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REVIEW

An Overview of the Management of the Most Important Invasive Fungal Infections in Patients with Blood Malignancies

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Abstract: In patients with hematologic malignancies due to immune system disorders, especially persistent febrile neutropenia, invasive fungal infections (IFI) occur with high mortality. Aspergillosis, candidiasis, fusariosis, mucormycosis, cryptococcosis and trichosporonosis are the most important infections reported in patients with hematologic malignancies that undergo hematopoietic stem cell transplantation. These infections are caused by opportunistic fungal pathogens that do not cause severe issues in healthy individuals, but in patients with hematologic malignancies lead to disseminated infection with different clinical manifestations. Prophylaxis and creating a safe environment with proper filters and air pressure for patients to avoid contact with the pathogens in the surrounding environment can prevent IFI. Furthermore, due to the absence of specific symptoms in IFI, rapid and accurate diagnosis reduces the mortality rate of these infections and using molecular techniques along with standard mycological methods will improve the diagnosis of disseminated fungal infection in patients with hematologic disorders. Amphotericin B products, extended-spectrum azoles, and echinocandins are the essential drugs to control invasive fungal infections in patients with hematologic malignancies, and according to various conditions of patients, different results of treatment with these drugs have been reported in different studies. On the other hand, drug resistance in recent years has led to therapeutic failures and deaths in patients with blood malignancies, which indicates the need for antifungal susceptibility tests to use appropriate therapies. Life-threatening fungal infections have become more prevalent in patients with hematologic malignancies in recent years due to the emergence of new risk factors, new species, and increased drug resistance. Therefore, in this review, we discuss the different dimensions of the most critical invasive fungal infections in patients with hematologic malignancies and present a list of these infections with different clinical manifestations, treatment, and outcomes.

Keywords: invasive fungal infection, blood malignancies, aspergillosis, candidiasis, fusariosis, mucormycosis, cryptococcosis, trichosporonosis

Introduction

Blood malignancies involve myeloid and lymphoid linages in the chronic or acute phase. In the acute form, the maturation arrest at the early stage of myeloid linage occurs, and mature cells fail to be produced. Nevertheless, the chronic form is characterized by the relentless accumulation of mature cells without apoptosis.[1] Acute myeloid leukemia (AML) and myeloproliferative disorders (MPDs) are related to the acute and chronic form of myeloid linage disorder, respectively.[2] Furthermore, acute lymphoblastic leukemia (ALL) and lymphoproliferative disorders (LPD) are

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classified as acute and chronic lymphoid linage disorder, respectively. Another form of blood malignancy is dysplastic syndromes (MDs), mostly occur in myeloid linage, characterized by dysplasia in this linage.[1,2] All of the blood malignancies involve the immune system. In patients with blood malignancies, it is more common to encounter opportunistic infections mainly invasive fungal infections (IFIs).[3] Other conditions in these malignancies are bone marrow transplantations (BMT), which have the highest rate of IFIs, with the incidence range of 5 to 20% in different studies.[4] LPDs are malignancy of elderlies, 70% of the patients are older than 65 years, characterized by a different grade of immunodeficiency with enhanced susceptibility to opportunistic diseases.[5]

In recent years, new drugs used in the treatment of blood malignancy are the main causes of susceptibility to IFIs. The B-cell receptor signaling pathway inhibitors (BCRi) are targeting therapies in LPD, and these drugs have high efficacy in treatment, relapse prevention, and refractory resistance. Among these drugs, the most important one is ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor that blocks the B cell receptor signaling and causes inhibition of cell survival and proliferation. Of note, pneumonia is common in the patients who are treated with BCRi, observed in 4% to 17% of patients. Varughese et al reported the incidence of all invasive infections in 378 patients who received BCRi (ibrutinib), and they found 84% of infections in the first year of treatment. Of these, 37.2% and 53.5% had fungal and bacterial infections, respectively.[6] Ibrutinib inhibited protein kinases such as BTK, tyrosine-protein kinase Fgr, bone marrow kinase on chromosome X (BMX), and breast tumor kinase. In patients with BTK inhibition (ibrutinib consumption), the neutrophils lack function against fungal infection. Neutrophils are recruited to sites of fungal inflammation from the bloodstream, and in this stage, cytokines play the main role. Recruiting neutrophils depends on E-selectin receptors.[7–9] E- and P-selectins are expressed on endothelial cells, which are affected by inflammation and bind to glycoprotein ligands on neutrophils. E-selectin has the key role in neutrophils' slow-rolling on endothelial cells, and they are essential to the fungal infection site. BTK has functions on E-selectin dependent neutrophils' slow-rolling by activation of β2-integrins among the PLCγ2 and Phosphoinositide 3-kinase (PI3K) pathway.[9,10] Another role for BTK in neutrophils is inducing the release of granule proteins and reactive oxygen species (ROS).[10] This activity depends on fungal recognition on β-glucan and integrin CR3 adhesion molecules. The adhesions trigger the PI3K pathway and the non-oxidative intracellular mechanism of killing.[9,10]

PI3K signaling pathways are considered as a critical component of the immune response regulation; this has lead researchers to focus on this pathway for more investigations profoundly. PI3K pathway activity is correlated with the promotion of cell growth, survival, and resistance to radiotherapy and chemotherapy. The PI3K inhibitors have various applications in the regulation of inflammations and hematologic cancers such as Hodgkin lymphoma and Lymphoid malignancies, but the new generation of these drugs has imposed some unclear side effects. The oral administration of CLR457, pan-PI3K inhibitor, prevents all PI3K kinase isoforms leading to apoptosis and growth inhibition in tumor cells that overexpress PI3K.[11,12] Also, idelalisib, an inhibitor of PI3K, is approved for the treatment of lymphoma and Chronic lymphocytic leukemia (CLL) in the relapsed/refractory setting. Administration of other PI3K inhibitors such as Duvelisib, TGR-1202, and PI3K p110δ inhibitor that are developed to target various isoforms of PI3K enzyme result in various toxicities and different efficacies in clinical settings.[13,14] Furthermore, significant infectious toxicities have been reported in several trails, like opportunistic infections frequently associated with immunocompromised patients. These infections appear in the context of therapy-/disease-related cytopenias, but it is likely to get influenced by PI3K inhibitors as the mediators of the immune system.[14,15] Finally, these inhibitors affect the immune system and lead to an immunocompromised immunity in the patients. This prepares the situation for the development of opportunistic organisms to infect people and worsen the patients' condition. Therefore, prophylaxis in hematologic malignancies patients treated with PI3K inhibitors can be helpful in the management of opportunistic fungal infections.

In chronic myelogenous leukemia (CML), the most common malignancy between MPDs, BCR/ABL1 fused protein, which has higher kinase activity, is the most frequent. In the treatment of CML patients with imatinib, a kinase inhibitor was prescribed. Also, dasatinib, a new generation of the imatinib, has the same inhibition effects as the imatinib. In this regard, also, PI3Kγ pathway was inhibited as the drug side effect. The inhibition of the PI3Kγ pathway causes defects in the neutrophil slow-rolling, the release of granule proteins, and the production of reactive oxygen species. Another MPDs point mutation (c.1849G>T) in the JAK2 gene, a protein in the JAK2-STAT5 signal-transduction pathway, causes the substitution of phenylalanine for valine (V617F) in the protein and has

been detected in MPNs especially in Polycythemia Rubra Vera (PRV or PV) by 65% to 97%, Essential Thrombocythemia (ET) (30%–57%) and, primary myelofibrosis (35%–95%) depending on the detection method.[16] In the treatment of these patients the AG490 and its analogues are introduced as new drugs for inhibition of mutated and highly activated JAK2V617F.[17] This can induce the inhibition of STAST5 and proliferation of other myeloid linage, except erythron. This prevention also affects neutrophil counts, and opportunistic syndrome can result in fungal like infections. At the end, using antibiotics in prevention of infection can cause neutropenia or WBC malfunction.[18] So, patients with blood malignancy who were treated by BMT, chemotherapy, target therapy, and antibiotics are more susceptible to opportunistic infections, especially fungal infections, because of the suppression of the immune system. In this review, we have considered the different dimensions of the most important IFI such as aspergillosis, candidiasis, fusariosis, cryptococcosis, trichosporonosis, and mucormycosis in patients with blood malignancy and present a complete list of these infections with different clinical manifestations, treatment, and outcomes.

