IJHOSCR

Review Article

International Journal of Hematology-Oncology and Stem Cell Research

The Iranian National Guideline for Invasive Fungal Infections (IFI) in Hematology–Oncology: An Expert Consensus Report

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Received: 29, Aug, 2025
Accepted: 3, Mar, 2026

ABSTRACT

Invasive fungal infections are a leading cause of death in patients with hematological malignancies and those receiving bone marrow transplants. Although standard guidelines exist globally, their direct application in Iran is not always possible due to differences in the types of common fungi and limited diagnostic and therapeutic facilities. To address this challenge, a national committee of experts in the field was formed to carefully review internationally recognized protocols published up to 2024 and solicit opinions from selected experts across the country to develop the first national guideline specifically for prophylaxis. To ensure methodological rigor, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework and Grading of Recommendations Assessment, Development and Evaluation (GRADE) system were utilized. The resulting consensus established a localized risk-stratification model identifying acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and active graft-versus-host disease (GVHD) patients as high-risk, recommending posaconazole as the primary standard. Notably, the guideline advises against routine azole use in acute lymphoblastic leukemia (ALL) to prevent neurotoxicity. Furthermore, a resource-tiered framework was developed for centers with varying diagnostic capabilities. The result of this effort was to present a tiered and local model that provides a practical solution for both well-equipped and limited facilities. The existence of this national guideline creates a major advantage in that treatment approaches are unified and standardized across the country. By eliminating discretionary decisions, this document helps to better manage medication use and ultimately improve patient outcomes, regardless of the city in which they are treated or the facilities they are treated at.

Keywords: Clinical guideline; Consensus report; Hematological malignancies; Invasive fungal infections; Prophylactic management

DOI: http://doi.org/10.18502/ijhoscr.v20i2.21783

INTRODUCTION

In Iran, invasive fungal infections (IFIs) are not only associated with a high mortality rate of 58.3% to 62.7% in patients with hematological malignancies (HM) and hematopoietic stem cell transplant (HSCT) recipients 1,2 but also directly impair the prognosis of the underlying disease by imposing significant morbidity and causing frequent interruptions in chemotherapy cycles. These alarming statistics, consistent with global trends[3], indicate the heavy clinical and economic burden of IFIs to the country's health system[4]. Although internationally recognized clinical guidelines such as the Infectious Diseases Society of America (IDSA) and European Conference on Infections in Leukemia (ECIL) guidelines are available as valuable scientific resources[5,6], their direct application in Iran is suboptimal due to local challenges and requires a localized approach.

There are two main obstacles to the direct use of these guidelines in Iran. First, resource and infrastructure constraints pose challenge – an issue also reported in other resource-limited health systems[7]. Inconsistent access to non-culture diagnostic methods, such as serum galactomannan assays, as well as to new and expensive antifungal drugs (such as lipid formulations of amphotericin B and echinocandins), renders many standard global recommendations impractical[8,9]. Second, and more importantly, are epidemiological differences. While in Europe, Aspergillus fumigatus is the most common cause of invasive aspergillosis (44.1%)[10], several studies in Iran show that Aspergillus flavus is the predominant cause of the disease[11,12]. The species variation is clinically significant, as A. flavus can exhibit a different antifungal susceptibility profile and be associated with a more aggressive disease[12].

In addition to these challenges, the inherent complexity of clinical decision-making—including choosing among multiple treatment options with varying efficacy, side effects, and drug-drug interaction profiles—reinforces the need for clear, evidence-based guidance for Iranian physicians.

In the absence of a national standard, these inconsistencies have led to wide variation in critical clinical decisions—including choice of prophylactic agent, timing of empirical therapy, and diagnostic algorithms—directly contributing to adverse patient outcomes. Recognizing this critical gap, a multidisciplinary panel of Iranian experts initiated the development of the first national clinical guideline. As a national initiative, the process of achieving this consensus and the key recommendations are presented to provide a standardized, evidence-based, and localized framework aimed at guiding clinical decision-making and ultimately improving the quality of patient care across the country.

