Review Article

Invasive fungal infections in hematologic malignancies: Incidence, management, and antifungal therapy

Fatemeh Shafiee[1], Rasool Soltani[2,3], Mohsen Meidani[4]

[1]Department of Pharmaceutical Biotechnology, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of Infectious Diseases, Imam Khomeini Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

The incidence of invasive fungal infections (IFIs) has increased in recent years as a result of increasing the incidence of hematologic malignancies (HMs). IFIs, as the opportunistic diseases, are the most important concern in these patients with a high mortality rate. These infections are one of the leading causes of morbidity and mortality in HM patients and an important factor in increasing the costs of patients' management because of the prolonged hospitalization and the inevitable need to use antifungal agents. Due to the changes in the pattern of organisms causing IFIs, unavailability of effective and safe antifungal drugs, and high rate of drug resistance as well as lack of fast and accurate diagnostic methods, these infections have become a serious and life-threatening problem necessitating effective prevention and treatment strategies using suitable antifungal agents, especially in high-risk patients. The aim of the present study was to review the pathogens causing various types of IFIs, diagnostic methods, and novel prophylactic and therapeutic antifungal regimens in HM patients according to the new published studies and clinical trials.

Key words: Antifungal, fungal infection, hematologic malignancy, neutropenic fever, treatment

How to cite this article: Shafiee F, Soltani R, Meidani M. Invasive fungal infections in hematologic malignancies: Incidence, management, and antifungal therapy. J Res Med Sci 2023;28:73.

INTRODUCTION

There are many types of hematologic malignancies (HMs), each with its own control and management methods. However, conventional chemotherapeutic agents and novel therapeutic strategies such as hematopoietic stem cell transplantation (HSCT) are the most common treatments for a variety of these disorders,[1] leading to improvement of the patient outcome.[2] Unfortunately, different infections including viral, bacterial, and fungal infections can make the health status of these patients more complicated. Fungal infections are the fourth most important health-related issue in the world and millions of people experience these life-threatening infections around the world.[3] Invasive fungal infections (IFIs) are among the most serious conditions in HM patients and one of the leading causes of morbidity and mortality in them.[4] In addition, IFIs are an important factor in increasing the cost of controlling and management of HMs.[5] In the last 20 years, the treatment of fungal infections has evolved substantially leading to the reduction of morbidity and mortality due to IFIs if the treatment is properly provided.[6] However, the number of people at high risk for IFIs has also increased substantially along with the elevated cost of treatment resulting from the longer duration of hospitalization and the resistance to routine antifungal drugs among causative pathogens.[7-10] In the US, for example, the hospitalization costs due to the invasive candidiasis and

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_1072_21

Address for correspondence: Dr. Mohsen Meidani, Department of Infectious Diseases, Imam Khomeini Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Blv. Keshavarz, Tehran, Iran.
E-mail: mohsenmeidani53@gmail.com
Submitted: 11-Dec-2021; **Revised:** 25-Jun-2023; **Accepted:** 17-Jul-2023; **Published:** 29-Sep-2023

aspergillosis, as the two most important IFIs, have been estimated about 218 and 630 million dollars, respectively.[6] Therefore, timely diagnosis and effective prophylactic and therapeutic measures are mandatory.

The interactions of antifungal agents with chemotherapeutic and immunosuppressive drugs are another concern in the treatment of these infections.[11] Finally, another challenge of IFIs is their difficult diagnosis due to the lack of specific signs and symptoms.[12] For this reason, it is recommended to start treatment following prolonged fever (more than 5 days) using effective and safe antifungal drugs in all hospitals around the world, although prevention is a more rational measure for patients at high risk of IFIs. This review focuses on the recent information about the epidemiology and etiology of IFIs in HM patients as well as their management with new therapeutic protocols based on the recent clinical trials.

EPIDEMIOLOGY

The prevalence of IFIs has increased along with the increase in the number of chemotherapeutic agents against HMs and their success.[13] IFIs incidence and their mortality rate varies in different patients and geographical areas.[14,15] Italy has published the most papers related to the IFIs epidemiology and etiology, while these data are lacking in Iran. The mortality rate of IFIs was reported 20% in Fracchiolla *et al*.'s study as a single-center study in Italy.[13] Although the epidemiological data of IFIs in Iran is limited, the mortality rate of IFIs resulted from *Aspergillus* spp. and *Candida* spp. is estimated to be 30%–80%.[16] The prevalence of IFIs was reported as 5.9% in HMs in Taiwan.[17] In 2008, among a total of 4393 cases with HM in Iran, only 24 cases experienced invasive aspergillosis (IA), while this rate has been estimated 50% in countries such as Australia and France.[18,19] The mortality rate for invasive candidiasis was reported as 50% in the USA.[20] The rate for aspergillosis was in the range of 40%–90% in Taiwan.[21] However, the mortality rate of IA in patients undergoing allogenic HSCT is higher with estimation of 95%.[22] For pediatric patients, on the other hand, IFI rate has been reported in 8%–17% of HM patients in Australia.[16,23] Acute myeloid leukemia (AML) in adults has been the most probable hematological malignancy predisposing to IFIs. For example, in a study in Italy, of 538 patients with IFI, 373 patients (69%) had AML.[24] However, in pediatric patients, ALL is the most frequent HM related to the IFIs; this could be due to the higher prevalence of ALL than other hematological malignancies in the pediatric population. The prevalence range of IA is 5%–10% in AML, with mortality rate being 20%–50% that which could increase to 80% in HSCT patients.[25] In another study, the prevalence of IFIs in leukemia was about 24%, with the rate being 10%–20% in patients undergoing allogeneic HSCT. The reported mortality rate in these patients was 30%–80%.[26] Finally, the IFI-related mortality rate in pediatric patients with HMs in Greece was 20%–70%, depending on the intensity of immune suppression, the presence of accompanying factors, intensity severity and site of infection, time of diagnosis, underlying diseases, and the time of treatment initiation.[27]