Immune System, Blood Malignancies, and Fungal Infection

The innate immune system of the body plays a crucial role in the regulation of host-fungi interaction. It protects the body against fungal infection by killing the fungal agent directly, modulating the microbial communities that affect fungal commensalism, and polarizing adaptive immune systems such as the polarization of Th1 and Th17. These host functions are accomplished through recognition of receptors of fungal determinants and sensing geometric signs (eg, size of the fungi).[19] Fungal ligands trigger a range of pattern recognition receptors (PRRs) like C-type lectin receptors (CLRs), NOD-like receptors, and Toll-like receptors (TLRs). Particularly, myeloid cells that identify fungal cell wall polysaccharides express some CLRs. Consequently, CLRs activate signaling pathways and cellular responses. As the primary phagocytes of the innate immune system, neutrophils express CLRs and produce reactive oxygen species (ROS) and facilitate host defense.[20,21] Deficiencies in the function of phagocyte NADPH oxidase (PHOX) result in chronic granulomatous disease (CGD). This disease is mostly characterized by the susceptibility of the host to get infected by invasive infections, including those by the generally non-pathogenic fungus *Aspergillus nidulans*. In immunocompetent individual fungal infections are usually harmless; nonetheless, susceptibility to the invasive infections in people with inherited immunodeficiency and patients treated with immunosuppressive medications that weaken the innate immune cell function, particularly patients with neutropenia, is considerably high.[22]

As mentioned, all blood malignancies engage the immune system and raise the chances of IFIs. There are some reasons for such susceptibility, including T cell (cell-mediated immunity) dysfunction, hypogammaglobinemia (humoral immunity), neutropenia caused by bone marrow involvement, and leukopenia due to chemotherapy or BMT.[3,23] Primarily, neutrophils are responsible for destroying hyphae post-germination, while in immunocompetent hosts, macrophages, and neutrophils both can inhibit germination or kill conidia. This is an essential response to fungal infection. Innate immunity plays a key role in the lung by Alveolar macrophage. Recent studies have suggested that alveolar macrophages identify and perform phagocytosis in various fungal species through attachment to dectin-1. Therefore, myeloid linage has the leading role in innate immunity and also in the second adaptive immune response against IFIs. In patients with blood malignancies, the WBCs decrease, and this leads to susceptibility to IFIs.[24,25] Infections mostly occur in patients with absolute neutrophil count (ANC) of $<500/mm^3$, and those with the ANC of $< 100/mm^3$ are at a higher risk.[26] Studies show that severe and prolonged neutropenia rises susceptibility to fungal infection. Furthermore, in AML, maturation arrest results in a decrease in the mature neutrophil count; also, the mature neutrophils present in the peripheral blood of these patients may be dysfunctional. Therefore, the ANC in AML patients may mislead the physician in estimating the risk of IFIs.[26–29] The ANC and function of neutrophils are regarded as a part of the innate immune system.

The lymphocytic leukemia is characterized by a deficiency in lymphocyte production and trafficking, and alterations in lymph organ function. Changing the lymphocyte function is related to the adaptive immune system. Noteworthy, this part of the immunity is the second line opposing IFIs like cryptococcosis.[30] In CLL, deficiency in innate immunity mostly includes hypocomplementemia, and dysfunctional neutrophils and NK cells. This can lead to a disrupted antibody function through CD20- targeting and complement-dependent cytotoxicity.[31,32] Moreover, deficiencies in the adaptive immune responses in CLL involve a decrease in CD4: CD8 ratio, a rise in immunosuppressive FoxP3+

regulatory T Cells, and helper T-cell impairment.[31,33] Consequently, a compromised innate and adaptive immunity in lymphocytic leukemia results in a higher risk of IFIs.

Aspergillosis

Aspergillosis can be categorized in many forms, such as invasive, chronic, saprophytic, and allergic.[34] Aspergillosis is a major concern for the healthcare system and scientific communities since they cause deadly diseases in patients with blood malignancies.[35,36] *Aspergillus* species specifically cause infections in the respiratory and gastrointestinal tract and skin. However, various clinical manifestations have been reported in patients with hematologic malignancies that some of them are listed in Table 1.[37] In previous studies, *Aspergillus* species such as *A. fumigatus, A. flavus, A. terreus*, and *A. niger*, were reported to be the most common pathogenic agent in patients.[36,38] In the intensive care unit (ICU), fungal infection is a major issue, and in vulnerable patients, it increases the morbidity and mortality rates. The IFI challenge in neutropenic patients is high, but in non-neutropenic individuals, the risk of IFI remains. The most common infections in the ICU are aspergillosis, candidiasis, and mucormycosis.[39] In non-neutropenic individuals and patients admitted to the ICU even with no signs of classic predisposing immunodeficiency, the emergence of aspergillosis has been identified increasingly. The invasive aspergillosis occurrence in ICU has been reported in ranges from 0.3% to 5.8%, with an overall mortality rate of >80%.[39–43] Moreover, in the other patients with blood or lymphoid tissue malignancies, liver, and bone marrow transplant recipients, the mortality rate related to the aspergillosis is reported 49%, 90%, and 80%, respectively.[39,44]

The incidence of invasive aspergillosis among patients with leukemia is estimated as high as 12.7%, and the most important factors causing invasive aspergillosis in patients with hematologic malignancies are mucosal damage, prolonged and profound neutropenia, and immunosuppressive drugs that make a patient susceptible to this infection.[45,46] Furthermore, hematopoietic stem cell transplantation is also prone to aspergillosis due to some factors such as the development of graft-versus-host disease, expansion of human leukocyte antigen (HLA) discordance, and the presence of respiratory virus co-infection or cytomegalovirus (CMV).[35,46–48] Therefore, because of the high risk of aspergillosis in these patients, prophylaxis with drugs such as caspofungin, micafungin, voriconazole, posaconazole, liposomal amphotericin B (LAMB), and caspofungin may be beneficial.[48–50] Noteworthy, depending on the patient's condition, these drugs can have different effects; however, side effects and toxicity of these drugs may limit their long-term use.[51] Fontana and his colleagues reported that, although isavuconazole was used for prophylaxis patients with hematologic malignancies or hematopoietic cell transplant recipients to prevent IFI, the results showed an increase in the rate of IFI, especially invasive pulmonary aspergillosis in these patients.[52] Therefore, it seems that using drugs alone to prevent invasive aspergillosis in patients with hematologic malignancies may not be sufficient and cause further difficulties. Thus, creating a protective environment for patients along with prophylaxis can be helpful. In this regard, regulating room ventilation, appropriate room sealing, and the application of high-efficiency particulate air (HEPA) filters can be noted.[53,54] For example, the results of one study showed that posaconazole prophylaxis in patients with AML, along with HEPA filtration, can be useful in preventing invasive aspergillosis during hospital building works.[55]

In addition to prophylaxis, the use of diagnostic methods that quickly detect fungal disease is also very effective in the treatment of the patient with blood malignancy. Previous studies have suggested that using different diagnostic methods such as β-D-glucan assays, *Aspergillus* galactomannan enzyme-linked immunosorbent assay (EIA), and a combined monitoring strategy based on serum galactomannan and polymerase chain reaction (PCR)-based detection of serum *Aspergillus* DNA are useful strategies for early diagnosis and lower incidence of invasive aspergillosis in high-risk hematological patients, because these methods can quickly detect invasive aspergillosis and determine the patient's treatment strategy.[45,56–59] Lateral flow assays for invasive aspergillosis offer the potential for rapid diagnosis, ease of performance, and point of care use. A murine monoclonal antibody attaches to an extracellular glycoprotein antigen that only releases during the active growth of *Aspergillus* hyphae. This antigen particularly secretes from *Aspergillus* hyphae, not conidia; therefore, this method also differentiates between hyphae and conidia.[60] In a study, Eigl et al reported that lateral-flow device (LFD) tests on the bronchoalveolar lavage (BAL) samples of ICU patients is a promising method in the diagnosis of invasive pulmonary aspergillosis (IPA). Since this test can be handled easily and enables rapid results; therefore, once the galactomannan test is not available, the LFD test could be a potential alternative for IPA diagnosis in ICU patients.[61] Also, the results of another study showed that *Aspergillus* LFD seems to be a promising alternative to galactomannan testing,[62] and its speed and accuracy provide a novel adjunct point-of-care test for diagnosis of IPA in

Table 1 Different Clinical Manifestations, Treatment, and Outcome of Most Important Invasive Fungal Infections in Patients with Hematologic Malignancies

