicine, Zagazig University

[2]Professor, Department of Journalism and New Media, College of Media and Communication, Imam Mohammad Ibn Saud Islamic University (IMSIU)

Abstract:

Fungal pathogens such as Candida, Aspergillus, Cryptococcus, and emerging species including Mucorales and Fusarium account for most cases of invasive fungal disease. These infections predominantly affect patients with hematological malignancies, stem cell and solid organ transplants, HIV/AIDS, or those receiving prolonged corticosteroid therapy. Despite therapeutic advances, IFIs remain life-threatening, with mortality rates ranging from 30% to over 70% depending on the pathogen and host condition. The global burden underscores the need for early risk stratification, better diagnostic modalities, and optimized antifungal stewardship.

Keywords: Invasive fungal infection; Immunocompromised host; Candida; Aspergillus; Mucormycosis; Antifungal therapy; Molecular diagnostics; Mortality.

Introduction:

Invasive fungal infections (IFIs) have emerged as a major cause of morbidity and mortality among immunocompromised patients worldwide. Their rising incidence is linked to advances in medical care such as chemotherapy, stem cell transplantation, and solid organ transplantation, all of which increase host susceptibility to opportunistic fungi **(1).**

The most frequent causative organisms include Candida spp., Aspergillus spp., and increasingly recognized molds such as Mucorales and Fusarium. These infections often present with nonspecific clinical symptoms, which delay diagnosis and contribute to high mortality rates despite antifungal advances **(2).**

Over the past decade, new diagnostic tools such as molecular assays, next-generation sequencing, and advanced imaging techniques have improved detection rates. Nevertheless, conventional culture-based methods remain insensitive, and delays in diagnosis are still a major barrier to successful outcomes **(3).**

The COVID-19 pandemic further underscored the global burden of IFIs, with COVID-19–associated pulmonary aspergillosis (CAPA) and mucormycosis increasingly reported in critically ill patients. These superinfections were associated with poor prognosis, particularly in individuals with diabetes or those receiving corticosteroids **(4).**

Management strategies for IFIs rely on early initiation of antifungal therapy, surgical intervention when required, and strict antifungal stewardship. Although novel antifungals such as newer triazoles and echinocandins have expanded therapeutic options, early recognition and multidisciplinary care remain essential to reducing mortality **(5).**

Fungal Infection:

Numerous fungal species exist globally, with nearly 500 species known to infect humans. Fungi are existed in the environment or may be part of the normal flora in humans and animals. In humans, fungal infections are of varied severity including mild, severe and life threatening invasive diseases especially in immunocompromised patients **(6)**.

Classification of fungal infection:

Generally fungal infections are classified according to the site of infection, such as superficial, cutaneous/mucosal, subcutaneous and invasive. Invasive fungal infections (IFI) occur when fungi are isolated from blood, other sterile sites and tissue showing invasion into specific organs. Characteristically, IFI are serious, deep sited, disseminated and commonly systemic. Following an episode of fungal infection, factors such as fungal pathogenicity, host immune response and site of infection are major contributing factors that affect the outcome of the episode **(7)**.

How invasive diseases occur?

To cause an invasive disease in humans, fungi must meet four criteria:

- The ability to grow at or above mammalian body temperature.
- The ability to reach internal tissues by penetrating or evading host barriers.
- The ability to lyse tissues and absorb their components.
- The ability to evade host immune defenses.

Humans are naturally resistant to most invasive fungal diseases (IFD). As such, most cases of invasive disease occur in patients with an underlying serious illness or condition. Moreover, advances in medical care and life-saving treatments, which may lead to an impaired immune function, have increased the number of susceptible patients or people at-risk for fungal infections **(8).**

Invasive fungal diseases:

According to standard criteria, an invasive or systemic fungal disease is proven when tissue damage due to fungal elements is observed by histopathologic examination and/or when the aetiologic agent is isolated by culture from clinical sterile samples such as blood, tissue or cerebrospinal fluid **(9)**.

Infection can be initiated by invasion of fungal microbiota into the mucosa, by the inhalation of fungal spores from the environment or by direct inoculation, which lead to colonization and dissemination. As clinical manifestations of IFD are not specific and the severity of the disease depends on the host's defenses and immune response, a high degree of suspicion is needed for the early diagnosis and optimal management of these infections **(10)**.