ETIOLOGY

In recent years, molds, especially *Aspergillus* spp. and yeasts, especially *Candida* spp., have been the most prevalent IFIs causative pathogens in patients with various types of hematological malignancies.[1] However, due to the increasing use of effective antifungal drugs against *Candida* species and suitable prophylaxis, the prevalence rate of IFIs caused by yeasts has decreased significantly.[24] For example, in a 20-year retrospective study conducted by Lewis *et al*. in the US, it was shown that the rate of IFIs decreased in the last 5 years. In the mentioned study, *Aspergillus* spp. were the most prevalent pathogens causing IFIs; however, its general rate decreased over time.[28] *Candida* infection, as the second most common IFI reported in the study, also declined over time. Similar results have been reported in a study on Brazilian HM patients, so that the reported frequency of *Candida*-induced infections was lower than that of *Fusarium* and *Aspergillus*.[29] Other fungal pathogens such as *Fusarium* spp., and Mucorales play a less important role in IFIs.[14,30] In the study of Lewis *et al*., the IFIs caused by *Fusarium* spp. were 10–50 times lower than *Aspergillus* spp. infections. In addition, Mucorales-induced infections had the least prevalence, though with a threefold increase over the time.[28] In another study published in 2006, it was shown that *Aspergillus* spp., especially *Aspergillus fumigatus*, were responsible for about 65% of IFIs in HM patients in Italy. *Aspergillus flavus* infections also increased by 2.6 times during the study period. Zygomycetes and *Fusarium* spp. have been reported to be responsible for 0.5% of IFIs. Of note, the various results from published studies indicate differences in the causative pathogens based on the geographical area. For example, in the study of Montagna *et al*. in Italy, the prevalence of IFIs resulted from *Candida* spp., especially *Candida albicans*, was more than that from other pathogens.[12] In Fracchiolla *et al*.'s study, about 69% of IFIs were attributed to *Candida* species;[13] however, the non-albicans Candida species such as *Candida glabrata*, *Candida guilliermondii*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei* showed a rising rate. In general, it seems that *Aspergillus spp.* and *Candida spp.* account for more than 95% of IFIs.[31] Finally, non-*Candida* yeasts, including *Trichosporon* spp., *Rhodotorula* spp., and *Saccharomyces* spp., cause IFIs in 4%–10% of cases.[28] *Cryptococcus neoformans* had the lowest probability to cause IFIs according to the Lewis *et al*.'s study.[28] The final study in this regard introduced Mucorales

as the third leading cause of IFIs after Aspergillosis and Candidiasis, especially in patients with metabolic acidosis or phagocytosis abnormalities.[32] According to a recent study in Iran (2018), the prevalence of mucormycosis in Iranian HM patients was estimated as 9.2 per 100,000 of population.[6] Furthermore, according to a study in 2008, the most prevalent HM developing IFI was AML, with IA being the most common infection.[33]

RISK FACTORS

Overall, all HM patients are at the risk of IFIs, but patients with AML and those who have undergone allogeneic HSCT are at the greatest risk for manifestation with IFIs.[34] Risk factors vary from person to person.[1] Neutropenia, relapse/refractory disease, pervious history of IFIs, and receiving high doses of corticosteroids are among the most important risk factors for IFIs.[34] A number of variables can alter the risk of IFI in patients with HM. For example, the severity and duration of neutropenia directly increase the risk of IFIs.[35-37] In general, neutropenia (<100/μL) lasting for more than 10 days is considered as prolonged neutropenia and is a serious risk for IFIs. Overuse of broad-spectrum antibiotics, on the other hand, may alter the gut normal flora and cause colonization of opportunistic fungi.[38] Furthermore, long-term use of antifungal agents (e.g., fluconazole) as prophylaxis can lead to an increase in the incidence of resistant pathogens.[39] In general, every condition leading to the suppression of immune system (e.g., immunosuppressive drugs such as alemtuzumab and antithymocyte globulin, immunosuppressive viruses such as HIV or cytomegalovirus, or myeloablation) can result in increase of IFIs.[40,41] Using immunosuppressive agents and systemic corticosteroids increases the risk of IA.[27] Old age (above 65 years), progression to higher stages of HM, and hematopoietic transplantation from mismatched donor can increase the risk of IFIs.[35,42] Some other factors related to the lifestyle and environmental factors are responsible for the prevalence of IFIs. For example, the incidence of fungal infections is higher in people who live in rural areas and in smokers.[43] Furthermore, some underlying conditions can contribute to the higher risk of IFIs in HM patients. For example, elevated serum iron levels, diabetes mellitus, prior respiratory disorders, hypoalbuminemia, and infections with influenza and parainfluenza increase the risk of IFIs in patients with HM.[34] In 2017, Rambaldi *et al*. listed various risk factors of IFIs in HM patients as a "letter to editor" that readers can refer to it for more information.[34] The detailed information about the risk factors for IFIs is shown in Table 1.

