Article

Not peer-reviewed version

Real-World Outcomes of Antifungal Prophylaxis in Adult Acute Lymphoblastic Leukemia: A Multicenter Comparison of Fluconazole and Micafungin

Unal Atas , Utku Iltar * , Orhan Kemal Yucel , Hasan Salur , Merve Cagla Bilek , Tayfun Ustabas , Ozlem Candan , Gulten Korkmaz , Selin Kucukyurt , Pinar Tiglioglu , Sureyya Yigit Kaya , Burak Deveci , Atakan Tekinalp , Rafiye Ciftciler , Aysun Senturk Yikilmaz , Tayfun Elibol , Tayfur Toptas , Ahmet Kursad Gunes , Omur Gokmen Sevindik , Leylagul Kaynar , Rabin Saba , Isik Atagunduz , Gulsum Ozet , Volkan Karakus , Ozan Salim , Erdal Kurtoglu , Levent Undar

Posted Date: 3 September 2025

doi: 10.20944/preprints202509.0283.v1

Keywords: acute lymphoblastic leukemia; antifungal prophylaxis; fluconazole; micafungin; invasive fungal infection

 doi:10.20944/preprints202509.0283.v1

Article

Real-World Outcomes of Antifungal Prophylaxis in Adult Acute Lymphoblastic Leukemia: A Multicenter Comparison of Fluconazole and Micafungin

Running Title: Fluconazole vs Micafungin in Adult ALL

Unal Atas [1], Utku Iltar [1,*], Orhan Kemal Yucel [1], Hasan Salur [2], Merve Cagla Bilen [1], Tayfun Ustabas [3], Ozlem Candan [4], Gulten Korkmaz [5], Selin Kucukyurt [6], Pinar Akyol Tiglioglu [7], Sureyya Yigit Kaya [8], Burak Deveci [9], Atakan Tekinalp [10], Rafiye Ciftciler [11], Aysun Senturk Yikilmaz [12], Tayfun Elibol [13], Tayfur Toptas [4], Ahmet Kursad Gunes [6], Omur Gokmen Sevindik [8], Leylagul Kaynar [8], Rabin Saba [9], Isik Atagunduz [4], Gulsum Ozet [5], Volkan Karakus [3], Ozan Salim [1], Erdal Kurtoglu [3] and Levent Undar [1]

[1] Akdeniz University, Faculty of Medicine, Division of Hematology
[2] Antalya City Hospital, Department of Internal Medicine
[3] Health Sciences University, Antalya Training and Research Hospital, Division of Hematology
[4] Marmara University, Faculty of Medicine, Division of Hematology
[5] Ankara Bilkent City Hospital, Division of Hematology
[6] Ankara Etlik City Hospital, Division of Hematology
[7] Istanbul Medeniyet University, Faculty of Medicine, Division of Hematology
[8] Istanbul Medipol University, Faculty of Medicine, Division of Hematology
[9] Antalya Bilim University, Faculty of Medicine, Division of Hematology
[10] Necmettin Erbakan University, Faculty of Medicine, Division of Hematology
[11] Selcuk University, Faculty of Medicine, Division of Hematology
[12] Denizli State Hospital, Division of Hematology
[13] Göztepe Prof Dr Suleyman Yalcin City Hospital, Division of Hematology
* Correspondence: utq_07@hotmail.com; Tel.: +90 5068522473; Fax: + 90- 242 249 64 80