First Author and Published Time	Species	Clinical Sign	Underlying Disease	Treatment	Surgery	Method for Diagnosis	Outcome	Reference
Duque (2018)	*Candida tropicalis*	Renal micro abscesses	A child with lymphoblastic leukemia	LAMB, micafungin and fluconazole	No	PCR	Treated	[88]
Niles (2019)	*Candida tropicalis*	Thyroiditis	An adolescent male with ALL	Micafungin	No	MALDI-TOF MS	Treated Although infections of the thyroid gland are rare, thyroiditis should be suspected in immunocompromised patients.	[114]
Ma (2016)	*Candida tropicalis*	Osteomyelitis	A 52 year-old man with AML	Micafungin	Placing of two tubes for postoperative drainage	MRI and pus culture	Treated Combination treatment using antifungal agents, surgical debridement, and sufficient drainage is a better way to treat *Candida* osteomyelitis.	[115]
Vicari (2003)	*Candida Tropicalis*	Septic arthritis as sign of fungemia	A 24-year-old man with ALL	AMB	No	Blood and synovial fluid cultures	Died Fluconazole prophylaxis has resulted in a rise in the proportion of hematogenous candidiasis.	[116]
Harada (2019)	*Fusarium solani*	Pre-engraftment disseminated fusariosis	A 47-year-old man with AML	AMB for a total of 19 weeks	No	Blood culture, MALDI-TOF and DNA sequencing	Treated with immediate definitive diagnosis, sufficient and long-term administration of appropriate antifungal medication and avoidance of the systemic administration of steroids.	[117]
Ichikawa (2020)	*Fusarium* species	Fungal endophthalmitis and disseminated fusariosis	16-year-old male with AML	AMB, itraconazole and caspofungin	Surgical resection for *Fusarium* sinusitis	Vitreal culture	Treated Continuous administration of antifungal agents and vigorous surgical intervention may be necessary for the management of disseminated fusariosis.	[118]
Mardani (2019)	*Fusarium* species	Ecthyma, gangrenosum-like lesions, sinusitis endophthalmitis, and disseminated fusariosis	35-year-old man diagnosed with AML and prolonged febrile neutropenic	AMB, voriconazole and caspofungin	Endoscopic sinus surgery	BacT/alert Microbial Detection System, PCR sequencing	Died Probably due to the nonrecovery of neutrophil.	[119]

(*Continued*)

Table 1 (Continued).

First Author and Published Time	Species	Clinical Sign	Underlying Disease	Treatment	Surgery	Method for Diagnosis	Outcome	Reference
Delia (2016)	*Fusarium solani*	Skin nodules and pneumonia in spite of posaconazole prophylaxis	A 44-year-old male with AML	Voriconazole and AMB	No	Blood culture, skin biopsy and molecular methods	Died Drug-resistant fusariosis.	120
Fadhel (2019)	*Mucorales* species	Disseminated lung disease with muscular involvement	A 53-year-old female with AML	AMB and posaconazole	Surgical debridement	Lung and muscle biopsy, 16S sequencing	Treated Diagnosis depends on the analysis of the tissue samples collected from the affected system.	121
Miura (2019)	*Mucorales* species	Pulmonary mucormycosis	A 59-year-old woman with AML	AMB	Right upper lobectomy	HE	Treated Pulmonary mucormycosis undergoing leukemia treatment should be considered for rapid surgical therapy if the infected lesion is limited.	122
Biddeci (2019)	*Mucorales* species	Systemic fungal infection complicated by aortitis	A 6 years old girl with ALL	AMB and posaconazole	Urgent surgical intervention and pulmonary lobectomy	HE	Treated Correct diagnosis using a biopsy can significantly help the treatment process.	123
Jeurkar (2019)	*Mucorales* species	Angioinvasive mucormycosis in frontal lobe that lead to cerebral edema, tonsillar herniation and brainstem infarction (source of infection was lung)	A 64-year-old female with AML	Prophylactic and treatment with voriconazole but AMB was not considered due to lack of consideration for mucormycosis.	No	HE	Died The combination of prolonged neutropenia, pulmonary nodules, and long-term voriconazole prophylaxis should have prompted further workup of mucormycosis prior to HSCT.	124
Ozhak-baysan (2010)	*Aspergillus alliaceus* and *Aspergillus flavus*	Pulmonary infection	A 64-year-old male with an AML	AMB and Voriconazole	No	Microscopic examination, BAL and fluid culture and PCR with sequences	Died Only voriconazole showed a low MIC against *A. alliaceus*, demonstrating that this drug is a better choice for the treatment of both strains.	125
Le (2020)	*Aspergillus fumigatus*	Central nervous system Aspergillosis infection	A 74-year-old male with CLL	Voriconazole	Craniotomy to evacuate the brain abscess	MRI and culture	Treated Early recognition and treatment of aspergillosis in CLL patients who present neurological symptoms can be lifesaving.	126

Rößler (2017)	*Aspergillus fumigatus*	Invasive pulmonary aspergillosis with multiple fungal abscesses	A patient in his early 70s with progressive AML	AMB and voriconazole	No	CT scan and BAL fluid culture	Died Azole resistance in *A. fumigatus* is an increasingly important phenomenon, leading to breakthrough infections despite prophylaxis.	127
Antonogiannaki (2019)	*Aspergillus* species	Invasive *Aspergillus* tracheobronchitis	A 50-year-old with hairy cell leukemia and previous *Plasmodium falciparum* infection	AMB	No	High resolution CT, BAL examination and direct smear	Died Previous *P. falciparum* infection was an additional predisposing factor for the manifestation of *Aspergillus* infection.	128
Turki (2017)	*Aspergillus* spp. and *Aspergillus fumigatus*	Cerebral aspergillosis and pneumonia	A 53 year old patient with LGL, Immune thrombocytopenia and combined antibody deficiency	AMB and voriconazole	No	MRI, chest radiography, CT and HE	Treated In cerebral involvement, prolonged treatment was recommended, and this patient showed no further relapse after 12 months of effective voriconazole treatment.	129
Inoue (2020)	*Cryptococcus* species	Cellulitis of the left mandible	31-year-old man with AML	LAMB, flucytosine and fluconazole	Surgical debridement	HE	Treated The surgical site healed after the operation.	130
Suleman (2019)	*Cryptococcus neoformans*	Cryptococcal meningitis and skin disease	60-year-old man with CLL	AMB, flucytosine and fluconazole	NO	Blood and CSF culture	Treated Physicians should be aware of possibility of disseminated cryptococcosis in patients with treatment-naïve CLL.	23
Ramirez 2019	*Trichosporon asahii*	Disseminated Infection	42-year-old male with AML	Caspofungin then LAMB and voriconazole.	NO	Culture, HE and MALDI-TOF	Died Invasive trichosporonosis is an acute fatal condition that occurs in immunosuppressed patients, usually under antifungal selective pressure.	131
Nguyen (2018)	*Trichosporon asahii*	Disseminated Infection	10-year-old boy with ALL	Micafungin, AMB and voriconazole	No	Culture	Died It is important to consider trichosporonosis in the evaluation of a critically ill individual with neutropenia and a rash, because the initial cutaneous presentation may appear benign and delayed therapy results in death.	132

Abbreviations: AMB, amphotericin B; LAMB, liposomal Amphotericin B; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; PCR, polymerase chain reaction; MALDI-TOF MS, matrix-assisted laser desorption/ionization mass spectrometry; MRI, magnetic resonance imaging; HSCT, hematopoietic stem cell transplant; BAL, bronchoalveolar lavage; CT, computed tomography; HE, histopathologic examination; CSF, cerebrospinal fluid; MIC, minimum inhibitory concentration.

patients with blood malignancies.[63] A 7-study meta-analysis reported that the sensitivity and specificity of the *Aspergillus* LFD on the serum specimens for the identification of proven or possible cases of invasive aspergillosis is 68% and 87%, respectively.[64] Also, in another study, a specificity of 98.0% and a sensitivity of 81.8% was reported for LFD. Along with PCR, the LFD enables 100% sensitivity and specificity. The outcomes of this study suggest that developing an LFD assay that targets a unique biomarker is a promising and straightforward diagnostic method that provides excellent clinical performance, especially in combination with PCR.[65] So, although LFD commercial availability is still pending in the United States, in different studies, the test has shown excellent performance and results; this suggests a feasible alternative to the *Aspergillus* Galactomannan EIA. Finally, it should be noted that a monoclonal antibody 476-based LFD for point-of-care diagnosis of urinary excreted fungal galactomannan like antigens has been developed but needs further validation.[66]