Table 1: The most important risk factors for invasive fungal infections in patients with hematologic malignancies (with the risk above 5%)

Risk factor	Underlying HM
Age (above 65 years)	HSCT, AML, ALL
Pervious history of IFI	HSCT, AML
Diabetes mellitus	HSCT
Mucositis	HSCT
CMV infection	HSCT
Smoking	HSCT
Recurrent candidiasis	HSCT, AML
Prior respiratory diseases	HSCT, AML
Neutropenia	HSCT, AML, ALL
Hypoalbuminemia	HSCT

IFI=Invasive fungal infection; HSCT=Hematopoietic stem cell transplantation; AML=Acute myeloid leukemia; ALL=Acute lymphoblastic leukemia; HM=Hematologic malignancy; CMV=Cytomegalovirus

DIAGNOSIS

Rapid diagnosis of the causative organisms is very important for decision on the type and duration of treatment, the necessity of surgery, monitoring, and prophylaxis of patients.[44] IFIs do not have specific signs or symptoms[45] and this can make it harder to diagnose the infection, a challenge that delays rational treatment.[46] To ensure diagnosis, it is best to use both histological exam and culture of biopsy or sterile body samples.[44] However, according to the most researchers, these tests cannot be used in the early stages of the disease due to the nonspecific symptoms. Furthermore, if the patient has a prolonged neutropenia, he/she should start taking antifungals based on the clinical evidence such as persistent fever and pulmonary signs and symptoms.[44] In addition to the similarity of the symptoms of fungal infections to bacterial ones, the symptoms and signs of different types of IFIs can be alike.[44] Pulmonary aspergillosis may present as cough, hemoptysis, and pleuritic chest pain. Necrotic lesion in combination to the prolonged neutropenia is a sign of mold infections.[44] In general, diagnostic methods for IFIs in HM patients are based on various procedures including culture methods, fungal antigens detection, specific antibodies detection, imaging, and histological tests.[44] In microscopic assays, hyphae can be visualized using special fungal dyes such as acid-Schiff, Grocott's methenamine silver, Calcofluor white, and hematoxylin and eosin[16,44] or using their morphological features including diameter, presence of septa, or their ramification pattern.[44] Culture-based techniques for at least 20 days in 25°C–35°C are the gold standard methods for IFIs diagnosis.[16] However, especially for molds in comparison to the yeast, the isolation from the biological samples is difficult. Furthermore, the blood culture shows negative result in the case of mold infections and for patients with liver or spleen involvement.[44] Another challenge for culture-based methods is its time-consuming nature as well as low sensitivity.[47] Furthermore, there is a need to repeat the experiment several times to increase its sensitivity.[48] Finally, for some fungal

species (e.g., Zygomycetes), it is possible for the fungi to die during the sample preparation before the culture.[49]

Diagnosis by detection of the specific antigens or antibodies is another test which can be used for all fungal species including *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans*. ELISA for detection of galactomannan antigen can be used for the diagnosis of *Aspergillus* spp. Beta D-glucan detection is used for the diagnosis of *Candida*, *Aspergillus*, *Fusarium*, *Acromoniyum*, and *Pneumocystis jirovecii*[50] but not for Cryptococcus or Zygomycet infections.[51] Of note, it is better to combine antibody detection tests with antigen detection to increase the reliability of the results. However, antibody detection tests cannot be used for *Aspergillus* spp.[44]

Furthermore, magnetic resonance imaging, computed tomography (CT), and high-resolution CT are good imaging procedures helping for diagnosis of IFIs, but not usually for the early stages of the involvement.[44] On the other hands, endoscopic procedures, especially bronchoscopy and nasal endoscopy are complementary methods for accurate diagnosis.[52]

Organ biopsies of suspicious areas or autopsies are other valuable methods for determining the causative fungal pathogens.[44] It is recommended that biopsy samples be investigated using culture methods with staining and pathological surveys.[53,54]

Various types of polymerase chain reaction (PCR) methods, both qualitative and quantitative types, such as nested PCR, real-time PCR, etc., are novel methods used for identification of the specific genes of each fungal genus or species. These tests are more affordable, more repeatable, and faster than culture-based methods.[55] 28S rRNA, as a taxonomic marker, has been used for diagnosis of IFIs via PCR methods.[44] In a recent study conducted by Sheikhbahaei *et al*., it was shown that fungal culture established only 17% of samples as positive, while all of the surveyed samples (with clinical presentation related to IFIs) showed positive results when analyzed using reverse transcription-PCR.[56]

Recently, the use of combination of different tests has been recommended in order to increase the reliability of diagnostic methods.[57] For example, concomitant usage of several antigen detection methods (galactomannan and beta-D-glucan) has been suggested.[58] In several studies, galactomannan detection in combination with the PCR method increased the sensitivity of diagnosis of IA compared to when each experiment was used alone.[59-61]

Generally, serologic and molecular methods are powerful diagnostic tools for IFIs.[16]

PREVENTION AND PROPHYLAXIS

Almost all HM patients are in the highest risk of IFIs; therefore, these people should take preventive measures to reduce the risk of infection. Reducing exposure to fungal spores, especially in village areas and in spring season is a key step in these people. Furthermore, hand washing for the patient and medical staff is an important preventative action against fungal infections.[62]