Abstract

Background: Adult acute lymphoblastic leukemia (ALL) patients are at increased risk of invasive fungal infections (IFIs) due to intensive therapy and prolonged neutropenia. While pediatric guidelines support fluconazole or mold-active agents, evidence in adults is limited. This study presents the first multicenter retrospective comparison of fluconazole and micafungin in this setting. **Methods:** We retrospectively analyzed 336 adult ALL patients from 11 centers in Türkiye (2010–2024) who received fluconazole (n=230) or micafungin (n=106) during induction chemotherapy. IFIs were classified according to EORTC/MSG criteria. **Results:** The median age was 38.5 years, and 38.7% were female. Proven/probable IFIs occurred in 8.9% of patients, with similar rates between fluconazole and micafungin groups (8.7% vs. 9.4%; p=0.82). Multivariate analysis confirmed no significant association between prophylactic antifungal type and IFI incidence, indicating comparable outcomes across groups. Median prophylaxis duration was longer with fluconazole, while discontinuation rates, switch patterns, and subsequent antifungal use were comparable. Overall infection rates (~60%) and distribution of bacterial, viral, and polymicrobial infections were similar between the two groups. Prior bacterial infection increased IFI risk 2.7-fold, and IFI-positive patients had longer neutropenia. At induction end, remission, refractory, and mortality rates were similar between groups. The median overall survival was 24 months. **Conclusion:** Fluconazole and micafungin showed similar efficacy as primary antifungal prophylaxis in adult ALL. In accordance with current guidelines, these agents may be preferable to mold-active triazoles, with selection best guided by institutional aspergillosis risk, potential drug–drug interactions, and cost considerations. Prospective randomized trials are warranted to confirm these findings.

 doi:10.20944/preprints202509.0283.v1

Keywords: acute lymphoblastic leukemia; antifungal prophylaxis; fluconazole; micafungin; invasive fungal infection

1. Introduction

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in patients with acute leukemias and in those undergoing allogeneic hematopoietic stem cell transplantation (HSCT). The introduction of newer antifungal classes, such as broad-spectrum triazoles and echinocandins, appears to have significantly reduced mortality. In a pediatric acute lymphoblastic leukemia (ALL) study, the 5-year cumulative incidence of infection-related mortality was 2.4%, accounting for 30% of all deaths; of these, ~70% were attributable to bacteria and ~20% to IFIs. [1] In ALL patients, the reported incidence of IFIs ranges from 4% to 18%, comparable to rates observed in acute myeloid leukemia (AML). [2–6] Despite methodological differences and heterogeneous patient populations, the reported incidence of IFIs in pediatric and adult ALL patients appears to be within a similar range. [3–6] Pediatric guidelines recommend primary antifungal prophylaxis in high-risk patients, with fluconazole advised in centers with a low incidence of invasive mold infections due to its efficacy against *Candida* species. [7] Evidence on the efficacy of antifungal prophylaxis in adult patients remains limited and heterogeneous. Prophylaxis is generally not recommended for those receiving tyrosine kinase inhibitors (TKIs) therapy alone, although fluconazole may be cautiously considered in standard-risk patients to prevent *Candida* infections. In high-risk patients, particularly those with prolonged neutropenia following intensive chemotherapy, mold-active agents such as liposomal amphotericin B or echinocandins may be considered; however, current literature provides no definitive evidence of clear clinical benefit in this setting. [2]

In ALL patients, the heightened risk of *Candida* infections, together with the increased susceptibility to mold infections in high-risk subgroups, underscores the need to determine the optimal choice of antifungal prophylaxis. [5,7] Echinocandins are active against most *Candida* species, including *C. krusei* and *C. glabrata*, which are frequently resistant to fluconazole, and exert fungicidal activity against *Pneumocystis jirovecii* and fungistatic effects against *Aspergillus* species. While these features make them appealing for prophylaxis in ALL patients, current evidence remains insufficient to recommend their routine use in this setting. [3,8] Prospective and retrospective studies comparing mold-active agents (e.g., voriconazole, micafungin, caspofungin) with non–mold-active agents (e.g., fluconazole) have been conducted primarily in pediatric patients undergoing ASCT or diagnosed with AML. [2,7] A meta-analysis of these studies suggested that mold-active prophylaxis was more effective than fluconazole in preventing IFIs, but without a significant impact on overall survival (OS). Moreover, these agents carry specific drawbacks, including toxicity, drug–drug interactions, and high cost. [9]

However, evidence in adults is limited and heterogeneous, and recommendations are often extrapolated from pediatric cohorts. While fluconazole has been the traditional choice due to its activity against *Candida*, echinocandins such as micafungin offer broader coverage and fewer drug–drug interactions, yet their routine use remains unsupported by strong evidence. In adult ALL, the choice of primary antifungal prophylaxis remains unclear, with practice varying across institutions. To address this gap, we conducted the first multicenter retrospective study directly comparing fluconazole and micafungin as primary prophylaxis during induction therapy in adult ALL. This study also evaluated overall infection incidence, treatment outcomes, and survival, providing real-world evidence to guide prophylaxis strategies in this high-risk population.

