PERSPECTIVES IN HEMATOLOGY
DOI: 10.4274/tjh.galenos.2026.32559

Antifungal Management in Patients with Hematologic Malignancies: From Primary Prophylaxis to Empirical and Diagnostic-Driven Treatment

Hematolojik Maligniteli Hastalarda Antifungal Yönetim: Primer Profilaksi, Ampirik Tedavi ve Tanı Odaklı Yaklaşımlar

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March 8, 2026
July 29, 2026

Abstract
Invasive fungal diseases (IFDs) remain a significant cause of morbidity and mortality among patients with hematologic malignancies, especially those undergoing intensive chemotherapy or hematopoietic stem cell transplantation (HSCT). This review provides a comprehensive, risk-adapted framework for antifungal prophylaxis, stratifying patients into high, intermediate, and low-risk categories. Mold-active prophylaxis, primarily with posaconazole, is recommended for high-risk patients such as those with acute myeloid leukemia (AML) during remission induction or those with grade III–IV graft-versus-host disease (GVHD) post-allogeneic HSCT. Fluconazole remains an option for yeast-active prophylaxis in intermediate-risk patients, while low-risk groups generally do not require prophylaxis.
The evolving landscape of targeted therapies—such as venetoclax, fms-like tyrosine kinase 3 (FLT3) inhibitors, and CD19 chimeric antigen receptor T-cell (CAR-T) therapy—poses new challenges, particularly due to drug–drug interactions with triazole antifungals. In patients receiving venetoclax, azole co-administration necessitates significant dose adjustments. We also present algorithms for antifungal management in the context of CD19 CAR-T therapy and novel agents, emphasizing the role of individualized risk assessment.
Beyond prophylaxis, timely diagnosis and early treatment of IFDs are critical. The role of thoracic computed tomography, serum and bronchoalveolar lavage galactomannan, and fungal biomarkers is discussed within diagnostic-driven strategies. We outline treatment pathways for suspected pulmonary or sinus fungal infections, including when to escalate antifungal therapy or consider surgical intervention.
This review offers a practical and evidence-based guide for clinicians navigating antifungal strategies in a rapidly changing therapeutic landscape, aiming to reduce IFD-related mortality while balancing toxicity, resistance, and healthcare costs.
Keywords: Antifungal prophylaxis; Hematologic malignancies; Invasive fungal infections; Posaconazole; Risk stratification; CAR-T cell therapy; Venetoclax; CD19-directed therapies
Özet
Hematolojik maligniteli hastalarda invaziv fungal enfeksiyonlar (IFE), özellikle yoğun kemoterapi veya hematopoietik kök hücre nakli (HKHN) alan hastalarda morbidite ve mortalitenin önde gelen nedenlerinden biridir. Bu derlemede, hastaların IFE riski doğrultusunda yüksek, orta ve düşük risk gruplarına ayrıldığı kapsamlı ve kanıta dayalı bir antifungal profilaksi yaklaşımı sunulmuştur. Akut miyeloid lösemi (AML) indüksiyon tedavisi alanlar ve allojenik HKHN sonrası **derece III–IV** graft-versus-host hastalığı (GVHH) gelişen hastalarda posakonazol ile küf-aktif profilaksi önerilmektedir. Orta riskli hastalar için fluconazol ile maya-aktif profilaksi uygunken, düşük riskli gruplar genellikle profilaksiye ihtiyaç duymaz.

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Hedefe yönelik ajanların (örneğin venetoklaks, fms-like tirozin kinaz 3 (FLT3) inhibitörleri, CD19 kimerik antijen reseptörü T-hücre (CAR-T) tedavisi) kullanımı, azollerin farmakokinetik etkileşimleri nedeniyle yeni zorluklar doğurmuştur. Venetoklaks alan hastalarda eş zamanlı posakonazol veya fluconazol kullanımı doz ayarlaması gerektirir. Ayrıca, CAR-T tedavisi veya yeni nesil tedaviler sırasında profilaksi algoritmaları sunulmuştur. Tanısal yaklaşımlarda toraks bilgisayarlı tomografi, serum/bronkoalveolar lavaj galaktomannan ve mantar biyobelirteçlerinin yeri vurgulanmıştır. Akciğer ve sinüs fungal enfeksiyonlarının tanı ve tedavi yolları, ampirik tedaviye geçiş kriterleri ve cerrahi müdahale endikasyonları açıklanmıştır.
Bu çalışma, antifungal profilaksi ve tedavinin en güncel kanıtlarını sunarak, klinisyenlere enfeksiyon riskini en aza indirme ve mortaliteyi azaltma konusunda rehberlik etmeyi amaçlamaktadır.
Anahtar Kelimeler: Antifungal profilaksi; Hematolojik maligniteler; İnvaziv fungal enfeksiyonlar; Posakonazol; Risk sınıflaması; CAR-T hücre tedavisi; Venetoklaks; CD19-hedefli tedaviler

1. Introduction

Invasive fungal diseases (IFDs) remain a major cause of morbidity and mortality in patients with hematologic malignancies. The risk of IFDs varies widely by disease type and treatment phase, reaching its highest levels in acute leukemia and following allogeneic hematopoietic stem cell transplantation (HSCT), where prolonged neutropenia, mucosal damage, and intensive immunosuppression markedly increase susceptibility.

Primary antifungal prophylaxis has therefore become a cornerstone of supportive care in high-risk settings, particularly during acute myeloid leukemia (AML) remission induction and in selected post-transplant scenarios. However, the therapeutic landscape of hematology has evolved substantially. The widespread use of targeted agents, venetoclax-based regimens, and immune-based therapies such as CD19 chimeric antigen receptor T cells (CAR-T cells) has altered traditional fungal risk profiles while introducing clinically relevant drug–drug interactions with triazole antifungals.