Prevention is a logical step for high-risk patients.[15] Use of prophylactic antifungal agents during immunosuppressive therapy can reduce the rate of IFIs.[63,64] Timing is an important issue in the antifungal prophylaxis.[27] The best condition for prophylaxis is to start antifungal prophylaxis when neutropenia occurs and at the start of chemotherapy.[15] Of note, prophylaxis should be discontinued after neutrophil count recovery to >500/μL). The optimal time for continuation of the prophylaxis is up to 3 months after HSCT.[65] If the prophylactic agent does not show enough efficacy or if drug-associated side effects occur, it should be stopped.[27] GI disorders and abnormalities in liver function tests are the most important adverse events with antifungals.[15] A prophylactic regimen must be safe, available, fairly bioavailable, usable for long term, well tolerated, and effective against various types of fungi.[66] There is no single antifungal agent to prevent all types of fungal infections; therefore, although the use of combination therapies for antifungal prophylaxis is not common, it may sometimes be necessary and prophylaxis monitoring is an important aspect in these situations.[66]

It is recommended to use fluconazole as prophylaxis for all pediatric patients with AML, allogeneic HSCT, and ALL.[67] Posaconazole, on the other hand, is recommended for HM patients more than 13 years old.[68] However, due to the high cost of this drug, it should be used in patients with high risk of IFI.[67,69,70] In one study, about 90% of AML patients underwent prophylaxis with posaconazole, while fluconazole and itraconazole were in the second and third steps of usage frequency, respectively.[13] Voriconazole is another triazole antifungal agent used for IFIs prophylaxis.[71] In one study, HM patients underwent either posaconazole or voriconazole therapy as prophylactic agent with the safety/efficacy profile of the drugs being investigated.[45] Despite receiving voriconazole, three patients developed IFIs within the 1st month of prophylaxis, while the patients who received posaconazole didn't show any IFIs. Furthermore, 11% and 7% of patients who received voriconazole and posaconazole, respectively, developed related side effects. So, it was concluded that posaconazole is safer and more effective than voriconazole as a prophylactic regimen in HM patients.[45] In a case report, on the other hand, an AML patient who received fluconazole

as prophylaxis developed IA. However, the patient was successfully treated with Amphotericin B followed by voriconazole.[72] Nevertheless, the failure rate of fluconazole as a prophylactic agent is not significant. For example, in a study, of 19 patients who received fluconazole, only two developed IFI.[56]

TREATMENT

An empiric antifungal agent is indicated in high-risk patients with prolonged (>4 days) fever, in whom no specific cause has been detected by reassessment.[73] Depending on the type of infection and the causative pathogen, the antifungal treatment is different.[74] It is difficult to compare data among clinical trials of empiric antifungal therapy in neutropenic cancer patients because of differences in several aspects including inclusion of low-risk patients, lack of blinding, and concomitant antibacterials, prior antifungal prophylaxis, use of composite end points of efficacy, and outcome criteria.[75] The antifungal spectrum, safety profile, required dose, and the cost are important factors for the regimen selection.[74]

In patients who have not been on antifungal prophylaxis (usually fluconazole), *Candida* spp. are the most common cause of IFIs. In these patients, caspofungin (or another echinocandin) is an appropriate choice.[73] In a randomized trial that compared caspofungin with liposomal amphotericin B in 1095 patients with persistent neutropenic fever, the overall efficacy and the rates of fungal infections and fever resolution were equal in both groups.[76] Of note, other echinocandins (micafungin and anidulafungin) have not been sufficiently evaluated in these patient populations; however, they can be used as alternatives to caspofungin in the shortage situations.[77] In patients receiving prophylaxis, fluconazole-resistant *Candida* spp. and invasive mold infections, especially aspergillosis, are the most likely causes. Patients with pulmonary nodules or nodular pulmonary infiltrates are more likely to have invasive mold infection. In these situations, voriconazole or a lipid formulation of amphotericin B are preferred.[77] According to the present data, it is unknown whether voriconazole or amphotericin B is optimal. In an open-label randomized trial comparing voriconazole to liposomal amphotericin B in 837 neutropenic patients with persistent fever, the mortality rate was similar in both arms. However, there was a trend toward a better success with liposomal amphotericin B.[78] The choice of the initial agent is dependent to the most likely diagnosis. In situations which mucormycosis is also a suspected differential diagnosis, amphotericin B is preferred, while when aspergillosis is the most likely IFI, voriconazole is usually selected as the first choice. In these patients, posaconazole and isavuconazole are alternative agents; of note, these two azoles have activity against *Aspergillus* spp. and mucormycosis agents.[77]

In spite of *in vitro* activity against *Aspergillus* spp., echinocandins are unable to completely kill or inhibit these species.[77] There are no comparative randomized trial for echinocandins in this regard. However, caspofungin is Food and Drug Administration-approved for use as salvage therapy in patients who are refractory to or intolerant of other mentioned therapies.[79]

Currently, there are insufficient data for combination therapy of IA. Combined use of voriconazole and anidulafungin versus voriconazole alone was evaluated in a clinical trial of patients with IA.[80] According to the results, compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival. However, due to the insignificant difference and the limitations in the study power, definitive conclusions about the superiority of the combination regimen were impossible. Therefore, at present, there is no firm recommendation for the use of combination therapy.