2. Material and Method

Between January 2010 and December 2024, archival records of patients diagnosed with ALL at 11 centers across Türkiye were retrospectively reviewed. Adult patients (aged ≥18 years) with a confirmed diagnosis of ALL who had received at least one cycle of intensive induction chemotherapy

 doi:10.20944/preprints202509.0283.v1

and were administered either fluconazole or micafungin as primary antifungal prophylaxis were included in the study. Patients were excluded if they did not receive antifungal prophylaxis, received agents other than fluconazole or micafungin, or had incomplete or missing clinical records. The study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine and was conducted in accordance with the principles outlined in the Declaration of Helsinki and all applicable regulations (Ethics committee date and approval number: 16.02.2022/KAEK-22).

For each patient, the following data were collected: age, sex, comorbidities, performance status, date of diagnosis, ALL subtype, Philadelphia (Ph) chromosome status (and the TKIs used if Ph-positive), induction regimen, antifungal agent used for prophylaxis, baseline leukocyte and neutrophil counts, duration of neutropenia, occurrence of fungal infection during induction, duration and discontinuation status of antifungal prophylaxis, post-induction remission status, receipt of consolidation therapy, autologous HSCT status, disease status at last follow-up, survival status, and OS time. Neutropenia was defined as absolute neutrophil count (ANC) $<1 \times 10^9$/L, and its duration as the cumulative number of days below this level during follow-up. OS was defined as the time from diagnosis to last follow-up or death.

IFIs were classified according to the criteria established by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG), which are widely adopted in clinical studies to standardize definitions among immunocompromised populations such as those in hematology-oncology cohorts. Based on these criteria, IFIs are categorized as proven, probable, or possible depending on the combination of host factors, clinical features, and mycological evidence. Proven IFI requires histopathologic or microbiological confirmation; probable IFI includes the presence of host risk factors, consistent clinical signs, and mycological findings; while possible IFI includes compatible clinical findings and host factors in the absence of mycological evidence. In accordance with conventional methodology in prospective or randomized trials, only proven and probable cases were considered IFI-positive in this study. [10]

The primary objective was to compare the incidence of IFIs and the rate of prophylaxis discontinuation or switching to another antifungal agent between patients who received fluconazole and those who received micafungin as primary prophylaxis. The secondary objective was to evaluate the current incidence and distribution of infections in ALL patients, assess clinical responses based on recent treatment approaches, and determine OS outcomes.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed with the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables as median (min–max). Categorical variables were reported as frequencies and percentages. Group comparisons were conducted using the independent samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normal distributions. Categorical variables were analyzed using Pearson's Chi-square test, Fisher's exact test, likelihood ratio, or linear-by-linear association where appropriate. For multiple comparisons, the Benjamini–Hochberg false discovery rate (FDR) correction was applied.

Time to infection during induction therapy was evaluated using the Kaplan–Meier method according to the type of antifungal prophylaxis, and survival curves were compared with the log-rank test. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient Demographics, Clinical Features, and Treatment Characteristics

A total of 336 patients were included, with a median age of 38.5 years (range, 18–86), and 130 (38.7%) were female. At least one comorbidity was present in 62 patients (18.5%), most commonly hypertension (10.1%) and diabetes mellitus (7.7%). ECOG performance status was available for 279

 doi:10.20944/preprints202509.0283.v1

patients, of whom 241 (71.7%) had a score of 0–1. The median duration of neutropenia during induction was 16 days (range, 0–55), with 297 patients (88.4%) experiencing neutropenia ≥10 days.

Overall, 80% of patients had B-cell ALL, and the HyperCVAD regimen was the most commonly used treatment protocol (225 patients; 66.9%). Eighty-six patients (25.6%) had Philadelphia chromosome–positive ALL and all received TKI-based therapy during induction (imatinib in 57 [16.7%], dasatinib in 31 [9.2%]).