Drugs such as voriconazole and LAMB are used to treat infections caused by *Aspergillus* species, also other new drugs such as anidulafungin and isavuconazole are considered to be used widespreadly but this requires further studies.[54,67,68] For example, the results of a recent study showed that prophylaxis with isavuconazole is not effective in preventing invasive *Aspergillus* infections, and further studies are needed to use this drug widely.[52] Furthermore, drug resistance is a critical issue in *Aspergillus* species. *A. calidoustus* and *A. terreus* can be inherently resistant to azoles and AMB, and *A. fumigatus* can also be resistant to azoles.[69–71] Noteworthy, the incidence of invasive aspergillosis caused by azole-resistant *A. fumigatus* is increasing in patients with hematologic malignancies.[72] One study reported that azole-resistant *A. fumigatus*, despite treatment with isavuconazole, caused the death of two AML patients, and this indicates the importance of drug-resistant *Aspergillus* species and the need for rapid detection of these isolates.[73] Non-culture based molecular methods such as conventional PCR assays and a quantitative assay detecting a single-nucleotide polymorphism can help diagnose drug resistance in *Aspergillus* species, effectively.[72,74] Therefore, drug resistance in aspergillosis can increase mortality, and if resistance is detected or suspected, changing the treatment line or drug combinations can be a useful strategy for a better control of the infection. In addition to the therapeutic role of different drugs, other strategies are used to control different *Aspergillus* infections in patient with blood malignancy. Dong and his colleagues reported that surgical resection of focal invasive pulmonary aspergillosis can be a safe and applicable treatment in patients with fatal hemoptysis risk, also, long-term treatment with ineffective antifungal medications may interfere life-saving cancer chemotherapy.[75] On the other hand, another study found that despite the extended surgery and antifungal therapy for ALL patient with infection of the gastro intestinal tract by *Aspergillus* species, the outcome of disseminated invasive aspergillosis with intestinal involvement remains poor.[76] So, surgery is not applicable to patients with leukemia with unstable conditions and disseminated infection and the use of surgery should be tailored to the patient's condition.[36,54] In addition, some new immunotherapy strategies such as colony-stimulating factors, granulocyte transfusions, recombinant interferon gamma and adoptive transfer of pathogen-specific T lymphocytes can be used to control invasive aspergillosis and improve outcome in patients with leukemia, although widespread use of these methods needs further study.[46,48,54,77,78]

Therefore, infections caused by *Aspergillus* species are very dangerous and deadly in patients with leukemia. Prophylaxis, early diagnosis, appropriate drug treatment, and providing a safe environment for patients (Figure 1) can help control invasive aspergillosis. Furthermore, drug resistance in *Aspergillus* species is essential, and inappropriate use of drugs can easily cause death in patients with blood malignancy. Thus, an accurate diagnostic approach is necessary for selecting a better treatment line.

Candidiasis

Candida species are one of the most frequent isolated nosocomial agents that can involve various organs, particularly eyes, liver, kidney, and brain in patients with hematological malignancies such as acute leukemia, lymphoma, and myelodysplastic syndrome.[79] The most common members of this species that are capable of infecting humans are *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis*, and *C. krusei*.[80] Recently, studies have reported that within ICU patients with invasive candidiasis, candidemia will develop in two-thirds of the patients, and 80% of non-candidemia patients will develop intra-abdominal candidiasis. It has been documented that candiduria occurs in almost 20% of ICU patients, although associated tissue infection or secondary candidemia occurs in less than 5% of them.[81–84]

In patients with blood malignancies that undergo remission-induction chemotherapy for AML or myelodysplastic

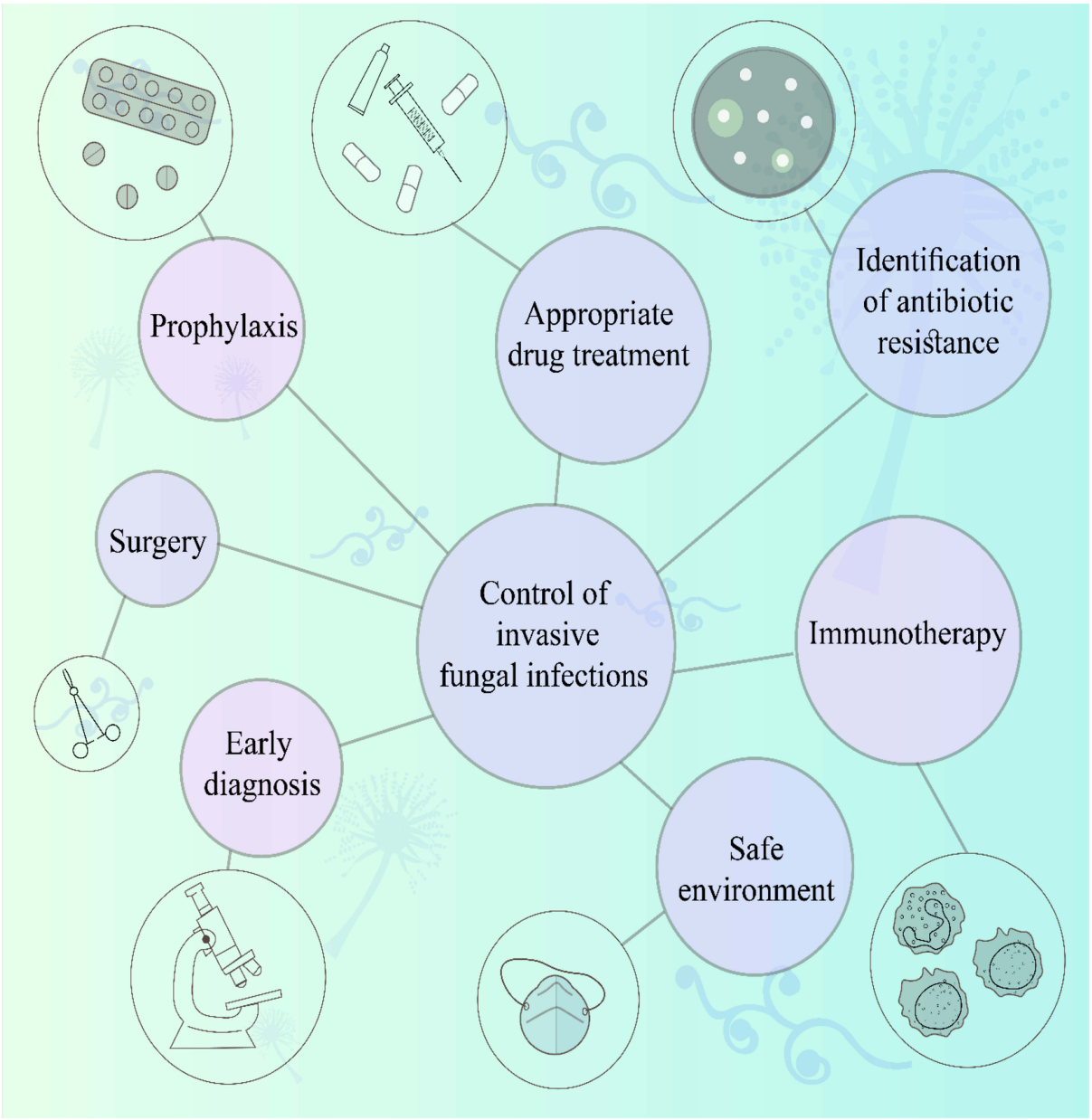

Figure 1 Strategies for controlling invasive fungal infections in patients with hematologic malignancies.

syndrome and the recipients of allogeneic hematopoietic stem cell transplants, the chance of infection by these microorganisms is increased because of the disorders in the immune system of the body especially a sharp decrease in the number of neutrophils. Also in these patients, the mucus is usually damaged, which can lead to the increased growth of the *Candida* species, and the chances of entering the blood and causing candidemia.[85,86] In different studies, different species of *Candida* have been identified pathogenic in patients with varying types of leukemia.[87,88] The source of infections in people with *Candida* is usually endogenous because it is present in the body as normal flora, and proper prophylaxis can help controlling it.[89] A study in China after a seven-year experience reported that *C. tropicalis* is the most common cause of candidemia among patients with acute leukemia, and the vast majority of these infections are endogenous. The results of this study showed that empiric antifungal treatment before the first positive culture helps patients to survive, and utilizing prophylaxis new drugs, including voriconazole and posaconazole, may result in a decreased candidemia incidence and a better chance of cure and survival.[90,91] Furthermore, *Candida* species such as *C. albicans* and *C. glabrata* can overgrow in the mouth of people with leukemia. Once it becomes systemic, it is hard to

diagnose, control, and treat the disease in such patients. Therefore, controlling oral infections in these patients can be very effective in hindering aggressive infections caused by *Candida* species.[92] In children with hematologic malignancies due to persistent febrile neutropenia, candidiasis can lead to high mortality and lack of prophylaxis can worsen the prognosis. A recent study reported that abnormal chest x-ray and clinical sinusitis are important predictors of invasive candidiasis in these patients, and protocols that include early empirical antifungal therapy covering this infection is essential.[93] Thus, as noted, prophylaxis may be effective in reducing the rate of disseminated candidiasis in people with leukemia, but long-term use of antifungal drugs may impose some difficulties, and the results of some studies have shown that despite prophylaxis, IFI has occurred in patients with blood malignancies.