For invasive zygomycosis, as the most resistant fungal infection, clinical trials have shown that liposomal amphotericin-B can be used as the most effective agent.[81] In addition, posaconazole and isavuconazole are appropriate alternative therapeutic agents in the cases of resistant zygomycosis.[82]

Regarding the comparison of amphotericin B deoxycholate (conventional) and lipid formulations of amphotericin B in neutropenic patients, one clinical trials has been published. In a randomized, double-blind, multicenter trial, using a composite end-point, liposomal amphotericin B and conventional amphotericin B were equivalent in overall efficacy. However, the liposomal amphotericin B treatment group had fewer proven fungal infections, fewer infusion-related side effects and less nephrotoxicity.[83]

For pediatric HM patients, empirical antifungal treatment must be administered in the cases of persistent fever (more than 4 days).[61] For IA, voriconazole is the first-line treatment, while liposomal amphotericin-B can be used as an alternative for children under 2 years of age or when the patient cannot tolerate voriconazole.[66] For invasive candidiasis, it is mostly recommended to use echinocandins.[84-87] Caspofungin and micafungin both can be used for pediatric patients. Amphotericin-B is an alternative therapeutic option in patients with central nervous system or cardiac involvement. After the first course of treatment, fluconazole can be used,

but not against *C. kruzei, and C. glabrata* because of high rate of fluconazole resistance. For children with liver or spleen involvement, echinocandins are the best suggestion.[84,85,87-89] In pediatrics with invasive fusariosis, voriconazole is the first-line treatment and amphotericin-B is used as alternative agent.[90]

CONCLUSION

The epidemiologic data of IFIs in Iranian population are lacking. However, HMs are among the most important clinical concerns in Iranian hospitals and these disorders are serious risk factors for IFIs. We discussed about the IFIs causative pathogens and aggressive risk factors in HMs for IFIs. Generally, among *Aspergillus* spp., *A. flavus* and *A. fumigatus*, and of *Candida* spp., *C. albicans* are the most prevalent IFI related pathogens. The IFI prevention in high risk patients is a vital measure in order to increase their quality of life and decrease the mortality and morbidity rate. Preventive measures such as restriction of spore exposure, suing of rooms with positive pressure, HEPA filter usage in special departments of hospitals, decreasing the humidity of environment, and use of fair ventilation condition can be used to diminish the risk of IFIs in these patients. Prophylactic regimen for patients undergoing chemotherapy or HSCT is another supportive procedure to prevent the IFIs. Various types of antifungal agents can be used as prophylaxis in these situations as discussed in this paper. Finally, we explained different therapeutic antifungal regimens for patients with the clinical presentation of IFIs based on the diagnostic pathogen. This review presented the new information about new diagnostic methods to identify the causative pathogen as soon as possible with the most sensitivity and specificity. However, there is no definitive solution for the IFIs and we hope that the incidence of hematological malignances will be reached to a minimum point.

Authors' contribution

FS contributed to the conception of the work, conducting the review, drafting the manuscript, approval of the final version of the manuscript, and agreed for all aspects of the work. RS contributed to the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM contributed to the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pagano L, Busca A, Candoni A, Cattaneo C, Cesaro S, Fanci R, *et al.* Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations. Blood Rev 2017;31:17-29.
2. Perfect JR, Hachem R, Wingard JR. Update on epidemiology of and preventive strategies for invasive fungal infections in cancer patients. Clin Infect Dis 2014;59 Suppl 5:S352-5.
3. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: Human fungal infections. Sci Transl Med 2012;4:165rv13.
4. Herbrecht R, Bories P, Moulin JC, Ledoux MP, Letscher-Bru V. Risk stratification for invasive aspergillosis in immunocompromised patients. Ann N Y Acad Sci 2012;1272:23-30.
5. Heimann SM, Vehreschild MJ, Cornely OA, Franke B, von Bergwelt-Baildon M, Wisplinghoff H, *et al.* A cost and resource utilization analysis of micafungin bridging for hemato-oncological high-risk patients undergoing allogeneic stem cell transplantation. Eur J Haematol 2015;94:526-31.
6. Hedayati MT, Taghizadeh Armaki M, Yazdani Charati J, Hedayati N, Seyedmousavi S, Denning DW. Burden of fungal infections in Iran. J Infect Dev Ctries 2018;12:910-8.
7. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in *Aspergillus fumigatus*: Can we retain the clinical use of mold-active antifungal azoles? Clin Infect Dis 2016;62:362-8.
8. van der Linden JW, Arendrup MC, Melchers WJ, Verweij PE. Azole resistance of *Aspergillus fumigatus* in immunocompromised patients with invasive aspergillosis. Emerg Infect Dis 2016;22:158-9.
9. Wang E, Farmakiotis D, Yang D, McCue DA, Kantarjian HM, Kontoyiannis DP, *et al.* The ever-evolving landscape of candidaemia in patients with acute leukaemia: Non-susceptibility to caspofungin and multidrug resistance are associated with increased mortality. J Antimicrob Chemother 2015;70:2362-8.
10. Kontoyiannis DP, Patterson TF. Diagnosis and treatment of invasive fungal infections in the cancer patient: Recent progress and ongoing questions. Clin Infect Dis 2014;59 Suppl 5:S356-9.
11. Niwa T, Imagawa Y, Yamazaki H. Drug interactions between nine antifungal agents and drugs metabolized by human cytochromes P450. Curr Drug Metab 2014;15:651-79.
12. Montagna MT, Giglio O, Napoli C, Lovero G, Caggiano G, Delia M, *et al.* Invasive fungal infections in patients with hematologic malignancies (aurora project): Lights and shadows during 18-months surveillance. Int J Mol Sci 2012;13:774-87.
13. Fracchiolla NS, Sciumè M, Orofino N, Guidotti F, Grancini A, Cavalca F, *et al.* Epidemiology and treatment approaches in management of invasive fungal infections in hematological malignancies: Results from a single-Centre study. PLoS One 2019;14:e0216715.
14. 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. Clin Infect Dis 2010;50:1091-100.
15. Akan H, Antia VP, Kouba M, Sinkó J, Tănase AD, Vrhovac R, *et al.* Preventing invasive fungal disease in patients with haematological malignancies and the recipients of haematopoietic stem cell transplantation: Practical aspects. J Antimicrob Chemother 2013;68 Suppl 3:i5-16.
16. Badiee P, Hashemizadeh Z, Ramzi M, Karimi M, Mohammadi R. Non-invasive methods to diagnose fungal infections in pediatric patients with hematologic disorders. Jundishapur J Microbiol 2016;9:e41573.