IFD are an emerging problem worldwide, are generally very difficult to cure and the associated mortality remains very high depending on the pathogen and patient population. Recent studies have estimated that globally, fungal infections kill more than 1.5 million people per year, which is similar to the mortality due to tuberculosis and about three-times more than malaria **(11)**.

Fungal pathogens:

In the late 2022, the World Health Organization, in response to the rising threat of invasive fungal diseases, released a first fungal priority pathogens list the (WHO FPPL). They're all microscopic fungi, some of which have the potential to kill. The priority list breaks down 19 of the most common fungal pathogens into three priority tiers based upon surveys and discussions with fungal infectious disease experts. The most dangerous is the "critical group," which contains just four fungal pathogens: Cryptococcus neoformans, Aspergillus fumigatus, Candida albicans and Candida auris **(12, 13).**

Risk factors:

1- Medical interventions:

- The placement of central venous catheters and intravascular or intracranial devices plus the use of broad-spectrum antibiotics, which are associated with medical interventions, are responsible for the vast majority

of IFD acquired in hospital settings. Candidemia, the most frequent life- threatening mycosis in the world, appears among the most common causes of health care-associated blood stream infections (BSI), with about 80% of cases occurring in the absence of evident immunosuppression but rather among patients with common iatrogenic and/or nosocomial conditions that is associated with prolonged stays in hospital and intensive care units **(14).**

- Medical devices disrupt the normal skin barriers and provide direct access for the commensal yeasts of the genus Candida to the body's interior. In addition, it has been long recognized that antibiotics suppress the growth of normal bacterial microbiota, which favors the proliferation of Candida species (spp.), thus leading to colonization and an increased risk of disseminated candidiasis **(15)**.

- Candida albicans and other Candida species also have the ability to form biofilms on indwelling venous and bladder catheters, heart valves, joint replacements and even on different tissues in the host. Biofilms are a physical barrier intrinsically resistant to the host immune system **(16)**.

2- Treatment-induced immunosuppression:

- **Chemotherapy:**

Hematological malignancies, mainly acute leukemia, account for most cases of IFD among patients immunosuppressed in the classical sense. Prolonged severe neutropenia, resulting from intense chemotherapy regimens and defined as more than 10 days with a peripheral blood absolute neutrophil count less than 500/μL, is still the single major risk factor for invasive infection caused by the environmental mold Aspergillus fumigates (> 80% of cases) and other species of Aspergillus **(17)**.

Mechanism:

Neutrophils are known to be the primary host defense mechanism against Aspergillus infection, which commonly starts by the inhalation into and establishment of fungal spores in the lower respiratory tract. When mucosal barriers have been injured, neutrophils function in the innate immune response through the killing of conidia and hyphae by both oxidative and nonoxidative mechanisms. In neutropenic patients, therefore, neutrophil dysfunction represents an impairment to efficiently recruit and kill Aspergillus infectious elements **(18)**.

- **Immunosuppressive drugs:**

Thousands of solid organ transplant (SOT) recipients in the world are at risk of IFD as a result of organ damage, neutropenia, administration of immunosuppressive drugs and surgical factors such as prolonged operation time, increased technical complexity and bleeding complications. In these patients, Candida spp., Aspergillus fumigatus are reported as the most common fungal pathogens causing invasive disease **(19)**.

Mechanism:

Cytopaenia and administration of therapies to prevent and treat graft- versus-host disease (GvHD), which leads to an impaired cell immunity, are major risk factors of haematopoietic stem cell transplant (HSCT) recipients for acquiring IFD **(20)**.

Due to induced neutropenia and lack of adequate immune reconstitution, invasive aspergillosis has been noted to be the most commonly observed IFD in HSCT recipients, followed by invasive candidiasis, Pneumocystis pneumonia, mucormycosis (caused by Mucormycetes). Gastrointestinal tract mucositis, defined as the disruption of the gastrointestinal tract mucosa, together with the presence of venous catheters in patients who require transfusion support, allow for gut and skin microbiota, including Candida spp., to invade and cause BSI **(21)**.