One study reported that long-term use of voriconazole can lead to serious complications such as actinic keratosis, squamous cell carcinoma, and skeletal fluorosis, and another study reported that administration of this drug leads to hallucinations, visual changes, and photosensitivity in patients.[94,95] Furthermore, Casero et al reported that prophylaxis was less effective in patients with acute leukemia after allogeneic stem cell transplantation, and the risk of candidemia was high in these patients.[96] It should be noted that in some patients with hematologic malignancies, despite drug prophylaxis, disseminated infections with *Candida* species may occur as a consequence of drug resistance in this microorganism.[97] You and his colleagues reported that *C. tropicalis* that caused disseminated candidiasis in a patient with ALL resulted in death when posaconazole was used as a prophylactic drug. The results of this study showed that enhanced efflux pumps and changes in the azole target enzyme Erg11p, caused *C. tropicalis* resistance to azoles, and infection with this microorganism may lead to a longer period of hospitalization, administration of more expensive/toxic drugs, and a higher rate of mortality.[98] Noteworthy, the candidiasis appears with different clinical manifestations in patients with hematological malignancies and it is difficult to detect this microorganism due to the absence of specific symptoms (Table 1).

Rapid detection of candidiasis is necessary to control infection and reduce mortality. Methods used to diagnose candidiasis include blood culture and serological tests to detect β-D-glucan.[88,89] In addition, molecular methods, such as PCR-RFLP, Real-time PCR Fluorescence Resonance Energy Transfer probe assay and T2 Magnetic Resonance (T2MR), can help to control the chronic disseminated candidiasis as they allow rapid identification of the *Candida* species.[99–101] T2MR-based biosensing is able to detect different targets within complex matrices such as blood. This method needs a specific instrument and identifies *Candida* species in the blood samples directly; however, unlike the blood cultures, viable organisms are not essential in this method.[60] T2MR is a qualitative molecular diagnostic method approved by the FDA. In this method, PCR molecular assay and nuclear magnetic resonance are joined to identify the five most frequent *Candida* species, including *C. tropicalis, C. glabrata, C. krusei, C. albicans*, and *C. parapsilosis* in approximately 5h.[102,103] The results of a recent study showed that T2MR with clinical sensitivity of 89% can diagnose candidemia at the time of positive blood cultures. Furthermore, this test could diagnose infected patients with negative blood cultures who had received antifungal therapy before their tests.[104] Furthermore, specificity 76.1% and sensitivity 100% was reported for T2MR in another study, and these results suggested that this test may be a better marker of complicated infection than follow-up blood cultures or blood β-d-glucan[105]. Also, Mylonakis et al reported overall sensitivity 91% and specificity 98% with a mean time of 4.4 ± 1.0 hours for diagnosing and identifying species using the T2MR method.[103] Therefore, T2MR is a novel and fully automated technology to analyze whole blood specimens to diagnose the *Candida* species without preceding isolations. This test represents a step forward in the new era of molecular diagnosis. On the other hand, the T2MR has some limitations; for example, the test can detect only five species of *Candida*, the reliability of the test has not examined in the deep-seated candidiasis, and the data to assess the performance of the T2MR in invasive candidiasis without candidemia is not sufficient.[102] Thus, more studies are required to shed light on further implications of T2MR in medical settings for the diagnosis of such infections.

Another microorganism identification tool, matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, is a novel technology that detects bacteria, and most recently, yeast, within minutes with reliable results than the conventional methods.[107–110] Many laboratories are equipped with this instrument due to its high simplicity and reliability.[108–111] Some researchers believe that mass spectrometry could substitute the microscopy identification method as the first-line detection of microorganisms isolated from patients' specimen cultures.[109,112,113] Noteworthy, Niles et al detected disseminated candidiasis in males with ALL using MALDI-TOF mass spectrometry. Peripheral blood cultures from admission

grew budding yeast at 22 hours of incubation, and the yeast was ultimately speciated as *C. tropicalis* by MALDI-TOF mass spectrometry.[114] The identification of fungal species is essential since many isolates show different susceptibility profiles opposing common antifungal agents, and MALDI-TOF mass spectrometry is a beneficial method because it needs low sample volumes, and it has rapid turnover time and accuracy in identifying fungal infection at the species and subspecies level. However, this technology requires further developments to be adapted for recognizing all microorganisms grown in biological samples, and the performance of this technology can significantly boost when its database upgrades with more spectra of appropriate reference strains.[109,110]

Therefore, *Candida* species cause different infections in patients with leukemia, and given the endogenous nature of this microorganism, prophylaxis may be efficient in reducing mortality although long-term use of the drugs may lead to toxicity and results in different outcomes in patients with different conditions. Finally, the non-culture-based tests can be performed with each other to increase the detection of invasive candidiasis, significantly, to establishing an early diagnosis of infection.

Mucormycosis

Aspergillosis and Candidiasis cause dangerous fungal diseases in people with blood malignancies. However, mucormycosis causes in pediatric oncology patients.[122,133] Mucormycosis is a dangerous progressive disease caused by the filamentous fungi of the *Mucorales* order of the class of *Zygomycetes*.[134] The order *Mucorales* consist of varieties of species such as *Mucor, Saksenaea, Syncephalastrum, Cunninghamella, Rhizopus, Absidia, Rhizomucor*, and *Apophysomyces* that are involved in human diseases most frequently.[135] These microorganisms are mostly opportunistic and produce much airborne spore, and usually, they are not problematic in people with normal immunity, although they can cause aggressive, malignant and lethal infection in patients with underlying diseases such as solid-organ malignancies, chronic renal failure, malnutrition children, immunocompromising conditions and diabetes mellitus.[136–139] Mucormycosis in ICU patients is mostly related to massive injuries, including natural disasters or complex combat trauma and motor vehicle accidents.[140–143] A comprehensive epidemiologic data related to the mucormycosis in the ICU is not available, but frequent cases of mucormycosis have been reported by individuals or small series in ICUs.[39,144–146]

Also, patients with hematologic malignancies are highly susceptible to mucormycosis due to abnormalities in their immune systems. In severe neutropenia, a poor prognosis can lead to a 75 to 80% mortality rate, and delay in initiating treatment for these patients is hazardous and fatal.[138,147] Mucormycosis can present a localized or disseminated form of infection, and lung is the most prevalent site of infection in patients with blood malignancies, although other organs such as the paranasal sinuses, skin, brain, and gastrointestinal tract can also be involved.[148–150] In patients with low levels of immunity, mucormycosis develops as a deadly disease, whereas cutaneous disease is rarely disseminated and is associated with better outcomes.[151] Noteworthy, people with a healthy immune system can also get involved with *Mucorales* (the genera *Apophysomyces* and *Saksenaea*); this situation is observed in patients with severe burns and penetrating trauma.[152]

Several principles work together to prevent and treat mucormycosis in patients with hematologic malignancies. The first line of treatment for mucormycosis is the use of AMB; the application of this drug in combination with some triazoles, such as posaconazole and isavuconazole, can improve its efficacy.[136] It should be noted that other members of the triazoles family, such as itraconazole, voriconazole, and fluconazole, have a minimal inhibitory effect on the *Mucorales*, and they are not recommended for the therapeutic purposes.[153,154] Also, combination therapy, including AMB with echinocandins or posaconazole, can be helpful.[155,156] Nevertheless, the results of previous studies on the use of combination therapy for different patients have been conflicting. For example, combination therapy with AMB and echinocandins has been beneficial in diabetic patients with rhino-cerebral mucormycosis, whereas the same combination treatment has not been successful in patients with blood malignancies.[157] Therefore, further studies are required to determine the performance of combination therapies in patients with different conditions. Along with the mentioned treatments, it is important to control the patient's underlying conditions, which can assist the treatment process. For instance, controlling diabetes, malnutrition and discontinuing immunosuppressive drugs, if possible, can help control mucormycosis.[158] Granulocyte colony-stimulating factor (G-CSF), granulocyte (macrophage) colony-stimulating factor (GM-CSF), and interferon-γ (IFN-γ) can be used to treat mucormycosis in patients with blood malignancy with deep neutropenia.[159,160] These compounds increase phagocytosis, oxidative burst, and ultimately enhance the

antifungal function of neutrophils. Furthermore, IFN-γ stimulates T-helper cell type 1 (Th1) immunological response, which increases the body's resistance to IFI.[161,162] On the other hand, immunotherapy can cause side effects and inflammation in different organs such as inflammatory lung injury, and further studies are needed for widespread use of them.[163] Surgery can also be helpful to treat mucormycosis depending on the condition of the patient because in some cases mucormycosis causes extensive thrombosis, tissue infarction, and necrosis, this process prevents the penetration of antifungal drugs, so surgery can help control the infection and inhibit its spread.[158] Surgical debridement in patients with soft tissue infection, localized pulmonary lesion and rhino-orbito-cerebral disease can be beneficial, while in patients with disseminated mucormycosis this strategy is not applicable and should be used according to the patient's condition.[122,164–168] Delay in initiation of mucormycosis treatment in patients with hematologic malignancies results in an increased mortality rate, which requires proper and reliable diagnosis.