These developments necessitate a modern, risk-adapted approach that extends beyond prophylaxis alone. This review summarizes current evidence and guideline-based recommendations for antifungal management across the continuum of care—from primary prophylaxis to empirical and diagnostic-driven treatment—providing practical algorithms tailored to contemporary hematologic practice.

2. Scope and Methods

This narrative review provides a practical, risk-adapted framework for the prevention and early management of IFD in adults with hematologic malignancies, including recipients of HSCT and patients treated with contemporary targeted and cellular therapies; pediatric management is beyond its scope. Recommendations are based on current international guidelines, principally the updated European Conference on Infections in Leukaemia (ECIL-10) guidelines [1], together with relevant guidance from the Infectious Diseases Society of America (IDSA) [2,3], the European Society of Clinical Microbiology and Infectious Diseases–European Confederation of Medical Mycology–European Respiratory Society (ESCMID-ECMM-ERS) [4], and the European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) [5,6]. Where applicable, recommendations are annotated with the ECIL/ESCMID strength-of-recommendation (A–D) and quality-of-evidence (I–III) grades. Throughout, IFD is categorized as proven, probable, or possible according to the 2020 EORTC/MSGERC consensus definitions [6].

3. Primary Antifungal Prophylaxis in Patients with Hematologic Malignancies

3.1. Why Is Primary Antifungal Prophylaxis Needed?

Patients with acute leukemia, particularly during remission induction chemotherapy, frequently experience profound neutropenia lasting longer than 10 days. This condition predisposes them to severe infections, most notably invasive aspergillosis caused by mold species [1,7,8,9,10,11,12,13].

Reduction of morbidity and mortality: IFDs represent a major cause of morbidity and mortality in patients with acute leukemia. Effective prophylaxis significantly decreases both the incidence of these infections and the associated mortality [14].

Treatment costs: Empirical or targeted antifungal therapies initiated after the onset of IFDs are costly and frequently prolong hospitalization. Prophylaxis can mitigate these additional expenses and lessen the overall burden on healthcare resources [15].

3.2. How Should Hematologic Malignancies Be Stratified for Antifungal Prophylaxis?

High-risk group: This category includes patients with AML during remission induction, those with intermediate- or high-risk myelodysplastic syndrome (MDS) receiving AML-like induction chemotherapy, and allogeneic HSCT recipients who develop grade III–IV graft-versus-host disease (GVHD) after engraftment [9,10]. Primary antifungal prophylaxis is strongly recommended in this group (A-I) [1].

Intermediate-risk group: This group includes patients with AML in consolidation, those with acute lymphoblastic leukemia (ALL) receiving induction therapy, allogeneic HSCT recipients in both pre- and post-engraftment phases,

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and autologous HSCT recipients [1,9]. Yeast-active prophylaxis is generally recommended in this group, with mold-active prophylaxis reserved for those with additional mold risk factors.

Low-risk group: This category encompasses the remaining hematologic malignancies, including chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myeloproliferative neoplasms (MPNs), multiple myeloma (MM), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and low-risk MDS (Figure 1). Routine antifungal prophylaxis is not recommended in these patients (D-II) [7,12].

3.3. What Do Mold-Active and Yeast-Active Prophylaxis Mean?

High-risk patients with hematologic malignancies are at risk of developing both yeast- and mold-related IFDs during induction chemotherapy. Among these infections, *Aspergillus* and *Candida* species account for most cases. *Aspergillus fumigatus* is the predominant *Aspergillus* species, while mucormycosis represents the second most common cause of invasive mold infection after aspergillosis. Both pathogens are associated with a high risk of mortality [4,15,16].

The risk is influenced by multiple factors, including the chemotherapy regimen, the duration of neutropenia, and the underlying disease status-newly diagnosed, in remission, relapsed, or refractory. It is known that environmental factors such as construction and intense exposure to dust, as well as respiratory viral pathogens like the influenza and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) viruses, are risk factors for IFDs.

Mold-active prophylaxis: Patients at risk for aspergillosis include those receiving intensive or multiple chemotherapy regimens, with increased iron overload, delayed engraftment (e.g., after umbilical cord transplantation), or prolonged corticosteroid exposure (≥1 mg/kg/day of methylprednisolone or prednisone-equivalent for at least 3 weeks).

Yeast-active prophylaxis: *Candida* infections are strongly associated with severe mucositis and the presence of a central venous catheter.

3.4. Which Antifungal Agent Should Be Chosen Based on Patient Characteristics?

In patients with AML undergoing induction therapy, the risk of invasive mold infections is particularly high; therefore, posaconazole prophylaxis is strongly recommended based on evidence from randomized controlled trials, including subsequent independent randomized studies confirming the initial findings. In allogeneic HSCT recipients undergoing transplantation at centers with a high incidence of invasive aspergillosis, antifungal prophylaxis with voriconazole or posaconazole may be considered during the pre-engraftment period in the setting of profound and prolonged neutropenia (>10 days, <500/mm³). However, in the early post-engraftment phase, patients with GVHD requiring corticosteroid therapy should receive mold-active prophylaxis. Posaconazole is the preferred agent for AML and high-risk MDS remission-induction prophylaxis (A-I) [1,13,15,17]. Isavuconazole and micafungin—the latter upgraded from C-II to B-II in ECIL-10—are acceptable alternatives, particularly when posaconazole is unsuitable because of hepatic dysfunction, QTc prolongation, drug–drug interactions, or impaired enteral absorption (both B-II) [1,18,19]. Itraconazole is a further pre-engraftment option but is limited by tolerability and variable absorption; classic itraconazole was downgraded to C-I in ECIL-10, whereas SUBA-itraconazole is graded C-II [1]. Recipients of haploidentical allo-HSCT with post-transplant cyclophosphamide are now classified as low risk for IFD by the ECIL-10 panel and do not warrant intensified mold-active prophylaxis on that basis alone [1].