17. Chen CY, Sheng WH, Tien FM, Lee PC, Huang SY, Tang JL, *et al.* Clinical characteristics and treatment outcomes of pulmonary invasive fungal infection among adult patients with hematological malignancy in a medical Centre in Taiwan, 2008-2013. J Microbiol Immunol Infect 2020;53:106-14.
18. Lortholary O, Gangneux JP, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, *et al.* Epidemiological trends in invasive aspergillosis in France: The SAIF network (2005-2007). Clin Microbiol Infect 2011;17:1882-9.
19. Perkhofer S, Lass-Flörl C, Hell M, Russ G, Krause R, Hönigl M, *et al.* The nationwide Austrian *Aspergillus* registry: A prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients. Int J Antimicrob Agents 2010;36:531-6.
20. Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. Crit Rev Microbiol 2010;36:1-53.
21. Sun KS, Tsai CF, Chen SC, Huang WC. Clinical outcome and prognostic factors associated with invasive pulmonary aspergillosis: An 11-year follow-up report from Taiwan. PLoS One 2017;12:e0186422.
22. Lee JY, Jung CW, Kim K, Jang JH. Impact of previous invasive pulmonary aspergillosis on the outcome of allogeneic hematopoietic stem cell transplantation. Korean J Hematol 2012;47:255-9.
23. Mor M, Gilad G, Kornreich L, Fisher S, Yaniv I, Levy I. Invasive fungal infections in pediatric oncology. Pediatr Blood Cancer 2011;56:1092-7.
24. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, *et al.* The epidemiology of fungal infections in patients with hematologic malignancies: The SEIFEM-2004 study. Haematologica 2006;91:1068-75.
25. Valerio M, Vena A, Bouza E, Reiter N, Viale P, Hochreiter M, *et al.* How much European prescribing physicians know about invasive fungal infections management? BMC Infect Dis 2015;15:80.
26. Barreto JN, Beach CL, Wolf RC, Merten JA, Tosh PK, Wilson JW, *et al.* The incidence of invasive fungal infections in neutropenic patients with acute leukemia and myelodysplastic syndromes receiving primary antifungal prophylaxis with voriconazole. Am J Hematol 2013;88:283-8.
27. Sipsas NV, Pagoni MN, Kofteridis DP, Meletiadis J, Vrioni G, Papaioannou M, *et al.* Management of invasive fungal infections in adult patients with hematological malignancies in Greece during the financial crisis: Challenges and recommendations. J Fungi (Basel) 2018;4:94.
28. Lewis RE, Cahyame-Zuniga L, Leventakos K, Chamilos G, Ben-Ami R, Tamboli P, *et al.* Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: A 20-year autopsy study. Mycoses 2013;56:638-45.
29. Nucci M, Garnica M, Gloria AB, Lehugeur DS, Dias VC, Palma LC, *et al.* Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. Clin Microbiol Infect 2013;19:745-51.
30. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, *et al.* Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: Analysis of multicenter prospective antifungal therapy (PATH) alliance registry. Clin Infect Dis 2009;48:265-73.
31. Tacke D, Buchheidt D, Karthaus M, Krause SW, Maschmeyer G, Neumann S, *et al.* Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the infectious diseases working party of the German society for haematology and oncology. Ann Hematol 2014;93:1449-56.
32. Stefaniak M. Mukormykoza – Obraz Kliniczny, Diagnozowanie I Leczenie. Zakażenia XXI Wieku 2018;1:1-9.
33. Badiee P, Kordbacheh P, Alborzi A, Ramzi M, Shakiba E. Molecular detection of invasive aspergillosis in hematologic malignancies. Infection 2008;36:580-4.
34. Rambaldi B, Russo D, Pagano L. Defining invasive fungal infection risk in hematological malignancies: A new tool for clinical practice. Mediterr J Hematol Infect Dis 2017;9:e2017012.
35. Gamaletsou MN, Walsh TJ, Zaoutis T, Pagoni M, Kotsopoulou M, Voulgarelis M, *et al*. A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies. Clin Microbiol Infect 2014;20:O50-7.
36. Valerio M, Muñoz P, Rodríguez-González C, Sanjurjo M, Guinea J, Bouza E, *et al.* Training should be the first step toward an antifungal stewardship program. Enferm Infecc Microbiol Clin 2015;33:221-7.
37. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, *et al.* Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. Clin Infect Dis 2009;48:1042-51.
38. Kouni S, Kourlaba G, Mougkou K, Maroudi S, Chavela B, Nteli C, *et al*. Assessment of hand hygiene resources and practices at the 2 children's hospitals in Greece. Pediatr Infect Dis J 2014;33:e247-51.
39. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, *et al.* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 2011;52:e56-93.
40. Kontoyiannis DP, Lewis RE. Treatment principles for the management of mold infections. Cold Spring Harb Perspect Med 2014;5:a019737.
41. Siopi M, Gamaletsou M, Sipsas N, Pirounaki M, Stamouli M, Zerva L, *et al.* Determination of voriconazole levels in serum of hematological patients with a microbiological assay. Acta Microbiol Hellen 2013;58:33-42.
42. Gamaletsou MN, Drogari-Apiranthitou M, Denning DW, Sipsas NV. An estimate of the burden of serious fungal diseases in Greece. Eur J Clin Microbiol Infect Dis 2016;35:1115-20.
43. Stanzani M, Lewis RE, Fiacchini M, Ricci P, Tumietto F, Viale P, *et al*. A risk prediction score for invasive mold disease in patients with hematological malignancies. PLoS One 2013;8:e75531.
44. Ruhnke M, Böhme A, Buchheidt D, Cornely O, Donhuijsen K, Einsele H, *et al.* Diagnosis of invasive fungal infections in hematology and oncology – Guidelines from the infectious diseases working party in haematology and oncology of the German society for haematology and oncology (AGIHO). Ann Oncol 2012;23:823-33.
45. Hachem R, Assaf A, Numan Y, Shah P, Jiang Y, Chaftari AM, *et al.* Comparing the safety and efficacy of voriconazole versus posaconazole in the prevention of invasive fungal infections in high-risk patients with hematological malignancies. Int J Antimicrob Agents 2017;50:384-8.
46. Grim SA, Berger K, Teng C, Gupta S, Layden JE, Janda WM, *et al.* Timing of susceptibility-based antifungal drug administration in patients with *Candida* bloodstream infection: Correlation with outcomes. J Antimicrob Chemother 2012;67:707-14.
47. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev 2014;27:490-526.
48. Meyer MH, Letscher-Bru V, Jaulhac B, Waller J, Candolfi E. Comparison of mycosis IC/F and plus Aerobic/F media for diagnosis of fungemia by the bactec 9240 system. J Clin Microbiol 2004;42:773-7.
49. Galgóczy L. Molecular characterization of opportunistic pathogenic zygomycetes. Acta Biol Szegediensis 2005;49:1-7.