Primary antifungal prophylaxis consisted of fluconazole in 230 patients (68.4%) and micafungin in 106 patients (31.6%). Compared with fluconazole, patients in the micafungin group were older (median 40 vs. 36 years, p=0.016) and more frequently had ECOG 0–1 performance status (97.4% vs. 82.2%, p<0.001). Treatment distribution also differed, with HyperCVAD used more frequently in the micafungin group (77.4% vs. 62.2%), while adult asparaginase-containing protocols were more common in the fluconazole group (14.8% vs. 3.8%; p=0.003). Details of baseline demographic, clinical, laboratory, and induction treatment characteristics are presented in Table 1.

3.2. Antifungal Prophylaxis and Infectious Complications

The median duration of prophylactic antifungal use in the cohort was 24 days (range, 5–110). No IFI was observed in 286 patients (85.1%), possible IFI occurred in 20 (5.9%), and 30 patients (8.9%) developed IFI (23 probable, 7 proven). HRCT revealed findings compatible with fungal infection in 28 patients (8.3%), and serum Aspergillus antigen was positive in 7 (2.1%). Prophylaxis was discontinued in 51 patients (15.2%), with amphotericin B (51.0%) and voriconazole (37.3%) being the most frequent alternatives. Antifungal characteristics and IFI status are summarized in Table 2.

Non-fungal infections occurred in 208 patients (61.9%). Bacterial infections were the most common (30.9% of all patients), while viral infections were rare (1.8%). Mixed infections occurred in 17 patients (5.0%). Infection sites were documented in 113 patients, with the respiratory tract (11.9%), bloodstream/catheter (6.5%), and urinary tract (3.9%) as the leading foci. Microbiological confirmation was obtained in 39.4% of infection cases, most frequently *Escherichia coli* (22 patients), *Staphylococcus spp.* (16 patients), and *Klebsiella spp.* (13 patients). IFIs were microbiologically proven in 7 patients (4 *Candida*, 3 *Aspergillus*). Except for *SARS-CoV-2* in 5 patients and *respiratory syncytial virus* in 1 patient, no other viral pathogens were confirmed.

3.3. Antifungal Prophylaxis and Infectious Characteristics by Group

The duration of prophylaxis was longer with fluconazole (25 vs. 21 days; p=0.003), but discontinuation rates and subsequent antifungal switches were comparable between groups. The incidence of proven/probable IFI was similar (8.7% vs. 9.4%; p=0.82), and no significant difference was observed in time to IFI development (Table 2).

With respect to non-fungal infections, the overall infection rate was similar between groups (~60%; p=0.29). The distribution of bacterial, viral, fungal, and polymicrobial infections did not differ significantly (p=0.95). However, subgroup analyses revealed some differences in infection patterns: respiratory tract infections were more frequent in the fluconazole group (48.6%), while urinary tract infections (15.0%) and multi-site infections (20.0%) were more common in the micafungin group (likelihood ratio test: χ^2=15.668, df=8, p=0.047; Fisher's Exact test: p=0.026, Monte Carlo 99% CI: 0.022–0.030).

3.4. Predictors of Invasive Fungal Infection

The incidence of IFI did not differ by age (≥65 vs. <65 years, 10.7% vs. 8.9%; p=0.44), ALL subtype, treatment regimen, or Ph chromosome status. IFI rates across treatment groups were 10.7% in HyperCVAD, 8.2% in pediatric-inspired protocols, 2.6% in adult asparaginase-containing regimens, and 0% in low-intensity regimens (p=0.272).

Patients with bacterial infection had a significantly higher incidence of IFI compared to those without infection (16.7% vs. 6.6%; p=0.008). Similarly, IFI-positive patients had a significantly longer

 doi:10.20944/preprints202509.0283.v1

neutropenia duration than IFI-negative patients (23.6 ± 9.8 vs. 16.6 ± 7.6 days; p<0.001). As the majority of patients had neutropenia lasting ≥10 days, the risk of IFI appeared similar between ≥10 and <10 days (9.4% vs. 5.6%, p=0.44); however, ROC analysis identified 15 days as the optimal cut-off, with neutropenia ≥15 days conferring a 5.4-fold higher risk (AUC=0.719; p<0.001; OR=5.36; 95% CI: 1.83–15.75). In contrast, prophylactic antifungal type, duration of prophylaxis, and baseline leukocyte counts were not associated with IFI risk.