Reported rates of breakthrough IFDs (predominantly invasive aspergillosis) during echinocandin prophylaxis generally cluster around 5–7%, although figures ranging as widely as 1% to 28% have been described across different series [20]. These rates tend to exceed those reported with mold-active azole prophylaxis. In line with this, one study identified echinocandin prophylaxis as an independent predictor of breakthrough IFD when compared with voriconazole- or posaconazole-based regimens during induction chemotherapy for acute leukemia [21]. In a prospective, randomized phase II trial in HSCT recipients, no significant difference in the incidence of IFDs was observed between micafungin and fluconazole prophylaxis (7.3% vs 8.2%; p=0.786); 100-day mortality was likewise similar between the two arms (9.1% vs 12.9%; p=0.345). This finding supports the notion that micafungin does not offer superior mold protection over fluconazole in this population [22]. A study from our country identified caspofungin use as a significant risk factor for *Saprochaete capitata* fungemia, while another local study noted a notable rise in echinocandin minimum inhibitory concentration values among *Candida* species in parallel with increasing echinocandin consumption [23,24]. Taken together, these findings suggest that micafungin prophylaxis may be more appropriately reserved for specific situations such as significant drug–drug interactions or bioavailability concerns rather than used as a routine choice.

In allogeneic HSCT recipients without a specific risk for mold infection, oral fluconazole 400 mg/day is recommended for *Candida* prophylaxis [1,9,25]. Autologous HSCT recipients do not routinely require prophylaxis; however, in cases of severe mucositis, *Candida* prophylaxis may be considered [26]. As noted above, allogeneic HSCT recipients who develop grade III–IV GVHD and receive methylprednisolone (or prednisone-equivalent) at ≥1 mg/kg/day should receive mold-active prophylaxis, continued while significant immunosuppression persists [1,27,28].

For mold-active prophylaxis, posaconazole delayed-release tablets are preferred, with a loading dose of 300 mg twice daily on Day 1, followed by 300 mg once daily as maintenance dose. The oral suspension of posaconazole demonstrates highly variable bioavailability, with significant interpatient variability in absorption. To address this

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limitation, a delayed-release tablet formulation was developed, providing more consistent and higher plasma concentrations while minimizing the impact of food intake [1,29].
Posaconazole prophylaxis should be initiated on the same day as chemotherapy, or on the last day of anthracycline administration in patients receiving anthracycline-based regimens. The drug should be discontinued if another antifungal agent is initiated for therapeutic purposes. Concomitant use of proton pump inhibitors and histamine-2 receptor antagonists should be avoided; if unavoidable, a minimum separation of 2 hours is recommended. In the presence of severe mucositis, nausea, or vomiting, the intravenous formulation should be used. In grade III–IV GVHD, posaconazole prophylaxis should be continued until immunosuppressive therapy is discontinued or another antifungal agent is introduced for treatment [13,15,28,29].
In intermediate-risk patients, fluconazole 400 mg once daily should be started concurrently with chemotherapy and continued until neutropenia resolves, defined as an absolute neutrophil count >500/mm³ sustained for at least seven consecutive days. The drug should be discontinued if switched to another antifungal agent for therapeutic purposes (Figure 1).

3.5. Antifungal Prophylaxis in Patients with MDS or Receiving Hypomethylating Agents

Patients with low- or intermediate-risk MDS managed with supportive care or erythropoiesis-stimulating agents are not at increased risk of IFD and do not require antifungal prophylaxis (D-I). In contrast, patients with high-risk MDS undergoing intensive AML-like induction chemotherapy should receive prophylaxis as for AML (A-I). An important ECIL-10 update concerns intermediate- and high-risk MDS (and AML) treated with hypomethylating agents (HMAs): the risk of IFD is highest during the first four cycles, with reported incidences of approximately 3%–12%, being higher in cohorts where prophylaxis was infrequently used. Accordingly, mold-active prophylaxis—most commonly posaconazole—is now recommended during the first four cycles of azacitidine-based therapy in these patients (B-IIu) [1,30,31,32,33,34].

3.6. Which Patients Do Not Require Antifungal Prophylaxis?

In MM, MDS not receiving AML-like therapy, CML, other MPN, CLL, and lymphomas (Hodgkin and non-Hodgkin), the risk of IFDs is estimated to be approximately 1–2%. Antifungal prophylaxis is not recommended for these patient groups **(D-II)** [1].
Antifungal prophylaxis is generally not indicated for autologous HSCT recipients. In cases of severe mucositis (Grade 3–4), however, yeast-active prophylaxis may be considered.

3.7. What Is the Optimal Duration of Antifungal Prophylaxis?

Antifungal prophylaxis, both primary and secondary, should be continued until neutrophil recovery is achieved. In the setting of secondary prophylaxis, after discontinuation of therapy, patients require close monitoring for an additional 2–4 weeks with fungal biomarkers such as galactomannan, supplemented by thoracic computed tomography (CT) imaging when clinically indicated [1,2].
For patients receiving repeated courses of myelosuppressive therapy, prophylaxis is recommended to be continued throughout the entire treatment period. In allogeneic HSCT recipients, antifungal prophylaxis should be continued until discontinuation of immunosuppressive therapy.

3.8. Who Should Receive Secondary Antifungal Prophylaxis, and With Which Agents?

Secondary prophylaxis is recommended for patients with a history of invasive aspergillosis who are expected to develop prolonged neutropenia lasting longer than 14 days during subsequent myelosuppressive therapy. Voriconazole is considered an appropriate option for secondary prophylaxis in this setting. Liposomal amphotericin B or posaconazole should be used for secondary prophylaxis in patients who experienced mucormycosis. Secondary prophylaxis choices should be individualized based on the patient's clinical response to the initial IFD treatment course [1,35].