50. Odabasi Z, Mattiuzzi G, Estey E, Kantarjian H, Saeki F, Ridge RJ, *et al.* Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: Validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis 2004;39:199-205.
51. Pazos C, Pontón J, Del Palacio A. Contribution of (1->3)-beta-D-glucan chromogenic assay to diagnosis and therapeutic monitoring of invasive aspergillosis in neutropenic adult patients: A comparison with serial screening for circulating galactomannan. J Clin Microbiol 2005;43:299-305.
52. Hohenadel IA, Kiworr M, Genitsariotis R, Zeidler D, Lorenz J. Role of bronchoalveolar lavage in immunocompromised patients with pneumonia treated with a broad spectrum antibiotic and antifungal regimen. Thorax 2001;56:115-20.
53. Hodgman EI, Compton J, Qureshi FG, Murphy JT. Diagnosis of invasive fungal infection among pediatric oncology patients. J Pediatr Hematol Oncol 2019;41:596-600.
54. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, *et al.* Treatment of aspergillosis: Clinical practice guidelines of the infectious diseases society of America. Clin Infect Dis 2008;46:327-60.
55. Wong G, Wong I, Chan K, Hsieh Y, Wong S. A rapid and Low-Cost PCR thermal cycler for low resource settings. PLoS One 2015;10:e0131701.
56. Sheikhbahaei S, Mohammadi A, Sherkat R, Naeini AE, Yaran M, Najafi S. Invasive fungal infection in febrile patients with hematologic malignancies undergoing chemotherapy in Iran. Endocr Metab Immune Disord Drug Targets 2019;19:302-7.
57. Ruhnke M, Behre G, Buchheidt D, Christopeit M, Hamprecht A, Heinz W, *et al.* Diagnosis of invasive fungal diseases in haematology and oncology: 2018 update of the recommendations of the infectious diseases working party of the German society for hematology and medical oncology (AGIHO). Mycoses 2018;61:796-813.
58. Ceesay MM, Desai SR, Berry L, Cleverley J, Kibbler CC, Pomplun S, *et al.* A comprehensive diagnostic approach using galactomannan, targeted β-d-glucan, baseline computerized tomography and biopsy yields a significant burden of invasive fungal disease in at risk haematology patients. Br J Haematol 2015;168:219-29.
59. Boch T, Spiess B, Cornely OA, Vehreschild JJ, Rath PM, Steinmann J, *et al.* Diagnosis of invasive fungal infections in haematological patients by combined use of galactomannan, 1,3-β-D-glucan, *Aspergillus* PCR, multifungal DNA-microarray, and *Aspergillus* azole resistance PCRs in blood and bronchoalveolar lavage samples: Results of a prospective multicentre study. Clin Microbiol Infect 2016;22:862-8.
60. Gupta P, Ahmad A, Khare V, Kumar A, Banerjee G, Verma N, *et al.* Comparative evaluation of pan-fungal real-time PCR, galactomannan and (1-3)-β-D-glucan assay for invasive fungal infection in paediatric cancer patients. Mycoses 2017;60:234-40.
61. Eigl S, Hoenigl M, Spiess B, Heldt S, Prattes J, Neumeister P, *et al.* Galactomannan testing and *Aspergillus* PCR in same-day bronchoalveolar lavage and blood samples for diagnosis of invasive aspergillosis. Med Mycol 2017;55:528-34.
62. Carlesse F, Daudt LE, Seber A, Dutra ÁP, Melo AS, Simões B, *et al.* A consensus document for the clinical management of invasive fungal diseases in pediatric patients with hematologic cancer and/or undergoing hematopoietic stem cell transplantation in Brazilian medical centers. Braz J Infect Dis 2019;23:395-409.
63. Baddley JW, Andes DR, Marr KA, Kauffman CA, Kontoyiannis DP, Ito JI, *et al.* Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis. Med Mycol 2013;51:128-35.
64. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: How do we prevent and treat them? Clin Infect Dis 2010;50:405-15.
65. Slavin MA, Heath CH, Thursky KA, Morrissey CO, Szer J, Ling LM, *et al.* Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy. Intern Med J 2008;38:468-76.
66. Lee CH, Lin C, Ho CL, Lin JC. Primary fungal prophylaxis in hematological malignancy: A network meta-analysis of randomized controlled trials. Antimicrob Agents Chemother 2018;62:e00355-18.
67. Groll AH, Castagnola E, Cesaro S, Dalle JH, Engelhard D, Hope W, *et al.* Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol 2014;15:e327-40.
68. Science M, Robinson PD, MacDonald T, Rassekh SR, Dupuis LL, Sung L. Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. Pediatr Blood Cancer 2014;61:393-400.
69. O'Sullivan AK, Pandya A, Papadopoulos G, Thompson D, Langston A, Perfect J, *et al.* Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among neutropenic patients in the United States. Value Health 2009;12:666-73.
70. Aguado JM, Manuel O. Editorial for ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: An infectious diseases perspective. Clin Microbiol Infect 2018;24 Suppl 2:S1.
71. Zabalza A, Gorosquieta A, Equiza EP, Olavarria E. Voriconazole and its clinical potential in the prophylaxis of systemic fungal infection in patients with hematologic malignancies: A perspective review. Ther Adv Hematol 2013;4:217-30.
72. Safai Nodeh SR, Dehghan Manshadi SA, Jahanbin B, Khodaveisi S, Giasvand F, Seifi A, *et al.* Invasive fungal consecutive infections in a patient with acute myeloid leukaemia. Niger J Clin Pract 2019;22:582-4.
73. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, *et al.* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 2011;52:427-31.
74. Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: Diagnosis & clinical management. Indian J Med Res 2014;139:195-204.
75. Drew RH. Prevention and treatment of infections in neutropenic cancer patients. In: Zeind CS, Carvalho MG, editors. Applied Therapeutics, the Clinical Use of Drugs. 11th ed. Philadelphia: Wolters Kluwer; 2018. p. 1563.
76. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, *et al.* Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004;351:1391-402.
77. Wingard JR. Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients). In: Post TW, editor. Waltham, MA: UpToDate; 2022.
78. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-34.
79. 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. Clin Infect Dis 2016;63:e1-60.