In univariate logistic regression, prolonged neutropenia duration and presence of bacterial infection were significantly associated with IFI development, while age, sex, comorbidity, ECOG performance, ALL subtype, Ph positivity, and prophylactic antifungal type were not predictive (all p>0.05). In the multivariate model, including the entire cohort, both prolonged neutropenia and bacterial infection were identified as independent predictors of IFI. Each additional day of neutropenia increased the risk of IFI by approximately 9% (OR=1.09; 95% CI: 1.04–1.13; p<0.001). Patients with concurrent bacterial infections had a 2.5-fold higher risk of IFI compared to those without (OR=0.40; 95% CI: 0.18–0.88; p=0.023, reverse-coded). The overall model was significant (χ^2=22.3, p<0.001), with a Nagelkerke R^2 of 0.14, indicating moderate explanatory power (Table 3).

Table 3. Univariate and multivariate logistic regression analysis of factors associated with IFI development.

Variable	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Sex (Female vs. Male)	1.43 (0.68–3.05)	0.349	–	–
Age at diagnosis	1.01 (0.99–1.03)	0.370	–	–
Philadelphia chromosome (Ph+ vs. Ph–)	0.87 (0.36–2.11)	0.759	–	–
Comorbidity (Yes vs. No)	0.90 (0.35–2.30)	0.819	–	–
White blood cell counts at diagnosis	1.00 (1.00–1.00)	0.301	–	–
Prophylactic antifungal (Fluconazole vs. Micafungin)	0.91 (0.41–2.03)	0.825	–	–
Duration of induction neutropenia (days)	**1.09 (1.05–1.13)**	**<0.001**	**1.09 (1.04–1.13)**	**<0.001**
Bacterial infection (Yes vs. No)	**0.35 (0.16–0.76)**	**0.008**	**0.40 (0.18–0.88)**	**0.023**
ECOG performance status (0–1 vs. 2–4)	0.52 (0.16–1.69)	0.279	–	–
ALL subtype (B-ALL vs. T-ALL)	0.68 (0.26–1.77)	0.423	–	–

Abbreviations: IFI, invasive fungal infection; OR, odds ratio; CI, confidence interval; Ph, Philadelphia chromosome; ECOG, Eastern Cooperative Oncology Group; ALL, acute lymphoblastic leukemia. A p-value <0.05 was considered statistically significant. Variables with p<0.10 in univariate analysis entered into multivariate model.
The final model was significant (χ^2=22.3, p<0.001) with a Nagelkerke R^2 of 0.14, indicating moderate explanatory power. While overall classification accuracy was 91.0%, the sensitivity for IFI-positive patients remained low (3.3%).

3.5. Treatment Responses, Disease Course, and Survival Outcomes

Of 318 evaluable patients, 265 (78.9%) achieved remission, 40 (11.9%) had refractory disease, and 13 (3.9%) died before response assessment, including 9 infection-related deaths (1 fungal). Response rates were comparable between the fluconazole and micafungin groups (remission: 83.6% vs. 82.7%; refractory: 11.8% vs. 14.3%; death: 4.5% vs. 3.1%; p=0.70).

During the disease course, 126 patients (37.5%) developed relapse or refractory disease, and 157 (46.7%) underwent allogeneic HSCT. At last follow-up, 91 (27.1%) had active disease and 181 (53.9%) had died, including 72 infection-related deaths (7 due to IFIs). The median OS was 24 months (range, 1–170).

Multivariate Cox regression identified age (HR=1.035; 95% CI: 1.018–1.052; p<0.001), relapse/refractory disease (HR=0.492; 95% CI: 0.338–0.717; p<0.001), and T-ALL subtype (HR=0.597;

 doi:10.20944/preprints202509.0283.v1

95% CI: 0.364–0.980; p=0.041) as independent predictors of OS, while prophylactic antifungal type was not associated with survival outcomes.