4. How Should Antifungal Prophylaxis Be Managed in the Era of Novel Therapies?

Contemporary treatment of hematologic malignancies increasingly relies on targeted small molecules, monoclonal and bispecific antibodies, and cellular therapies. For most of these agents the intrinsic risk of IFD is low, so routine antifungal prophylaxis is generally not required; the dominant fungal-related consideration is instead the potential for clinically significant interactions between triazole antifungals and agents metabolized by CYP3A4. Prophylaxis should therefore be individualized according to the underlying disease, the depth and duration of neutropenia, corticosteroid exposure, and the specific agent used. The subsections below summarize the principal targeted agents and the antifungal implications of the most relevant drug–drug interactions [1].
The targeted agents currently used in hematologic malignancies include the following:
AML: fms-like tyrosine kinase 3 (FLT3) inhibitors (quizartinib, midostaurin, sorafenib, gilteritinib), B-cell lymphoma 2 (BCL-2) inhibitor (venetoclax), monoclonal antibody gemtuzumab ozogamicin, Hedgehog pathway inhibitor glasdegib, isocitrate dehydrogenase 1/2 (IDH1/2) inhibitors (ivosidenib, enasidenib), and liposomal cytarabine–daunorubicin (CPX-351) [36,37].
ALL: Blinatumomab (anti-CD19), inotuzumab ozogamicin (anti-CD22), and tyrosine kinase inhibitors (imatinib, nilotinib, dasatinib, ponatinib).
NHL: Bruton tyrosine kinase (BTK) inhibitor ibrutinib, monoclonal antibodies such as rituximab and ofatumumab, PI3K inhibitor idelalisib, and bispecific antibodies.

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Hodgkin lymphoma: Brentuximab vedotin (anti-CD30) and the immune checkpoint inhibitor nivolumab (programmed cell death 1 [PD-1]).
MM: Immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), monoclonal antibodies (daratumumab [anti-CD38], elotuzumab), anti-B-cell maturation antigen (BCMA) therapies, and bispecific antibodies.
CLL: BTK inhibitors (ibrutinib, zanubrutinib, acalabrutinib), monoclonal antibodies (ofatumumab, obinutuzumab), phosphoinositide 3-kinase (PI3K) inhibitor idelalisib, and the BCL-2 inhibitor venetoclax.
In patients with AML receiving venetoclax in combination with hypomethylating agents, both mold- and yeast-active prophylaxis may be considered. Given significant pharmacokinetic interactions, venetoclax dosing should be adjusted as follows: reduced to 25% of the standard dose when combined with posaconazole, and to 50% when combined with fluconazole. For quizartinib (a QT-prolonging CYP3A4 substrate), the dose should be reduced by approximately 50% with posaconazole and by approximately 30% with voriconazole; because both are strong CYP3A4 inhibitors, therapeutic drug monitoring and QTc surveillance are advised. For ivosidenib, concomitant posaconazole should be avoided owing to additive QTc prolongation (this combination is listed as contraindicated in the posaconazole label); when a triazole is unavoidable, ivosidenib should be reduced to 250 mg once daily (a 50% reduction) with close QTc monitoring. In addition, mold-active triazoles (posaconazole, voriconazole) are contraindicated with vincristine-containing regimens—relevant to ALL—because CYP3A4 inhibition markedly potentiates vincristine neurotoxicity; where antifungal prophylaxis is required in this setting, mold-active triazoles are not recommended (D-II) and fluconazole or isavuconazole may be considered with caution (C-III) [1,36,37,38] (Figure 2).

4.1. Any other drug–drug interactions when using posaconazole or voriconazole prophylaxis?

Both agents carry a significant risk of drug-drug interactions, which is generally lower with posaconazole. It is imperative to consult a verified drug-drug interactions database (e.g., Lexicomp, Micromedex) and perform a comprehensive review of all medications including over-the-counter drugs, chemotherapy, immunosuppressants, and antiemetics prior to prescribing [4,29].

4.2. Is therapeutic drug monitoring required during posaconazole or voriconazole prophylaxis?

Despite a lack of controlled studies, therapeutic drug monitoring (TDM) of voriconazole is recommended in the prophylactic setting because of its highly unpredictable pharmacokinetics; a trough concentration of approximately 1–1.5 mg/L is generally targeted for prophylaxis, whereas troughs above 5–6 mg/L are associated with toxicity. The delayed-release tablet and intravenous formulations of posaconazole provide more reliable exposure than the oral suspension; nonetheless, subtherapeutic concentrations may still occur with persistent diarrhea or concomitant interacting drugs, so TDM is advised in these situations, targeting a steady-state trough above 0.7 mg/L for prophylaxis. In contrast to the oral suspension, hypoalbuminemia and mucositis do not meaningfully alter exposure to the delayed-release tablet [39,40].

4.3. When Is Antifungal Prophylaxis Indicated During CD19 CAR-T Cell Therapy?

CD19-directed CAR-T cell therapy is approved for B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma, and is associated with a distinct, time-dependent risk of infection [1,41].
Fungal risk after CAR-T therapy is best considered in two phases. Pre-infusion risk reflects the cumulative burden of prior therapy—relapsed or refractory disease, multiple prior treatment lines, prolonged neutropenia, and previous HSCT. Post-infusion risk is driven by the depth and duration of neutropenia, hypogammaglobulinemia, and above all by the intensity and duration of immunosuppression used to manage cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), particularly corticosteroids and tocilizumab. Consistent with ECIL-10, mold-active prophylaxis is recommended for high-risk patients during both the pre- and post-infusion periods—those with pre-existing prolonged neutropenia, underlying acute leukemia, or grade ≥3 CRS/ICANS requiring corticosteroids for seven days or longer—whereas yeast-active prophylaxis is appropriate for lower-risk patients (B-II). Although invasive mold disease is uncommon after CAR-T therapy, mucormycosis has been increasingly reported and carries high mortality, underscoring the importance of mold-active cover and environmental precautions in the highest-risk patients [1,41].
In addition to appropriate chemoprophylaxis for preventing invasive mold infections, it should not be overlooked that it is crucial to protect patients from all situations that expose them to dust. Awareness in this regard should be increased for both patients and healthcare workers.