3-Disease-induced immunosuppression:

- **Human immunodeficiency virus (HIV):**

Defects in cell-mediated immunity, mainly a decrease in the number and function of CD4+ lymphocytes, which occurs in people infected with the human immunodeficiency virus (HIV), is the major risk factor for Pneumocystis pneumonia. Among people living with HIV, Pneumocystis jirovecii persists as the most common cause of serious and often fatal respiratory infection that continues to be a life-threatening defining illness in patients with acquired immunodeficiency syndrome (AIDS). Yearly, more than 400,000 cases of Pneumocystis pneumonia are estimated to occur worldwide, with mortality rates ranging from 10-60% or higher, depending on the patient population, comorbidities and time for diagnosis. Unlike other fungal species affecting humans, evidence suggests that Pneumocystis jirovecii colonises the respiratory tract of asymptomatic individuals and that person-to-person transmission is the most likely mode of infection, which is of clinical significance as colonised individuals may be at risk of development pneumonia or may transmit Pneumocystis to others **(22)**.

- **Uncontrolled diabetes mellitus:**

Diabetic patients and particularly patients having ketoacidosis, is the major predisposing factor for developing mucormycosis, which is the third most common angioinvasive fungal infection following candidiasis and aspergillosis. Mucormycetes species are vasotropic and cause tissue infarctions. Among them, Rhizopus oryzae is the most frequently recovered species in patients with mucormycosis (~ 70%). After inhalation of spores from environmental sources, immunocompromised hosts can develop upper and lower respiratory diseases, which if left untreated, can subsequently spread to the CNS causing rhinocerebral mucormycosis. In people with diabetes, monocytes and macrophages are dysfunctional and fail to phagocyte and kill the Mucormycetes spores, allowing their germination and subsequent proliferation as hyphal elements, which leads to rapid invasion of deeper tissues and dissemination. Despite several simultaneous approaches used for treatment, such as aggressive debridement or amputation, antifungal therapy and medical management or correction of the underlying condition, mucormycosis associated mortality rates continue to be very high, reaching almost 100% among patients with disseminated diseases **(23)**.

- **Chronic obstructive pulmonary disease (COPD):**

COPD represents an important, nonclassical underlying condition for the increasing number of acute invasive pulmonary aspergillosis, with a very high mortality rate. Associated with the pulmonary disease, structural modifications in the lung architecture that favour lung parenchyma invasion and necrosis due to Aspergillus species, in addition to prolonged use of immunosuppressive treatment, such as corticosteroid therapy, might increase the susceptibility of COPD patients to acquire an IFD. Furthermore, recurrent hospitalisation, invasive procedures, broad- spectrum antibiotic use and other factors such as tobacco smoke, alcoholism, diabetes mellitus and/or malnutrition could contribute to promote invasive aspergillosis in COPD patients**(24)**.

4-Bacterial and viral co-infections:

- **Tuberculosis:**

Fungal pulmonary infections can be acquired primarily or secondarily during tuberculosis infection. Co-morbidities such as immunodeficiency, mainly due to HIV, chronic illnesses and malignancy, together with inherent factors of the community like poverty and malnutrition, worsen the co-infection and the prognosis of patients **(25).**

- **COVID-19:**

A dysfunctional immune response, which can cause severe alveolar lung damage and even systemic pathology, has been reported to occur rarely in people with coronavirus disease 2019 (COVID-19), a viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first

reported in Wuhan, China, at the end of 2019. While unusual, this harmful interaction of SARS-CoV-2 with the immune system of patients with severe COVID-19 pneumonia seems to increase the susceptibility of these patients to acquire secondary infections, including certain mycoses **(26)**.

Although the incidence of IFD associated with COVID-19 is still unknown, Aspergillus infections have been, so far, the most commonly reported fungal co-infections in COVID-19 patients. Invasive aspergillosis, however, has been associated with admission to critical care because of COVID-19 pneumonia and severe acute respiratory syndrome. In addition, most co-infected patients were found to have previous history of underlying immunocompromised status or pre-existing comorbidities, mainly hypertension, diabetes, obesity and hematological malignancies. Much less frequently, candidiasis has been also reported as co-infection in hospitalised patients with COVID-19. **(27)**.

Diagnostic evaluation:

The safe and early diagnosis of invasive fungal infections is the central challenge in routine clinical practice and forms the crucial basis for targeted treatment **(28)**.

The diagnosis of an invasive fungal infection is based on three elements:

- Clinical examination.
- Imaging.
- Confirmation/proof of the causative agent.