80. Marr KA, Schlamm HT, Herbrecht R, Rottinghaus ST, Bow EJ, Cornely OA, *et al.* Combination antifungal therapy for invasive aspergillosis: A randomized trial. Ann Intern Med 2015;162:81-9.
81. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, *et al.* ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect 2014;20 Suppl 3:5-26.
82. Ruhnke M, Schwartz S. Recent developments in the management of invasive fungal infections in patients with oncohematological diseases. Ther Adv Hematol 2016;7:345-59.
83. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D, *et al.* Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National institute of allergy and infectious diseases mycoses study group. N Engl J Med 1999;340:764-71.
84. Skiada A, Lanternier F, Groll AH, Pagano L, Zimmerli S, Herbrecht R, *et al.* Diagnosis and treatment of mucormycosis in patients with hematological malignancies: Guidelines from the 3rd European conference on infections in leukemia (ECIL 3). Haematologica 2013;98:492-504.
85. Reed C, Bryant R, Ibrahim AS, Edwards J Jr., Filler SG, Goldberg R, *et al.* Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis 2008;47:364-71.
86. Colombo AL, Guimarães T, Camargo LF, Richtmann R, Queiroz-Telles Fd, Salles MJ, *et al.* Brazilian guidelines for the management of candidiasis – A joint meeting report of three medical societies: Sociedade Brasileira de Infectologia, Sociedade Paulista de Infectologia and Sociedade Brasileira de Medicina Tropical. Braz J Infect Dis 2013;17:283-312.
87. Nucci M, Thompson-Moya L, Guzman-Blanco M, Tiraboschi IN, Cortes JA, Echevarría J, *et al.* Recommendations for the management of candidemia in adults in Latin America. Latin America invasive mycosis network. Rev Iberoam Micol 2013;30:179-88.
88. 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. Clin Infect Dis 2016;62:e1-50.
89. Santolaya ME, de Queiroz Telles F, Alvarado Matute T, Colombo AL, Zurita J, Tiraboschi IN, *et al.* Recommendations for the management of candidemia in children in Latin America. Latin America invasive mycosis network. Rev Iberoam Micol 2013;30:171-8.
90. Arnoni MV, Paula CR, Auler ME, Simões CC, Nakano S, Szeszs MW, *et al.* Infections caused by *Fusarium* species in pediatric cancer patients and review of published literature. Mycopathologia 2018;183:941-9.