5. Approach to Empirical and Diagnostic Test–driven Mold-active Antifungal Treatment in the Neutropenic Patient

5.1. When should invasive fungal disease (IFD) be suspected in a febrile neutropenic patient?

The risk factors for IFD are duration and severity of neutropenia, antibiotic use, and number of treatment cycles, and therefore, IFD is most commonly encountered in the setting of persistent or recurrent fever. Suspicion of IFD develops in high-risk patients with persistent or recurrent fever after 4–7 days of broad-spectrum antibacterial therapy and without an identified source of fever [2,7,42].

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If the expected duration of neutropenia is more than 7 days and the patient is not on mold-active prophylaxis, serum galactomannan (GM) antigen monitoring should be performed at centers, where available, at least twice a week starting on the first day of chemotherapy until resolution of neutropenia. A positive test result should trigger evaluation of the patient for invasive aspergillosis even if there are no signs and symptoms (Figure 3) [2,4,42].
During mold-active prophylaxis, the sensitivity of serum galactomannan is reduced; a negative serum test does not exclude IFD, and galactomannan testing of bronchoalveolar lavage fluid is preferred when clinically feasible [4].

5.2. What imaging studies are recommended for early diagnosis of IFD, and how should they be tailored to clinical symptoms?

In the early stages of infection, clinical features may be non-specific and fever may be the only sign of IFD. In high-risk patients with persistent or recurrent fever, clinical site-specific reassessment, imaging and diagnostic testing for IFD are essential for early diagnosis [2].
A site-specific evaluation should be conducted, including the oral cavity and esophagus; the abdomen, liver, and rectum; the paranasal sinuses; the lungs; the skin, soft tissues, and vascular access sites; the urinary tract; and the central nervous system. The lungs represent the most common site of IFD. In neutropenic patients with fever, thoracic CT scan (low-dose, multislice, multidetector, spiral, high-resolution) should be performed when there are signs or symptoms of lower respiratory tract infection, including cough, shortness of breath, chest pain, and hemoptysis. In addition, because pulmonary IFD is frequently clinically occult in neutropenia, thoracic CT should also be performed in patients with prolonged or persistent/recurrent febrile neutropenia (typically beyond 4–7 days of broad-spectrum antibacterial therapy) even in the absence of respiratory signs or symptoms. An abdominal CT scan (preferred) or ultrasound should be utilized to investigate abdominal pain and/or diarrhea. Laboratory tests should include measurements of transaminases, alkaline phosphatase, and bilirubin levels. If symptoms such as headache, sinus pain, or localized pain radiating to the eye are present, a sinus CT scan and if necessary, an orbital magnetic resonance imaging (MRI) should be performed. Additional symptoms may include sinus tenderness, rhinorrhea, nasal ulcers with black eschar, and palatal ulceration. A cranial CT or MRI should also be considered in the presence of headaches or neurological symptoms [2,5,6].

5.3. What radiological findings are suggestive of pulmonary IFD (e.g., aspergillosis)?

Recent data suggest that high-resolution CT is the preferred imaging modality over chest X-ray, MRI, and positron emission tomography (PET) for diagnosing invasive pulmonary aspergillosis (IPA) and pulmonary mucormycosis in adults. In addition to its role in early diagnosis, CT imaging findings can aid in distinguishing fungal from non-fungal pulmonary infections [5,6].
The primary radiological feature of IPA on CT is the presence of well-circumscribed, rounded or irregular opacities (nodules). Nodules or masses accompanied by ancillary signs, such as the halo sign (a surrounding zone of ground-glass attenuation), are considered more suggestive of IPA [4,5,6].
Less specific and less common findings include bronchopneumonia, consolidation (a homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls, with or without an air bronchogram), pleural-based wedge-shaped consolidations, cavitary lesions, pleural effusions, ground-glass opacities, and the tree-in-bud pattern (centrilobular branching opacities resembling a budding tree). Additional findings include atelectasis, the reversed halo sign (a focal rounded area of ground-glass opacity surrounded by a ring of consolidation), the hypodense sign (a central area of lower attenuation within a nodule or mass), and the air crescent sign (a peripheral crescent-shaped area of cavitation within a nodule or mass). Broncho-invasive forms may manifest as tracheal or bronchial wall thickening [4,5,6].
The presence of nodular or cavitary lesions is highly suggestive of invasive filamentous fungal infections; however, differential diagnoses such as pneumonia caused by *Mycobacterium*, *Nocardia*, *Pneumocystis jiroveci*, or *Pseudomonas aeruginosa* should be considered [4,5,43].
The reversed halo sign is more specific for fungal pneumonia caused by Mucorales, though differential diagnoses including tuberculosis, sarcoidosis, or cryptogenic organizing pneumonia must also be ruled out. Multiple nodules (>10) and pleural effusions are more frequently observed in Mucorales infections. Diffuse bilateral perihilar infiltrates, patchy areas of ground-glass attenuation, cysts, septal thickening, consolidation, and centrilobular nodules are more characteristic of *Pneumocystis jirovecii* pneumonia [4,5,44].

5.4. Which diagnostic tests are required to confirm pulmonary IFD?

While characteristic imaging findings and biomarkers such as serum or bronchoalveolar lavage (BAL) fluid GM levels for aspergillosis are highly suggestive of IPA, definite diagnosis of IFD requires histopathologic examination of sterile biopsy material or growth of the organism in sterile specimens. Every effort must be made to grow the pathogen in culture for species identification and antifungal susceptibility testing [4,6].
In clinical practice, most patients are treated empirically or pre-emptively because of potential risks of biopsy or lack of resources. GM detection in body fluids (especially BAL) is more sensitive than culture for diagnosis of invasive *Aspergillus* (level of evidence: IA). A serum optical density index cut-off of 0.5 demonstrates high sensitivity and negative predictive value for invasive aspergillosis in neutropenic leukemia patients or allogeneic hematopoietic stem cell transplant recipients during the pre-engraftment period who are not receiving mold-active

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prophylaxis. GM in BAL is a good tool to diagnose IPA with a cut-off value 0.5–1.0. Aspergillus polymerase chain reaction (PCR), Aspergillus lateral flow device assay (LFA) and (1→3)-β-D-glucan (BDG) monitoring are alternative diagnostic methods with best results are obtained when GM is combined with another test [4,6].