The clinical diagnostic criteria for invasive fungal infections were defined by an international working group, the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG Study Group). These criteria selectively apply to immunosuppressed patients and were conceived primarily for clinical studies **(29).**

The relevant clinical risk factors include:

- Prolonged (>10 days) deep granulocytopenia (<0.55 × 109/L).
- Allogeneic stem cell transplantation.
- Medication-induced immunosuppression, or treatment with prednisone (the equivalent of at least 0.3 mg/kg/d for a minimum of 3 weeks).

This list is by no means complete and excludes important but less well defined risk groups. Examples include patients in intensive care wards, patients with structural lung disease, patients with severe influenza and other risk factors that were discussed before **(30).**

Indeed, tomography imaging yields crucial clues. Infections of the respiratory tract require computed tomography (CT), neurological infections require magnetic resonance imaging (MRI), and abdominal infections require CT or MRI scanning in order to identify abscesses that are characteristic for the special variety of hepatolienal candidiasis. Moreover, abdominal infections can also be visualized by using sonography.

Confirmation of the pathogen, Blood stream infections with Candida spp. are almost exclusively confirmed by blood cultures. The identification of Candida in specimens taken from the respiratory tract does not indicate an invasive infection; for other, non-sterile specimens, a decision always has to be made on the basis of the individual clinical situation as to whether it is a case of colonization or a clinically relevant situation. Because of their wide environmental spread, the confirmation of molds from physiologically non-sterile material should be interpreted with caution; this is also the case for all specimens from the respiratory tract **(31)**.

Serological diagnostic evaluation, Candida antigen/antibody confirmation is not recommended in current guidelines because of the lack of pertinent studies. Beta D-glucan (BDG) is not specific for Candida, but

it does indicate an invasive fungal infection. A patient's risk profile, symptoms, and imaging results will narrow down this differential diagnosis, however. The sensitivity and specificity of this marker vary substantially between different patient populations and depend on the test system used **(32)**.

To confirm Aspergillus fumigatus, galactomannan ("aspergillus antigen") is available in addition to BDG which can be determined from serum and bronchial secretions (and, if applicable, cerebrospinal fluid). The sensitivity for serum is about 78%, the specificity is 85%, depending on the cut-off value and the patient population. To confirm invasive aspergillosis, furthermore, reference protocols for molecular diagnostics have been developed that function as examples for molecular diagnostic evaluation of infections and, in combination with other methods, contribute to improved diagnostics **(33)**.

Treatment:

Depending on the indication, a choice needs to be made between:

-Prophylactic treatment

-Empirical treatment

-Pre-emptive treatment.

- **Antimycotic prophylaxis** is recommended primarily for hematology/oncology patients **(34**).

After allogeneic stem cell transplantation, prophylaxis against yeasts is usually sufficient. By contrast, a high-risk constellation such as granulocytopenia after myelosuppressive induction therapy or graft-versus-host disease requires prophylaxis that is effective against molds. Data for other patient populations are a less clear-cut. For patients with complications after abdominal surgery, for patients requiring intensive care and who have relevant risk factors, and for patients who have undergone lung transplantation surgery, prophylaxis can make sense **(35)**.

- **Empirical therapy** is used if an invasive fungal infection is suspected.

1- Invasive Candida infection:

The therapeutic schemes depend on the underlying disease and organ involvement. In most clinical situations, echinocandins are the treatment of choice in adult patients **(35).**

Fluconazole is, however, still relevant for oral treatment continuation after successful initial treatment with an echinocandin. Liposomal Amphotericin B (L-AmB) constitutes an alternative where resistance to other classes of substances is confirmed. Furthermore, L-AmB is important in treating chronically disseminated candidosis/candidiasis, endocarditis due to Candida, and in pediatric patients. Voriconazole usually does not provide any additional benefits over fluconazole with the exception of infection with C. krusei or where additionally a mold infection is suspected **(36)**.

Candidemia should be treated for at least two weeks after the blood stream infection has disappeared. The exact treatment duration can be defined only after follow-up blood cultures have been produced. In continuing symptoms or granulocytopenia, the treatment should be continued for a longer time. Chronically disseminated candidosis should be treated for a minimum of 8–12 weeks, and in some cases for several months, until the lesions have resolved. Central venous catheters should be removed as soon as possible if they are deemed the source of infection and can be safely removed. If this is not possible then the patient should be treated with an echinocandin or L-AmB, because of their effectiveness against biofilms in vitro. Because of possible relocation of the pathogen into the eyes, funduscopy is recommended during intravenous therapy **(37)**.