MATERIALS AND METHODS

A core group of 11 members, including experts from medical mycology, clinical pharmacy, infectious diseases, and hematology-oncology, was responsible for developing the national guideline. Before starting the process, all core members completed conflict of interest forms. To ensure a rigorous and transparent methodology, the steering committee followed the principles of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) standard throughout.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was also used to assess the quality of the articles and determine the strength of the recommendations[14]. According to the GRADE approach, the quality of evidence was evaluated based on study design, risk of bias, inconsistency, indirectness, and imprecision, while the strength of recommendations was determined by balancing desirable and undesirable effects, patient values, and resource use. The consensus process was carried out in several specific steps. Initially, the core group conducted a comprehensive search of databases such as PubMed, Scopus, Embase, and Web of Science (ISI), as well as guideline reference sites (such as ECIL and IDSA), to identify internationally recognized protocols published up to 2024. The search strategy utilized a combination of main keywords and MeSH terms, including "Invasive Fungal Infections," "Hematological Malignancies," "Hematopoietic Stem Cell Transplantation," "Prophylaxis," and "Clinical Guideline." Based on this review, an initial draft of the recommendations was prepared. This draft was then sent to a larger group of selected experts across the country for initial feedback. The experts submitted written comments on the applicability

and practicality of these recommendations in the Iranian context. After collecting comments, the core group of 11 members held a consensus meeting. Then, all comments were discussed and the draft was revised based on the collective agreement of the members. For greater certainty, the revised text was sent back to the external reviewers for their final comments. Finally, after the final comments were implemented and approved by the core group members, the guideline was finalized for publication.

RESULT

Expert Panel and Consensus Achievement

The steering committee successfully completed the localization process and produced a consensus-based national guideline. After carefully evaluating international reference guidelines, the panel held several rounds of discussion on challenging issues. Ultimately, high consensus was reached on all recommendations, ensuring the guideline is scientifically robust and aligned with the Iranian healthcare infrastructure. The panel specifically limited the guideline's scope to antifungal prophylaxis for adult and pediatric patients with HM and for HSCT recipients. Therefore, solid organ transplant recipients and general ICU patients were excluded to preserve the guideline's specialist focus.

Consensus on Risk Stratification

One of the main outcomes was the adoption of a localized risk stratification model. The panel unanimously agreed that patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) who are receiving intensive chemotherapy, as well as allogeneic transplant recipients with active graft-versus-host disease (GVHD), are in the high-risk group and definitely require mold prophylaxis. In contrast, standard autologous transplant recipients and lymphoma patients were classified as low-risk. For this group, the panel recommended a preemptive (diagnosis-driven) approach instead of routine prophylaxis, unless a specific risk factor, such as severe mucositis, is present.

Adaptation of Prophylactic Regimens

The guideline adjusted the drug algorithms according to the country's drug realities. Posaconazole was approved as the standard of care for high-risk groups. However, taking into account the potential for drug shortages, the panel also approved voriconazole as a valid alternative. Additionally, liposomal amphotericin B was considered a bridging option in cases of azole intolerance. An important consensus was reached regarding patients with acute lymphoblastic leukemia (ALL). To reduce the risk of severe neurotoxicity due to azole interactions with vincristine, the guideline strongly recommended that routine use of antifungal azoles be avoided and that fluconazole be used with caution. The use of echinocandins was also limited to specific circumstances (e.g., high infection rates in the ward). In addition, specific protocols were developed for patients receiving new immunomodulators (e.g., Bruton tyrosine kinase [BTK] inhibitors), with prophylaxis recommended only in the presence of additional risk factors.

Secondary Prophylaxis Protocol

The panel established a clear pathway for secondary prophylaxis in patients with a history of fungal infection who require chemotherapy or retransplantation. The panel agreed that prophylaxis should be continued throughout the period of immunosuppression. Importantly, drug selection should be based on the type of prior pathogen and the patient's response to initial treatment, specifically to prevent relapse.

Resource-Based Implementation Framework

Given the differences in diagnostic capabilities across the country, the guideline adopted a resource-led approach. For centers with advanced diagnostic capabilities (such as rapid biomarker assays and therapeutic drug monitoring [TDM]), targeted prophylaxis was recommended. However, for centers without immediate access to these tools, the panel determined that broad-spectrum prophylaxis (with anti-mold coverage) should be used to ensure that the inability to monitor closely does not compromise outcomes in high-risk patients.

Table 1 summarizes the localized prophylactic recommendations and risk stratification

Table 1: Summary of localized prophylactic recommendations and risk stratification for invasive fungal infections