5.5. What is the treatment approach for suspected pulmonary IFD in neutropenic patients, and how does prophylaxis history influence the choice?

Voriconazole or isavuconazole is recommended as first-line treatment for IPA in neutropenic patients in most international guidelines. Liposomal amphotericin B is an alternative. Diagnosis or suspicion of mucormycosis should prompt surgical debridement in addition to liposomal amphotericin B at 5–10 mg/kg/day, with the higher dose (up to 10 mg/kg/day) reserved for central nervous system involvement. If renal insufficiency precludes amphotericin B, isavuconazole or posaconazole could be administered alternatively [3,4,16,35].

Mold-active antifungal prophylaxis in AML patients undergoing induction chemotherapy has a significant influence in the therapeutic approach. Prophylaxis reduces invasive mold disease, but prolonged exposure may lead to selection of azole-resistant *Aspergillus* strains such as *CYP51A* mutations or non-*Aspergillus* molds (Mucorales, *Fusarium*, etc.). Mold-active prophylaxis may also blunt GM performance, thus decrease its sensitivity. In general, it is recommended to switch to another antifungal class – i.e., from posaconazole or voriconazole to liposomal amphotericin B – when IFD is suspected. If Aspergillus is the likely pathogen (positive GM, imaging features consistent with IPA, and absence of findings suggestive of mucormycosis), and any of the following conditions are present: a) sub-therapeutic serum levels of the azole drug, b) profuse diarrhea during oral azole prophylaxis, or c) prophylaxis duration is less than 7 days, intravenous voriconazole may be initiated or continued [4,16,35,42]. When azole-resistant *Aspergillus fumigatus* (e.g., CYP51A-mediated) is suspected—because of a lack of clinical response despite adequate azole exposure, or in regions with a high prevalence of environmental resistance—antifungal susceptibility testing should be pursued and empirical therapy broadened to another class such as liposomal amphotericin B; a voriconazole minimum inhibitory concentration above the clinical breakpoint warrants a change of therapy [4].

5.6. What clinical signs and symptoms should raise suspicion of fungal sinusitis in neutropenic patients?

Invasive fungal sinusitis (IFS) is a rare infection associated with high morbidity and mortality, primarily caused by *Aspergillus* species and Mucorales. Clinical signs and symptoms are often nonspecific, and delays in diagnosis may result in fatal outcomes [16,45].

The infection typically originates in the paranasal sinuses and can extend to adjacent structures, such as the orbit, eye, brain, and nasal cavity, often through bone destruction. Common symptoms of IFS include fever, nasal congestion, facial pain, sinus tenderness, facial swelling, and rhinorrhea. In early stages, pallor and discoloration in the nasal cavity, as well as necrosis, ulceration, or eschar formation on the nasal septum, may be observed. As the disease progresses, proptosis, palatal or palpebral fistulas, visual disturbances, extraocular muscle weakness, and cranial neuropathies may develop [16,45,46].

Intranasal examination and nasal endoscopy are recommended in cases with suspected IFS. In early stages, if the infection is confined to the nasal cavity, distinguishing it from benign etiologies can be challenging. Direct visualization and biopsy of the involved sinus mucosa, turbinates, or septum using rigid nasal endoscopy play a crucial role in both diagnosis and differential diagnosis [16,45,46].

Imaging is essential for early diagnosis of IFS. Both high-resolution techniques CT and MRI are recommended. While CT is mandatory for the initial evaluation and diagnosis, MRI is more sensitive in detecting early sinus involvement and assessing orbital or intracranial extension. Early CT findings may include sinonasal mucosal thickening, air-fluid levels, and infiltration of the periantral fat. Unilateral opacities should raise suspicion, and in more advanced stages, osseous erosion considered a more specific finding can be identified [16,43].

5.7. What is the initial treatment for suspected fungal sinusitis while awaiting microbiological/pathological results?

The likelihood that *Mucorales* or other non-*Aspergillus* molds are responsible is considerably higher in invasive fungal sinusitis than in pulmonary disease; liposomal amphotericin B is therefore recommended as empirical therapy. In the uncommon setting of a local outbreak of *Aspergillus terreus* or *Aspergillus flavus* in the hospital, voriconazole should be added until culture based diagnosis is finalized [16].

5.8. How should treatment response be monitored, and when should therapy be adjusted or discontinued?

The patient should be assessed daily during the initial phase of antifungal treatment. Symptoms attributable to IFD such as cough, hemoptysis, sinus pain are monitored closely. Fever usually subsides in 5–7 days. A decrease in serum/BAL GM level by >50% suggests a good response in invasive aspergillosis. Imaging studies may be repeated every 3–4 weeks unless there is clinical deterioration. Evolution of the halo sign to air-crescent sign or cavity is common with resolution of neutropenia. If feasible, therapeutic drug monitoring is recommended for voriconazole on days 3–5, and after the dose or formulation is changed, or a potential interacting agent is started or discontinued [3,4,35].

The patient should be switched to another antifungal in case of clinical deterioration (new fever, worsening of symptoms), radiologic progression or persistent positive biomarker levels after at least 2 weeks of therapy, and in

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rare cases suspected of breakthrough infection with another fungi. Combination treatment may be considered for refractory disease.

Duration of antifungal treatment depends on host factors (recovery from neutropenia), clinical response (resolution of symptoms), microbiological response (negative biomarkers), and radiological (stable lesions such as residual scarring or nodules) response. In general, invasive aspergillosis is usually treated for 6–12 weeks (minimum 4 weeks after neutrophil recovery), and mucormycosis much longer (up to 6 months) [3,35].