Reliable and accurate diagnosis of mucormycosis is a major challenge, since despite aspergillosis, antigen-based detection methods or other standardized serological methods cannot be used to identify mucormycosis.[164] Culturing method has great limitations and it has been reported that tissue sections are the best samples to be cultured.[169] Blood cultures are usually negative and the positive cases may indicate contamination.[158] Histological examination of the tissues sections obtained from surgery can reveal features such as tissue necrosis, angiogenesis, and ribbon-like hyphae.[138] Although histologic examination has been suggested as the gold standard for the diagnosis of mucormycosis, this method has some limitations for the diagnosis of infection in patients with hematologic malignancies. In these patients, due to severe thrombocytopenia, it is difficult to obtain tissue biopsies, and other biological specimens such as sputum should be used for diagnosis.[170,171] Noteworthy, molecular methods such as PCR sequencing and Real-time PCR have been used to detect mucormycosis, but little is known about their efficacy.[172–175] In patients with blood malignancies, the lungs and central nervous system are more infected with *Mucorales*, and evaluation of the efficacy of molecular methods to detect this microorganism in BAL and cerebrospinal fluid (CSF) samples are needed.[176]

According to the issues discussed earlier, rapid diagnosis, multidisciplinary approach and appropriate treatment to inhibit mucormycosis in patients with hematologic malignancies can reduce the mortality rate of these infections. It should be noted that inhalation and ingestion of sporangiospores is the most common route of mucormycosis transmission, so preparing a safe environment for patients can prevent this infection.[139,177] Due to the limitations of obtaining tissue biopsies in these patients and the time-consuming process of diagnosis, it is better to start treatment based on the patient's clinical symptoms, furthermore, developing molecular methods for the diagnosis of mucormycosis can be beneficial and lead to excellent outcomes.

Fusariosis

Fusarium species causes most common opportunistic fungal infection that is widely distributed in the environment (soil, plant debris, and air) because of the high ability of this fungal family to grow on a broad range of substrates and their competent mechanisms for dispersal.[178,179] Entry through the airways (inhalation of airborne microconidia) is the most common way of accessing the *Fusarium* species to the human body, but damaged mucous membranes and skin can also be the site of entry of these microorganisms.[180,181] Although more than 100 species of *Fusarium* have been identified so far, most of the human infections are caused by *F. solani, F. oxysporum, F. verticillioides*, and *F. proliferatum*.[182,183] This fungal family can cause local infections in people with healthy immune systems who have skin breakdowns or foreign bodies, but disseminated infections usually occur in immunocompromised patients, and patients with blood malignancies and allogeneic hematopoietic cell transplant recipients are susceptible to fusariosis.[183,184]

Onychomycosis and keratitis are the most common forms of fusariosis in patients, but in immunocompromised patients, *Fusarium* species can cause infections such as sinusitis, thrombophlebitis, osteomyelitis, pneumonia, and endophthalmitis.[185–188] In patients with hematologic malignancies, fusariosis like other fungal infections such as aspergillosis is highly invasive due to the immune-system disorders such as prolonged and deep neutropenia, T-cell immunodeficiency and administration of immunosuppressive drugs.[189] Along with neutropenia, no cellular inflammatory reactions occur, and this can lead to IFI, since macrophages and neutrophils which invade *Fusarium* hyphae, inhibit the germination of conidia and the growth of hyphae are absent in neutropenic patients.[182,190] Noteworthy, *Fusarium* species are capable of producing mycotoxins, such as trichothecenes, which

causes tissue damage and suppress humoral and cellular immunity.[191] Therefore, patients with hematologic malignancies are highly susceptible to fusariosis with a higher chance of spreading the infection due to immune disorders.

All of these indicate the importance of prophylaxis and prevention strategies in these patients. Also, *Fusarium* species have a very low sensitivity to antifungal drugs, and this causes therapeutic failures in patients with invasive fusariosis, therefore, in these patients, prevention seems to be essential.[192] Using broad-spectrum azoles, such as voriconazole and posaconazole, can be helpful as prophylaxis; however, few studies have been conducted in this area. On the other hand, some studies have reported that prophylaxis with these drugs does not prevent invasive fusariosis.[193,194] Also, creating safe environments that have proper filters and air pressure is beneficial for patients with blood malignancies. Furthermore, based on the recent findings, plumbing and water systems are the reservoirs of *Fusarium* species in hospital environments, and keeping them away from susceptible patients may help hinder fusariosis.[181,195] Few studies have evaluated the susceptibility of *Fusarium* species to various antifungal drugs; also, some studies have examined the efficacy of drugs in animal models. *Fusarium* studies on animal models have many limitations because *Fusarium* is less virulent in mice and is not pathogenic in guinea pigs that reduces the applicability of animal studies.[196–198] These microorganisms are not susceptible to echinocandins and itraconazole, and in general, LAMB, voriconazole, and posaconazole have been recommended or applied for the treatment and prophylaxis of fusariosis in adults, although the clinical response to these drugs were merely modest.[199,200] Harada and his colleagues reported that a patient with AML who also had a pre-engraftment disseminated fusariosis was treated with high doses of LAMB, and the results of another study also showed that a combination of LAMB and voriconazole in an ALL patient with disseminated fusariosis leads to complete recovery of the patient.[117,201] On the other hand, the results of another study on two acute leukemia patients who developed disseminated fusariosis showed that the *F. solani* isolated from the patients were resistant to amphotericin, and both patients died despite antifungal treatment.[202] So, antifungal drugs can have different efficacy in patients with different conditions, and this indicates the need for developing antifungal susceptibility tests. Furthermore, antifungal treatment in patients with hematological malignancies with disseminated fusariosis must be aggressive, with high doses of antifungals or combined therapy.

Diagnosis in patients with fusariosis is based on positive cultures of blood and skin lesions. Unlike aspergillosis, blood cultures are positive in this infection because of the production of yeast-like structures (adventitious sporulation) that allow the dissemination and growth of *Fusarium* species in the blood.[203] This microorganism grows on most cycloheximide-free media and histopathological examination, observing and finding fungal structures such as Adventitious sporulation, the hyphae, and yeast-like structures together can help confirm the diagnosis.[179] The 1,3-β-D-glucan test is usually positive in patients with invasive fusariosis, but it is not very helpful because it does not differentiate other IFI, such as candidiasis and aspergillosis.[204,205] Also, using molecular methods is helpful in the detection of *Fusarium* species. Herkert et al reported that the use of sequencing translation elongation factor 1-alpha gene showed a good ability to distinguish and differentiate clinical *Fusarium* species.[206]

Therefore, since *Fusarium* species cause disseminated infections in patients with hematologic malignancies and these infections are resistant to antifungal treatments, before starting immunosuppressive drugs, patients should be carefully investigated for the presence of infections that involve skin or nail, and more attention should be paid to the cutaneous lesions to reduce the risk of infections by these microorganisms in patients with blood malignancies. Of note, more clinical studies are needed to evaluate the precise function of antifungal agents to inhibit *Fusarium* species, because proper prophylaxis and treatment of patients with hematologic malignancies may prevent disseminated fusariosis with high mortality in these patients.