4. Discussion

This multicenter retrospective study is the first to directly compare fluconazole and micafungin as primary antifungal prophylaxis during induction therapy in adult ALL patients. IFI occurred in 8.9% of patients, and the incidence was similar between the fluconazole and micafungin groups. The median prophylaxis duration was longer with fluconazole, but discontinuation, switch rates, and subsequent antifungal use were similar. No associations were found with age, ALL subtype, Ph-positivity, or treatment protocol, whereas prior bacterial infection increased IFI risk 2.7-fold, and IFI was linked to longer neutropenia.

ALL patients are at increased risk of IFI due to disease-related factors such as prolonged neutropenia, intensive polychemotherapy, and corticosteroid use. [2,3,5] Direct comparison of IFI risk between adult and pediatric ALL is not appropriate because of differences in age, comorbidities, and genetic background. [11] Unlike pediatric ALL, where IFI risk is considered low, data in adults are limited, and some studies report incidences similar to AML in the absence of mold-active prophylaxis. [3,8,12] The role of mold-active prophylaxis in ALL has not been well established, as evidence relies mainly on retrospective studies. [11] While fluconazole is widely used in children, its adequacy in adults is questioned, and although echinocandins provide extended activity, their high cost and lack of oral formulations restrict routine use. [8]

Reported IFI incidence in pediatric and adult ALL ranges between 4–18%, [2–6] which is consistent with our findings. Additionally, IFI incidence among adults treated with pediatric-inspired regimens was 8.2%, similar to that reported in pediatric cohorts. [4–6] In a large pediatric study of 6,136 patients, the induction and consolidation phases, older childhood/adolescence, and poor initial response to therapy were identified as the highest-risk settings for IFI. [5] In adults, a study of 83 patients (83% receiving liposomal amphotericin B or posaconazole prophylaxis) showed no difference in IFI incidence between HyperCVAD (4%), BFM95 (15%), and Hoelzer (9%) protocols. [13] Similarly, in our cohort, IFI rates were comparable across HyperCVAD (10.2%), adult asparaginase-containing regimens (2.6%), and pediatric-inspired regimens (8.2%). Previous studies reported that IFI was associated with prolonged and profound neutropenia, whereas a simple 10-day threshold was not predictive. [5,6,12] Similarly, in our cohort, baseline neutrophil count and neutropenia ≥10 vs. <10 days were not significantly different; indeed, as the majority of patients had neutropenia ≥10 days (n=297, 88.4%), this cut-off lacked discriminatory power. In contrast, prolonged neutropenia was associated with higher risk, and ROC analysis identified 15 days as the optimal cut-off, with patients experiencing ≥15 days of neutropenia having a 5.4-fold higher incidence of IFI. These findings suggest that in the current era of routine primary antifungal prophylaxis, neutropenia lasting 15 days or more may represent a more relevant risk factor for IFI. Consistent with earlier reports, most IFIs were mold-related and originated from the respiratory tract, [4,6] and the incidence of IFI was also higher among patients who experienced bacterial infections.

Different antifungals have been evaluated for IFI prophylaxis across various hematologic malignancies, particularly in pediatric patients. [14–18] Two randomized controlled trials in pediatric and adult allo- and auto-HSCT recipients compared fluconazole with micafungin, showing higher prophylactic success with micafungin but no differences in proven/probable IFI, overall mortality, or fungal-related death; micafungin was also better tolerated in both studies. [14,15] A trial comparing micafungin with fosfluconazole, a phosphate prodrug of fluconazole, in pediatric malignancy and HSCT patients demonstrated comparable efficacy and safety. [16] Prophylactic amphotericin B did not provide superiority over placebo. [17] Additionally, in an another pediatric acute leukemia study (68% ALL), low-dose amphotericin B was compared with oral voriconazole, and no difference was found in proven or probable IFI incidence. [18] A meta-analysis of 20 studies reported that mold-active antifungals, including echinocandins, reduced the risk of IFI and IFI-related mortality compared with fluconazole, but this benefit did not translate into improved OS, and the risk of

 doi:10.20944/preprints202509.0283.v1

adverse events leading to discontinuation or modification was higher with other azoles. However, all included studies were conducted in HSCT recipients and/or patients with various hematologic malignancies, and none focused exclusively on ALL. [9]