A multidisciplinary team approach will enhance the likelihood of achieving the best possible treatment response and use the limited resources effectively [47].

6. Conclusion

Antifungal strategies in patients with hematologic malignancies must be individualized according to disease risk, treatment phase, and intensity of immunosuppression. Primary prophylaxis remains essential in high-risk settings such as AML induction and selected allogeneic HSCT scenarios, while unnecessary prophylaxis should be avoided in low-risk populations.

The increasing use of targeted and immune-based therapies has shifted antifungal management toward a more nuanced balance between infection prevention, drug–drug interactions, and toxicity. In this context, diagnostic test–driven approaches supported by early imaging and fungal biomarkers play a critical role in optimizing antifungal therapy.

A structured, risk-adapted framework that integrates prophylaxis, timely diagnostics, and appropriate therapeutic escalation offers the most effective strategy to reduce morbidity and mortality associated with IFDs while preserving antifungal efficacy in modern hematologic care.

In practical terms, high-risk patients—those undergoing AML or high-risk MDS remission-induction (including HMA-based therapy during the first four cycles) and allogeneic HSCT recipients with grade III–IV GVHD on high-dose corticosteroids—warrant mold-active prophylaxis, preferably posaconazole (A-I), with isavuconazole or micafungin (B-II) as alternatives when posaconazole is unsuitable. Intermediate-risk patients generally require only yeast-active prophylaxis with fluconazole, whereas low-risk groups need no prophylaxis. For patients receiving targeted agents, the emphasis shifts from prophylaxis toward the management of triazole drug–drug interactions, while CAR-T recipients are stratified to mold- or yeast-active prophylaxis according to pre- and post-infusion risk. Important evidence gaps remain, including the optimal prophylactic strategy in the eras of hypomethylating and targeted therapy, the role and thresholds of biomarker-driven monitoring during mold-active prophylaxis, and the management of emerging azole resistance. The maturing antifungal pipeline—including agents with novel mechanisms such as olorofim, fosmanogepix, rezafungin, ibrexafungerp, and inhaled opelconazole—may broaden future options, particularly against resistant or difficult-to-treat molds.

Ultimately, antifungal stewardship and individualized, risk-adapted decision-making—rather than uniform blanket prophylaxis—offer the best balance between preventing IFD and limiting toxicity, drug–drug interactions, resistance, and cost [1,47].

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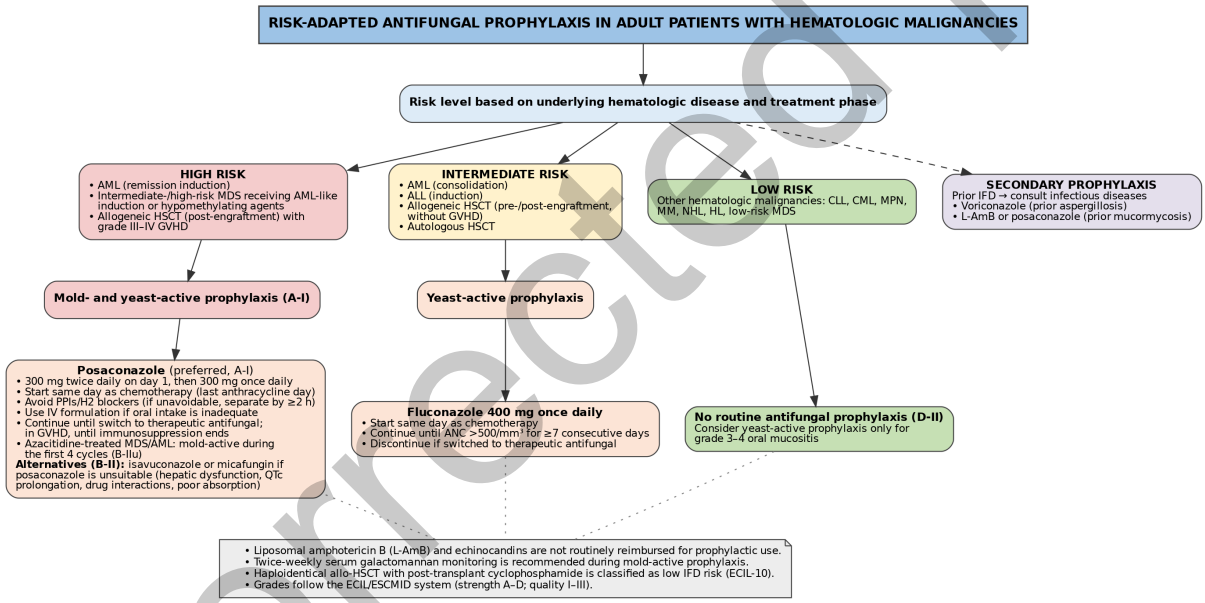


Figure 1. Risk-adapted antifungal prophylaxis in adult patients with hematologic malignancies