Cryptococcosis

Cryptococcosis is a fungal infection, and most of the time, it demonstrates as meningoencephalitis, pneumonia, and disseminated infection. This fungal infection is usually caused by two different species of *Cryptococcus gattii* and *Cryptococcus neoformans* [207]. *C. neoformans* have been found all around the world, and it is responsible for the majority of the infected cases. *C. gattii*, on the other hand, has been isolated from a range of plants in British Columbia, Australia, Canada, and the Pacific Northwest of the USA, but recently it has expanded throughout the other parts of the USA.[208] *Cryptococcus* species is a regular

saprophyte in the environment, acquiring nourishment from dying organic material. Exposure to *Cryptococcus* species occurs through the inhalation of aerosolized basidiospores. Most cases develop hematogenous dissemination with a particular predilection for the CNS, which results in cryptococcal meningitis (~90%) after pulmonary infection. Moreover, occurring lesions in other tissues is another indication for fungus spread.[209] When the yeasts contact with macrophages in the alveoli of healthy hosts, a type 1 T helper cell response activates. This pathogen, as a facultative intracellular pathogen, is well adapted to survive intracellularly in the host body. In this respect, *Cryptococcus* species and macrophages interaction play a significant role in cryptococcal pathogenesis.[210] Through the non-lytic exocytosis process, *C. neoformans* can extrude itself from the phagocytic cell. Also, it can alter its phenotype through phenotypic switching and replicative aging, leading to subverted immune responses in the host.[211,212]

The global incidence of *C. neoformans* disease is estimated one million cases leading to 625,000 fatalities each year.[213] In healthy hosts, the disease is usually asymptomatic, mild or self-limited, whereas patients with deficiencies in T-cell immunity are not capable of forming granulomas. Therefore, in these patients, local pulmonary or disseminated infection to the blood and CNS can occur and result in adverse consequences.[214] More specifically, the prevalence and history of *C. neoformans* disease are essential since it is highly related to the AIDS epidemic. In the sub-Saharan African region, access to antiretroviral therapy is limited; therefore, the highest rate of cryptococcosis has found in patients in such countries.[215] Other groups affected by *C. neoformans* infection are those with malignancy, solid organ transplant, cytotoxic chemotherapy, chronic organ failure and lung disease, rheumatologic disorders, splenectomy, idiopathic CD4 lymphocytopenia and even healthy immunocompetent hosts.[216] Recently, studies have suggested that administration of a high dose of chemotherapeutic regimens that result in depletion of lymphocytes such as rituximab, fludarabine, cyclophosphamide alemtuzumab and extended use of corticosteroids can lead to the elevated risk cryptococcal disease in patients with malignancy.[30,217,218] Furthermore, Abid et al report a patient with CLL who developed disseminated cryptococcosis (meningitis, probable pneumonia, and fungemia) while receiving ibrutinib therapy.[31] Another study also reports tow patients with cryptococcal meningoencephalitis and cryptococcal pneumonia who were receiving ibrutinib for CLL.[219] The results of these studies suggest that a compromised innate and adaptive immunity in CLL patients and further impairments in the humoral and cell-mediated immune system as a result of ibrutinib administration increase the chance of cryptococcal infection. Therefore, patients who develop acute illness and simultaneously receive ibrutinib should be examined for cryptococcal antigen.

As mentioned earlier, the association of cryptococcosis with CD4 lymphopenia that determines AIDS is remarkable; therefore, in immunocompromised cancer population with neutropenia, this infection is not typical.[30] On the other hand, lymphocytic leukemia patients are likely to show hypogammaglobinemia, suppression of helper T-cells, reduced T-cell response to proliferative signals, imbalanced in T-cell subset with an inversion in CD4: CD8 ratio, and a decline in the CD4 T-cell count. Consequently, these patients are mostly associated with higher rates of cryptococcosis.[23,220] The results of a systematic review study (adult patients published from 1970 to 2014) showed that hematological malignancies are responsible for 82% of cryptococcal infections in the setting of malignancy. The underlying diseases in such infection were lymphomas, leukemias, and myelomas in 66%, 29%, and 4% of the cases, respectively. There are two factors accounted for this skewed distribution, including the immune dysfunction associated with each malignancy and the particular chemotherapeutic regimen. Patients with lymphoma seem to be at higher risk, and this may be due to a combination of alteration in the immunity-related to cancer and using lymphoma therapeutics that result in T-cell depletion.[30]

Cryptococcosis is typically caused by *C. neoformans* and *C. gattii*; however, over the past four decades, opportunistic infections associated with non-gattii and non-neoformans species such as *C. albidus* and *C. laurentii* have increased significantly. Park et al stated in a study that in disseminated cryptococcosis with skin manifestation in a female with refractory AML after allogeneic hematopoietic stem cell transplantation, the skin biopsy showed fungal hyphae, also, repetitive blood cultures revealed yeast infection that later was detected as *C. laurentii* using Vitek-II.[221] Also, another study on pediatric cancer patients with ALL reported that *C. magnus* and *C. chernovii* were isolated from cultures inoculated with nasal specimens.[222] Therefore, severely immunocompromised patients with persistent febrile neutropenia should be considered for non-neoformans, and non-gattii cryptococcosis infections.

As a result of the atypical presentation, most of the patients receive antibacterial treatments before the accurate diagnosis of cryptococcosis was determined. Recently, most scientists have focused on developing a rapid diagnostic test for cryptococcal disease to enhance its prevention and treatment in infected patients. Conventionally, the diagnosis of such infections relied on lumbar puncture followed by CSF India ink preparation, detection of cryptococcal antigen (CrAg), or culture.[223] Most recently, researchers have presented a CrAg test utilizing point-of-care lateral flow test to identify cryptococcal capsular polysaccharide antigens (particularly glucuronoxylomannan) in blood, CSF, urine, or serum samples. The sensitivity and specificity of this test with 93–100% and 93–98%, respectively, are comparable to those of latex agglutination, enzyme-linked immunosorbent assay (ELISA), and cultures.[224,225]

The treatment of cryptococcosis relies on the clinical indications and the immunological situation of the patients. Currently, AMB and its lipid formulation, flucytosine, and fluconazole are three drugs known as clinical antifungal assets against cryptococcosis.[208] In addition to the limited therapeutic options, high rates of attendance and recurrence have been reported due to increase resistance of *Cryptococcus* species to fluconazole and flucytosine. A recent meta-analysis (29 studies from 1988 to May 2017) reports meaning fluconazole resistance 10.6% and 24.1% for the incident isolates and relapse isolates, respectively. Furthermore, 18.7% of isolates had minimum inhibitory concentration (MIC) above the ecological cut-off value.[226] Assing et al reported a case of fluconazole-resistant cryptococcal meningitis in a CLL patient that treated with AMB for almost six weeks. Therefore, it seems that fluconazole resistance is a growing concern in *Cryptococcus* isolates collected from patients with relapses. Thus, susceptibility testing of *C. neoformans* isolates in all patients with meningeal cryptococcosis is crucial, even in the patient without previous exposure to fluconazole.[227] Furthermore, the search for new alternatives for the treatment of cryptococcal infections is essential and in previous studies, the use of therapeutic strategies such as IFN-γ[228] mycograb,[229] a monoclonal antibody directed against the capsular polysaccharide,[230] sertraline,[231] and tamoxifen[232] to control cryptococcosis has been studied.

Trichosporonosis

As an uncommon, lethal, and opportunistic fungal infection, trichosporonosis affects immunocompromised patients with neutropenia, especially patients with underlying hematologic malignancies.[132] *Trichosporon* species that are opportunistic fungal pathogens can lead to a superficial infection known as white piedra, allergic pneumonitis, and invasive infections in humans.[233] Amongst *Trichosporon* species, *T. asahii* and *T. cutaneum* (formerly: *T. beigelii*) are the most common ones. After candidiasis, trichosporonosis was considered as the second most frequent infection leading to fungemia in patients with hematological malignancies.[234,235] Neutropenia is the primary risk factor for trichosporonosis. The other risk factors leading to trichosporonosis are cytotoxic chemotherapy, consumption of systemic corticosteroid, indwelling central catheters, prosthetic valve surgery, organ transplantation, and peritoneal dialysis.[132,236]

A recent systematic review reported that hematological diseases (38.9% of the cases), mainly acute leukemia, are the most frequent underlying diseases that provide a condition for invasive trichosporonosis (IT). Neutropenia was observed in 85% of patients with hematological diseases; this supports the fact that neutrophils are, as for aspergillosis and candidiasis, essential for the prevention of IT.[234] The results of another systematic review on 19 pediatric patients with IT and underlying malignant or nonmalignant hematologic disorder revealed that ALL (47%) and then AML (21%) are the most frequent underlying hematologic disorder. Notably, the mortality rate of 58% was reported in this study.[235] Furthermore, another study conducted in Japan on 33 cases of *Trichosporon* fungemia (TF) in patients with hematologic malignancies reported that most of the patients with TF had acute leukemia (82%), neutropenia (85%), and 91% of them had a history of intensive chemotherapy. Also, in this study, a mortality rate of 76% was reported in patients with TF.[237]