In adult ALL, no randomized trials have evaluated antifungal prophylaxis, and available data are largely retrospective. In one study of 98 patients, 83 received primary prophylaxis during induction or consolidation, most commonly with liposomal amphotericin B (65%), posaconazole (18%), or fluconazole (8%). IFI occurred in 6% of prophylaxis recipients compared with 26.6% of those without prophylaxis. [13] In another retrospective study of 103 adult ALL patients, fluconazole and mold-active triazoles showed similar overall IFI incidence (17.6% vs. 15.9%), though mold-active triazoles tended to reduce invasive aspergillosis (11.8% vs. 1.4%; p=0.07). [19] In a study of 65 adult patients with acute leukemia, including 31 (47%) with ALL, IFI was reported in 3 patients (4.6%) under micafungin prophylaxis, one of whom had ALL. [20] In our study, which included a substantially larger cohort, the incidence of proven/probable IFI during induction was 9.4% among 106 adult ALL patients receiving micafungin prophylaxis, and 8.9% overall across the fluconazole and micafungin groups (n=336). Collectively, these findings indirectly suggest that fluconazole or micafungin may represent more suitable options for primary antifungal prophylaxis in adult ALL compared with amphotericin B or other triazoles, which carry higher risks of toxicity and drug interactions.

In summary, the risk of mold-active IFI is lower in pediatric ALL compared with AML and allogeneic HSCT, and the predominance of *Candida* infections makes fluconazole still a reasonable option. In adult ALL, however, a higher risk of mold-active IFI has been reported, although the available evidence remains limited. Overall, data on antifungal prophylaxis in adult ALL are insufficient and inconsistent. In line with the literature, both the European Conference on Infections in Leukaemia (ECIL) and the Infectious Diseases Working Party (AGIHO) recommend antifungal prophylaxis for patients receiving chemotherapy, except for those treated with TKIs monotherapy. Due to toxicity and drug–drug interactions, triazoles (voriconazole, posaconazole) are not generally favored, while fluconazole is considered safer despite limited adult data. Micafungin may be considered an alternative based on limited evidence, whereas liposomal amphotericin B is not recommended for prophylaxis because of suboptimal efficacy and toxicity concerns. [2,21]

This study has several limitations. First, its retrospective design may have introduced selection and reporting bias, and some relevant clinical data could not be uniformly captured across all participating centers. Second, treatment protocols were heterogeneous, reflecting real-world practice but limiting the ability to control for potential confounders. Third, although the logistic regression model was statistically significant, its explanatory power was modest (Nagelkerke R^2=0.14), and the sensitivity for identifying IFI-positive patients remained low (3.3%), indicating that additional unmeasured factors likely contributed to IFI risk. Finally, the results may not be generalizable to settings with different epidemiological profiles or institutional practices. Prospective, randomized trials are warranted to validate these findings.

In conclusion, in this first multicenter analysis of adult ALL, fluconazole and micafungin showed comparable efficacy as primary antifungal prophylaxis. Prolonged neutropenia and bacterial infections, but not antifungal type, were identified as independent predictors of IFI. These findings support the continued use of fluconazole or micafungin in this setting, with agent selection best guided by local epidemiology, drug interactions, and cost considerations.

Funding: There was no funding in conjunction with the preparation of this manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202509.0283.v1