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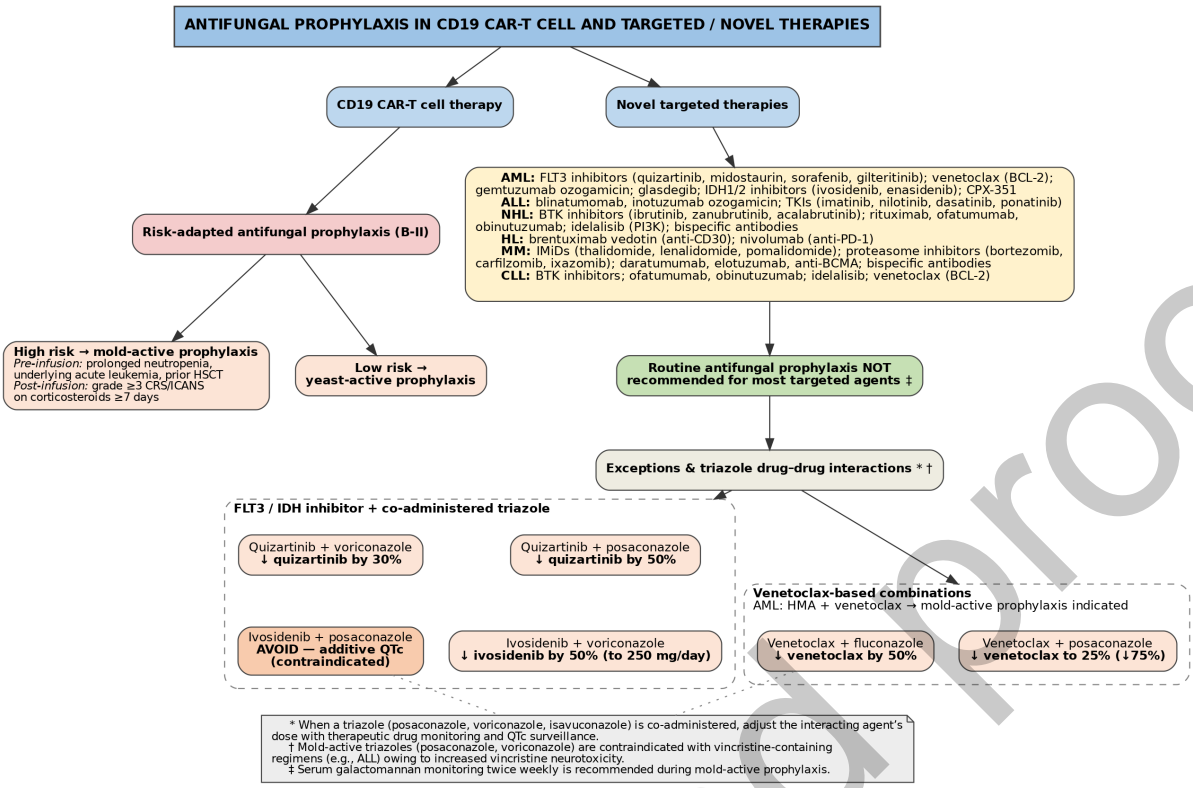


Figure 2. Antifungal prophylaxis algorithm in patients receiving CD19 CAR-T cell therapy or novel targeted agents

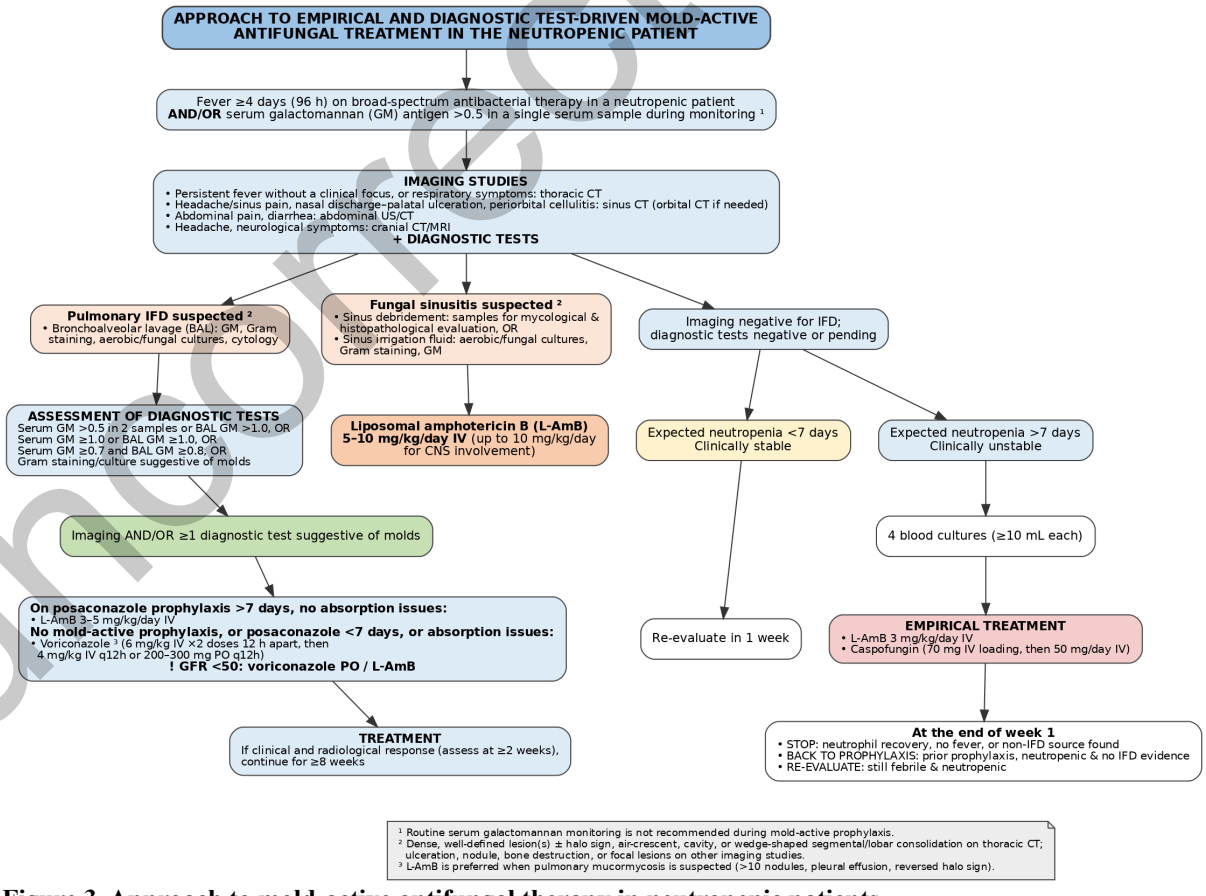


Figure 3. Approach to mold-active antifungal therapy in neutropenic patients

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