Category / Clinical Scenario	Risk Level	Recommended Prophylactic Strategy	Key Considerations / Local Adaptations
AML, MDS, Allogeneic HSCT with active GVHD	High-Risk	Primary: Posaconazole Alternative: Voriconazole Bridging (Azole intolerance): Liposomal Amphotericin B	Recommended universally due to intensive immunosuppression.
Autologous HSCT, Lymphoma	Low-Risk	Diagnosis-based approach (routine prophylaxis not recommended).	Consider prophylaxis only if a specific risk factor exists (e.g., severe mucositis).
ALL	Variable	Avoid routine use of antifungal azoles; use fluconazole with caution. Echinocandins limited to specific circumstances (e.g., high ward infection rates).	Specifically adapted to prevent severe neurotoxicity from azole-vincristine interactions.
Patients on Novel Immunomodulators (e.g., BTK inhibitors)	Conditional	Prophylaxis conditional on the presence of additional risk factors.	Individualized clinical assessment required.
Secondary Prophylaxis (Prior Fungal Infection)	High-Risk	Targeted prophylaxis based on the prior pathogen's susceptibility and initial treatment response.	Must be continued throughout the entire period of immunosuppression to prevent relapse.
Centers with Advanced Diagnostic Capabilities (Rapid biomarkers, TDM)	N/A	Targeted prophylaxis based on close monitoring.	Optimizes resource use and limits unnecessary drug exposure.
Resource-Limited Centers (Lacking rapid diagnostic tools)	N/A	Broad-spectrum prophylaxis with anti-mold coverage.	A critical adaptation to prevent the loss of high-risk patients when close monitoring is unavailable.

AML: Acute Myeloid Leukemia; **MDS:** Myelodysplastic Syndromes; **HSCT:** Hematopoietic Stem Cell Transplantation; **GVHD:** Graft-versus-Host Disease; **ALL:** Acute Lymphoblastic Leukemia; **BTK:** Bruton Tyrosine Kinase; **TDM:** Therapeutic Drug Monitoring

DISCUSSION

The primary purpose of this guideline was to create a local, evidence-based framework for preventing IFIs in patients with HM and to develop a structured approach for the prophylactic management of HSCT recipients in Iran. The framework included reliable and practical algorithms for risk stratification, primary prophylaxis, and secondary prophylaxis, based on epidemiological data, antifungal resistance patterns, and economic and administrative considerations specific to various regions of the country. An additional purpose of this guideline was to standardize clinical preventive approaches nationally, while also optimizing resource use and ultimately improving patient outcomes.

Because of localization, the Iranian guideline has notable differences from international guidelines such as IDSA, ECIL, and the National Comprehensive Cancer Network (NCCN), both in the structure and content of the recommendations. The guideline endorsed posaconazole and liposomal amphotericin B as preferred alternatives while also providing considerations for the increased emergence of *A. flavus*. A hierarchy of medications was developed based on availability. For instance, a critical adaptation was introduced for ALL patients to prioritize patient safety by avoiding neurotoxic drug interactions. The guideline defined at-risk populations and provided specific recommendations for subgroups such as haploidentical transplant recipients and patients with chronic GVHD.

Furthermore, a resource-based approach was established, creating distinct pathways for centers with advanced diagnostic capabilities versus those requiring empirical strategies, a key adaptation to national infrastructure disparities. Finally, the secondary prophylaxis section included type of drug and duration of therapy.

In particular, a number of aspects of the guideline are noteworthy because they focus on risk-adapted prophylaxis algorithms tailored for patients with hematological malignancies and bone marrow transplant recipients in Iran. The panel also drew on local antifungal susceptibility data and made recommendations that are sensitive to local resources. In addition, cost-effectiveness was incorporated into the guideline, providing practical suggestions for the optimal use of limited prophylactic resources available within Iran's healthcare system. Interdisciplinary teamwork and

stakeholder engagement were invaluable in aligning clinical practice with health policy and insurance coverage. It is also noteworthy that programs and methodologies such as GRADE-ADOLOPMENT (developed by the GRADE Working Group) and the EORTC/MSGERC consensus guidelines emphasize adapting global guidelines to local contexts without compromising methodological quality[15]. These standards were taken into account during the development of the Iranian guideline.

Furthermore, the guideline proposed the establishment of a national registry system for fungal infections, which facilitates the identification of patterns of antifungal resistance and changing epidemiology. Such a system could be used to update the guideline regularly based on local clinical practice and observed outcomes. In particular, it would significantly shape recommendations to reflect real-world clinical practice and pharmaceutical availability in the country.

The key challenges encountered included limited access to local epidemiological data (which led to careful interpretation of the evidence and emphasized the need for further research) and financial and infrastructure limitations, which affected both the established guideline objectives and anticipated implementation. Potential conflicts of interest for panel members were managed through transparency and disclosure. Some resistance to change and varied levels of awareness among health professionals were anticipated as barriers to guideline uptake, but these were addressed over time through education and system-level interventions.

CONCLUSION

In conclusion, this national guideline is a critical step toward standardizing the prevention of invasive fungal diseases for high-risk hematology patients in Iran. This document provides a practical and reliable framework, specifically adapted to local resources, drug availability, and epidemiological data—unlike many international guidelines that are not fully applicable. The success of the guideline now depends on its effective implementation across the country. Periodic updates based on local data, ideally collected through the proposed national registry, will also be essential.

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