There was a growing concern in patients who received a systematic antifungal, as therapy or prophylaxis, to develop breakthrough IFI (B-IFI). *Trichosporon* species has become a critical life-threatening opportunistic pathogen that causes B-IFI during exposure to antifungals.[238] Also, with higher use of wide-spectrum triazoles as prophylaxis in high-risk patients, infection with multidrug-resistant (MDR) *Trichosporon* species was reported.[239] A recent study reported a series of 68 cases who developed breakthrough *Trichosporon* species infections. The results of this study indicated that 95.5% of patients had an underlying hematological malignancy. Also, 61.8% of patients with breakthrough *Trichosporon* species received echinocandins, 22% received triazoles, 13.2% received amphotericin, and 3% received other combinations of antifungals. The mortality

Table 2 Other Invasive Fungal Infections Reported in Patients with Hematologic Malignancies

Fungal Infection	Species	Underlying Disease	Clinical Manifestation	Outcome	References
Coccidioidomycosis	*Coccidioides* species	ALL	Meningitis complicated by central nervous system vasculitis.	The patient was treated with AMB, intravenous fluconazole, Micafungin and prednisone.	250
Scopulariopsis	*S. alboflavescens*	AML	Pneumonia with large consolidation on the left side of the lung hilum.	AMB and voriconazole combination therapy was not successful and the patient died.	251
	S. brevicaulis	AML	Bronchial invasion that leads to mediastinal emphysema, bronchial bleeding, and bronchial obstruction before finally spreading to the entire lung.	The patient died because it was estimated that the patient had respiratory aspergillosis infection, and the optimal treatment was delayed.	252
	S. brevicaulis	AML	The patient with necrotic ulcers on his hard palate and his left tonsil.	Sinonasal infection was successfully treated with a combination of extensive surgical debridement and AMB.	253
	S. brevicaulis	AML	The patient with persistent fever that did not respond to wide spectrum antibiotics and AMB.	The fever subsided with itraconazole, and there was no recurrence of fungal infection with prolonged maintenance of oral itraconazole.	254
	S. brevicaulis	AML	Onychomycosis with local cutaneous invasion.	Unsuccessfully treated with high-dose micafungin, and the patient died from a cerebral hemorrhage in the context of chronic thrombocytopenia.	255
Geoterichosis	*G. capitatum*	ALL	The patient with fever and blood infection.	The patient died and fungal infection disseminated although caspofungin was used as prophylaxis.	256
	G. capitatum	Fanconi aplastic anemia	Neutropenic fever, multiple nodules were detected in liver and septic arthritis.	The patient treated with AMB and voriconazole but died due to sepsis and multiple organ failure.	257
	G. capitatum	AML with multilineage dysplasia	Blood infection and multiple nodular lesions in lung fields.	The patient treated with a combination of AMB, itraconazole, and voriconazole.	258
	G. capitatum	Plasma cell leukemia	Pneumonia	The patient treated successfully with an antifungal combination of voriconazole, caspofungin, and supportive therapy.	259
	G. capitatum	ALL	The infection involved lung, liver and skin	Caspofungin, AMB, and combination therapy with voriconazole improved patient condition, but the patient died due to heart and lung failure.	260
Ochroconis gallopavum	*Ochroconis gallopavum*	B-CLL	Disseminated Infection	AMB and itraconazole were used for treatment, but the patient died due to brain abscesses.	261
Scedosporium	*S. prolificans*	AML	Disseminated Infection	Combination of voriconazole and terbinafine in conjunction with central venous line removal and intravitreal voriconazole, contributed to the recovery of the patient.	262
	S. prolificans	ALL	Pneumonia	Successfully treated with liposomal AMB and who underwent autologous peripheral blood stem cells transplantation.	263
	S. prolificans	AML	Sepsis	Died AML and Fatal *S. prolificans* sepsis after Eculizumab treatment for paroxysmal nocturnal hemoglobinuria.	264
	S. prolificans	AML	Infective endocarditis	Died Multi-organ failure despite the combined use of voriconazole and terbinafine.	265

Abbreviations: AMB, amphotericin B; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia.

rate reported in this study was 68.7%, and both neutropenia and the presence of venous catheters were considered as crucial factors for developing infection.[131] Furthermore, Suzuki et al reported that TF occurred as a B-IFI during antifungal therapy in 30 patients (91%), 18 of whom were receiving micafungin. Therefore, they suggested that along with using antifungals without anti-*Trichosporon* activity, further care is needed to prevent the development of breakthrough trichosporonosis.[237] Another study also reported an elderly, a 73 years old man, with AML and *T. asahii* systemic infection who received itraconazole as prophylaxis during severe neutropenia. Notably, this case was successfully treated with voriconazole following LAMB.[240] Thus, breakthrough trichosporonosis is a severe and life-threatening infection that occurs in immunocompromised patients, commonly under antifungal selective pressure. Generally, underlying diseases accompanied by neutropenia are mostly accompanied by deleterious outcomes.[131]

Recent studies have shown that the tendency for trichosporonosis to evade detection on blood culture and to resemble other better-known pathogens such as *Candida* on histology present additional diagnostic challenges.[241] It has been suggested that compared with *Candida, Trichosporon* has thinner hyphae and pseudohyphae, and stain slightly on Gomori methenamine silver (GMS) in comparison to other fungi. Nonetheless, histopathological detection of *Trichosporon* without immunohistochemistry, ELISA, and/or PCR confirmation is challenging.[242,243] Galligan et al reported a disseminated *T. asahii* case in a relapsed ALL patient who received systematic antifungal therapy and indicated multiple cutaneous nodules suggestive a fungal infection. Although histological characteristics resembled neutrophilic eccrine hidradenitis but staining with periodic acid–Schiff stain (PAS) and GMS confirmed the clinical diagnosis.[241] Thus, trichosporonosis must be distinguished from candidiasis and other diseases, which share similar clinical and morphologic features in the disseminated form and their differences in treatment susceptibility.

Optimal therapy for disseminated trichosporonosis is not established. Recently, various organizations, including the European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology, suggested voriconazole as an optimal and fluconazole as a suboptimal therapeutic line for the treatment of trichosporonosis.[244] MDR *Trichosporon* has been reported with AMB, echinocandins, flucytosine, fluconazole, and itraconazole.[131,233,236] Another study reported that during multi-agent chemotherapy, two patients with hematologic malignancy developed endophthalmitis as a result of *T. beigelii* infection. *Trichosporonous* endophthalmitis in these patients was resistant to fluconazole and 5-fluorocytosine, and in both cases, systematic treatment with AMB efficiently resolved this infection, which was resistant to antifungal therapeutics. Therefore, the result of this study suggests that the treatment of endophthalmitis as a result of trichosporonosis is challenging.[245] In this respect, an urgent need for a novel antifungal drug appears. In vitro investigations indicates that new antifungals such as posaconazole and voriconazole are efficient against *Trichosporon*; also, other studies have reported good clinical outcomes.[246–248] On the other hand, recent researches reported that compared to antifungal treatments, improving trichosporonosis mostly depends on neutrophil recovery. This suggests that prophylaxis with antifungal drugs, even azoles, may not deliver complete prevention against trichosporonosis in patients with acute neutropenia.[240,249]

Therefore, trichosporonosis should be considered as a crucial factor in the evaluation of neutropenic immunocompromised patients, especially those with underlying hematologic malignancies, because it carries significant mortality and delayed diagnosis and therapy results in death. Moreover, this infection in severely neutropenic patients should be considered in the differential diagnosis of refractory fever regardless of using echinocandins and azoles as prophylaxis medication. Finally, Table 2 summarizes other IFI in patients with hematologic malignancies. Although these infections are less common, they lead to therapeutic failures and high mortality rates in patients with hematologic malignancies.

Conclusion and Perspective

The increasing prevalence of IFI in patients with hematologic malignancies has raised many concerns. These patients are prone to fungal infections due to disorders of the innate immune system. The incidence of drug resistance in different fungal species has increased the mortality rate of disseminated infection in patients with hematologic malignancies. Prophylaxis and prevention of patients' contact with environmental sources of microorganisms can be effective in preventing infection. Traditional diagnostic methods are limited due to the lack of access to suitable biopsy specimens in patients with hematologic malignancies, and rapid molecular methods with higher rates of accuracy can be used more widely. Finally, because of the infections in recent years,

further studies on the use of new drugs, immunotherapies, combination therapies and drug resistance in fungal infections is recommended to help prevent the high mortality rate of these infections in patients with hematologic malignancies.

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Disclosure

The authors report no conflicts of interest in this work.

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