References

1. O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. *Blood*. 2014;124(7):1056-1061. doi:10.1182/blood-2014-03-560847
2. Pagano L, Maschmeyer G, Lamoth F, et al. Primary antifungal prophylaxis in hematological malignancies. Updated clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL). *Leukemia*. Published online April 9, 2025. doi:10.1038/s41375-025-02586-7
3. Bhatt VR, Viola GM, Ferrajoli A. Invasive Fungal Infections in Acute Leukemia. *Ther Adv Hematol*. 2011;2(4):231-247. doi:10.1177/2040620711410098
4. O'Reilly MA, Govender D, Kirkwood AA, et al. The incidence of invasive fungal infections in children, adolescents and young adults with acute lymphoblastic leukaemia/lymphoma treated with the UKALL2011 protocol: a multicentre retrospective study. *Br J Haematol*. 2019;186(2):327-329. doi:10.1111/bjh.15798
5. Lehrnbecher T, Groll AH, Cesaro S, et al. Invasive fungal diseases impact on outcome of childhood ALL – an analysis of the international trial AIEOP-BFM ALL 2009. *Leukemia*. 2023;37(1):72-78. doi:10.1038/s41375-022-01768-x
6. Yeoh DK, Blyth CC, Clark JE, et al. Invasive fungal disease and antifungal prophylaxis in children with acute leukaemia: a multicentre retrospective Australian cohort study. *Lancet Reg Health – West Pac*. 2024;52. doi:10.1016/j.lanwpc.2024.101201
7. Groll AH, Pana D, Lanternier F, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol*. 2021;22(6):e254-e269. doi:10.1016/S1470-2045(20)30723-3
8. Dvorak CC, Fisher BT, Sung L, et al. Antifungal Prophylaxis in Pediatric Hematology/Oncology: New Choices & New Data. *Pediatr Blood Cancer*. 2012;59(1):21-26. doi:10.1002/pbc.23415
9. Ethier MC, Science M, Beyene J, Briel M, Lehrnbecher T, Sung L. Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patients receiving chemotherapy or haematopoietic stem-cell transplantation: a systematic review and meta-analysis of randomised controlled trials. *Br J Cancer*. 2012;106(10):1626-1637. doi:10.1038/bjc.2012.147
10. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2008;46(12):1813-1821. doi:10.1086/588660
11. Stafylidis C, Diamantopoulos P, Athanasoula E, Solomou E, Anastasopoulou A. Acute Lymphoblastic Leukemia and Invasive Mold Infections: A Challenging Field. *J Fungi*. 2022;8(11):1127. doi:10.3390/jof8111127
12. Oh SM, Byun JM, Chang E, et al. Incidence of invasive fungal infection in acute lymphoblastic and acute myelogenous leukemia in the era of antimold prophylaxis. *Sci Rep*. 2021;11:22160. doi:10.1038/s41598-021-01716-2
13. Doan TN, Kirkpatrick CMJ, Walker P, et al. Primary antifungal prophylaxis in adult patients with acute lymphoblastic leukaemia: a multicentre audit. *J Antimicrob Chemother*. 2016;71(2):497-505. doi:10.1093/jac/dkv343

 doi:10.20944/preprints202509.0283.v1

14. van Burik JAH, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2004;39(10):1407-1416. doi:10.1086/422312
15. Hiramatsu Y, Maeda Y, Fujii N, et al. Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. *Int J Hematol*. 2008;88(5):588-595. doi:10.1007/s12185-008-0196-y
16. Sawada A, Sakata N, Higuchi B, et al. [Comparison of micafungin and fosfluconazole as prophylaxis for invasive fungal infection during neutropenia in children undergoing chemotherapy and hematopoietic stem cell transplantation]. *Rinsho Ketsueki*. 2009;50(12):1692-1699.
17. Cornely OA, Leguay T, Maertens J, et al. Randomized comparison of liposomal amphotericin B versus placebo to prevent invasive mycoses in acute lymphoblastic leukaemia. *J Antimicrob Chemother*. 2017;72(8):2359-2367. doi:10.1093/jac/dkx133
18. Mandhaniya S, Swaroop C, Thulkar S, et al. Oral voriconazole versus intravenous low dose amphotericin B for primary antifungal prophylaxis in pediatric acute leukemia induction: a prospective, randomized, clinical study. *J Pediatr Hematol Oncol*. 2011;33(8):e333-341. doi:10.1097/MPH.0b013e3182331bc7
19. Wang Y, Xing Y, Chen L, et al. Fluconazole versus mould-active triazoles for primary antifungal prophylaxis in adult patients with acute lymphoblastic leukemia: clinical outcome and cost-effectiveness analysis. *Int J Hematol*. 2018;107(2):235-243. doi:10.1007/s12185-017-2342-x
20. Park H, Youk J, Shin DY, et al. Micafungin prophylaxis for acute leukemia patients undergoing induction chemotherapy. *BMC Cancer*. 2019;19(1):358. doi:10.1186/s12885-019-5557-9
21. Mellinghoff SC, Panse J, Alakel N, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Ann Hematol*. 2018;97(2):197-207. doi:10.1007/s00277-017-3196-2