2- Invasive aspergillosis:

The prognosis for invasive aspergillosis has improved substantially over the past decade. The treatment of choice usually consists of the administration of voriconazole or isavuconazole. Both azoles are effective

fungicides against A. fumigatus. In addition, Voriconazole reaches effective concentrations even for neurological infections **(38)**.

L-AmB is an alternative treatment after taking into consideration prior prophylactic administration of azoles, comorbidities, resistance of the pathogen, medication interactions, and local epidemiology. L-AmB is also recommended for initial therapy if co-infection with Mucorales is suspected. The value of combination therapy (for example, using voriconazole plus echinocandin) is unclear. In addition to systemic administration, local instillation of L-AmB may make sense, for example in aspergillosis of the central nervous system. In all cases, surgical treatment should be considered in addition to medication treatment. Supportive measures include the administration of granulocyte colony stimulating factor (G-CSF) or, in long-term granulocytopenia, granulocyte transfusions **(39)**.

The duration of treatment depends on the patient's individual clinical development while taking into account the type and extent of immunosuppression; it usually takes about 6–12 weeks**(40).**

3- Rare invasive mycoses:

No randomized controlled trials exist of the treatment of invasive mycoses caused by rare pathogens. Therapy is guided by the broad spectrum effectiveness of the antimycotics and by case series. Mycormycoses are caused by a large group of different pathogens with different sensitivity/susceptibility profiles. To treat these, L-AmB (at a minimum dosage of 5 mg/kg; 10 mg/kg if the central nervous system is affected) and azoles with effectiveness against Mucorales are the medications of choice. The surgical resection of infected tissue is an essential component of the therapeutic concept **(41)**.

References:

1. Lamoth F, Kontoyiannis DP. The spectrum of fungal infections in hematopoietic cell transplant and solid organ transplant recipients: Challenges, trends, and new opportunities. Curr Opin Infect Dis 2022;35:415–25.
2. Hoenigl M, Salmanton-García J, Walsh TJ, Nucci M, Neoh CF, Jenks JD, et al. Global guideline for the diagnosis and management of rare mold infections: An initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. Lancet Infect Dis 2021;21:e246–57.
3. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: 2021 update by the European Society for Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect 2021;27:S91–106.
4. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15:102146.
5. Thompson GR, Cornely OA, Pappas PG, Patterson TF, Hoenigl M, Jenks JD, et al. Invasive aspergillosis as an under-recognized superinfection in COVID-19: A multicenter, retrospective cohort study. Lancet Microbe 2021;2:e534–44.
6. Spellberg B. Vaccines for invasive fungal infections. F1000 Medicine Reports. 2011; 3:13.
7. Kaushik N, Pujalte GG, Reese ST. Superficial fungal infections. Primary Care. 2015 Dec;42(4):501-16.
8. Kohler JR, Hube B, Puccia R, Casadevall A, Perfect JR. Fungi that infect humans. Microbiology Spectrum. 2017 Jun;5(3):10.
9. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clinical Infectios Disease. 2020 Sep 12;71(6):1367–1376.
10. Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections diagnosis & clinical management. Indian Journal of Medicine and Research. 2014 Feb;139(2):195–204.

11. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. Journal of Fungi. 2017 Oct 18;3(4):57.
12. Fisher MC, Denning DW. The WHO fungal priority pathogens list as a game- changer. Natural Review of Microbiology. 2023 Apr;21(4):211-212.
13. Chen S, Chakrabarti A, Cornely O, Meis J, Perfect J. Informing the World Health Organization Fungal Priority Pathogens List (WHO-FPPL): A collection of systematic reviews. Medical Mycology. 2024 Jun 27;62(6):046.
14. Holmes CL, Albin OR, Mobley HLT, Bachman MA. Bloodstream infections: mechanisms of pathogenesis and opportunities for intervention. Nature Reviews. Microbiology. 2025 Apr;23(4):210-224.
15. McCarty TP, Pappas PG. Invasive candidiasis. Infectious Disease Clinics of North America. 2016;30(1):103–124.
16. Cavalheiro M, Teixeira MC. Candida biofilms: threats, challenges, and promising strategies. Frontiers in Medicine. 2018 Feb 13; 5:28.
17. Abers MS, Ghebremichael MS, Timmons AK, Warren HS, Poznansky MC, Vyas JM. A critical reappraisal of prolonged neutropenia as a risk factor for invasive pulmonary aspergillosis. Open Forum Infectious Diseases. 2016 Feb 12;3(1): 036.
18. Shopova IA, Belyaev I, Dasari P, Jahreis S, Stroe MC, Cseresnyes Z. Human neutrophils produce antifungal extracellular vesicles against. Aspergillus fumigatus. mBio. 2020;11(2):00596–00520.
19. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transplant Infectious Disease. 2010;12(3):220–229.
20. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clinical Infectious Disease. 2010;50(8):1091–1100.
21. Neofytos D. Antimicrobial prophylaxis and preemptive approaches for the prevention of infections in the stem cell transplant recipient, with analogies to the hematologic malignancy patient. Infectious Disease Clinics of North America. 2019;33(2):361–380.
22. Krajicek BJ, Thomas CF, Jr, Limper AH. Pneumocystis pneumonia: current concepts in pathogenesis, diagnosis, and treatment. Clinical Chest Medicine. 2009;30(2):265–278.
23. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clinical Infection Disease. 2012;54(1):23–34.
24. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis a clinical review. Europian Respiratory Review. 2011;20(121):156–174.
25. Amiri MRJ, Siami R, Khaledi A. Tuberculosis status and coinfection of pulmonary fungal infections in patients referred to reference laboratory of Health Centers Ghaemshahr City during 2007-2017. Ethiopian Journal of Health Science. 2018 Nov ;28(6):683–690.
26. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19 immunity, inflammation and intervention. Natural Review of Immunology. 2020;20(6):363–374.
27. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19 We should be prepared. Journal de Mycologie Medicale. 2020 Jun;30(2): 100971–100971.
28. Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC et al. European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clinical Microbiology and Infection. 2014 Apr;20(3):47-75.
29. Bassetti M, Azoulay E, Kullberg B, Ruhnke M, Shoham S, Vazquez J et al. EORTC/MSGERC Definitions of Invasive Fungal Diseases: Summary of Activities of the Intensive Care Unit Working Group. Clinical Infectious Diseases.2021 Mar 12;72(2):121-127

30. Mohedano Del Pozo RB, Rubio Alonso M, Cuetara Garcia MS. Diagnosis of invasive fungal disease in hospitalized patients with chronic obstructive pulmonary disease. Revista Iberoamericana de Micologia. 2018 Sep; 35(3):117–122
31. Meersseman W, Lagrou K, Spriet I, Maertens J, Verbeken E, Peetermans WE, et al. Significance of the isolation of Candida species from airway samples in critically ill patients: a prospective, autopsy study. Intensive Care Med. 2009; 35:1526–1531.
32. Friedrich R, Rappold E, Bogdan C, Held J. Comparative analysis of the wako beta- glucan test and the fungitell assay for diagnosis of candidemia and pneumocystis jirovecii pneumonia. Journal of Clinical Microbiology. 2018 Aug 27;56(9):00464-18.
33. Barnes RA, White PL, Morton CO, Rogers TR, Cruciani M, Loeffler J et al. Diagnosis of aspergillosis by PCR: Clinical considerations and technical tips. Medical Mycology. 2018 Apr 1;56(1):60-72.
34. Mellinghoff SC, Panse J, Alakel N, Behre G, Buchheidt D, Christopeit M, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). Annals of Hematology. 2018 feb; 97(2):197–207.
35. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID Fungal Infection Study Group. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clinical Microbiology and Infection. 2012 Dec;18 (70):19-37.
36. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clinical of Microbiology and Infection. 2012;18(7):38–52
37. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Infection Disease. 2016 Jun; 62:1–50.
38. Maertens JA, Raad, II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016; 387:760–769.
39. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clinical Infection Disease. 2016; 63:1–60.
40. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM- ERS guideline. Clinical Microbiology Infection. 2018; 24(1):1–38.
41. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clinical Microbiology and Infection. 2014 Apr;20 (3):5-26.