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The Evaluation of Invasive Fungal Infections in Patients with Hematological Malignancy

Selda Aydın, Ali Mert, Recep Öztürk

Department of Infectious Diseases and Clinical Microbiology, İstanbul Medipol University Medical Faculty, İstanbul, Türkiye

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What is already known on this topic?

- *The incidence and mortality of invasive fungal infections (IFIs) have markedly declined due to advances in diagnostic tools, as well as optimized antifungal prophylaxis and therapeutic strategies.*

What does this study add on this topic?

- *This study highlights the achievements and advancements in IFIs by tracing their evolution from the pre-2010 era, when diagnostic and treatment opportunities were limited, to the present day.*

Abstract

Objective: Invasive fungal infections (IFIs) are a major complication in patients with hematological malignancies, leading to significant morbidity and mortality. This study aimed to evaluate the epidemiological, clinical, and microbiological perspective of IFIs in febrile neutropenic patients with hematologic malignancies.

Methods: This prospective study was conducted in the hematology unit of a 1709-bed university hospital between April 2008 and December 2010. Among 727 hospitalized patients with hematological malignancies, 168 febrile neutropenic patients with suspected IFIs were followed during the study period. Diagnostic evaluation included blood cultures, galactomannan antigen testing, high-resolution computed tomography, respiratory tract, and other sampling. Samples were evaluated as microbiological and pathological in terms of IFI.

Results: Hundred out of 168 patients (59.5%, n = 100/168) were diagnosed with IFIs, corresponding to an incidence of 13.8%. Mold infections predominated (86%, n = 86/100), with invasive pulmonary aspergillosis accounting for the majority of cases, while candidemia represented the leading cause of proven infections (76.4%, n = 13/17). Less common pathogens included Fusarium spp., Trichosporon spp., and Pneumocystis jirovecii. The overall 30-day mortality rate was 54%, with the highest case fatality observed in probable and proven IPA.

Conclusion: This study highlights the substantial burden and high mortality associated with IFIs in patients with hematological malignancies during the 2008-2010 period, prior to widespread antifungal prophylaxis and advanced diagnostics. Despite recent progress leading to lower incidence and improved survival, IFIs remain a critical clinical challenge. Early diagnosis and optimized antifungal strategies are essential to improving outcomes in this patient population.

Keywords: Febrile neutropenia, galactomannan antigen test, hematological malignancy, invasive fungal infections, invasive pulmonary aspergillosis

Introduction

Invasive fungal infections (IFIs) represent a major complication in patients with hematological malignancies, significantly impairing treatment outcomes and contributing to increased morbidity and mortality.[1] A recent systematic review and meta-analysis of 34 publications before and after 2010 reported that the incidence of IFIs was 9.96% in patients receiving allogeneic stem cell transplantation, 5.22% in patients receiving induction-remission chemotherapy, and 3.39% in patients receiving autologous stem cell transplantation.[2] Early diagnosis and treatment of IFIs are critical to preventing adverse clinical outcomes. Diagnosis relies on a combination of histopathological, microbiological, and imaging methods. Diagnostic tools such as the galactomannan (GM) antigen test, beta-D-glucan test, and polymerase chain reaction (PCR) assay have been shown to facilitate earlier detection.[3]

The present study aimed to investigate the epidemiological, clinical, and microbiological perspective of IFIs in febrile neutropenic patients with hematologic malignancies. This article was derived

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Corresponding author: Selda Aydın, Department of Infectious Diseases and Clinical Microbiology, İstanbul Medipol University Medical Faculty, İstanbul, Türkiye **e-mail:** seldaaydin@medipol.edu.tr
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from my thesis study, which was presented in 2011 and discussed with current literature data.

Methods

Study Design

This study was conducted prospectively in the hematology unit of a university hospital with a capacity of 1709 beds between April 2008 and December 2010. This study was carried out in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Ethical approval for this study was obtained from İstanbul University Cerrahpaşa Medical Faculty's clinical research ethics committee (Date: April 7, 2008; Approval No.: 9424).

Patient Population

Patients aged ≥18 years who developed IFIs during the febrile neutropenia following chemotherapy or allogeneic stem cell transplantation were included in the study. In this study period, patients who underwent allogeneic stem cell transplantation received fluconazole to prevent IFIs, as well as trimethoprim-sulfamethoxazole to prevent *Pneumocystis jirovecii* infection. Informed consent was obtained from the patients.

Definitions

- Neutropenic fever: Defined as a single oral temperature ≥38.3°C (101°F) or ≥38.0°C (100.4°F) sustained for ≥1 hour, combined with an absolute neutrophil count <500/μL, or <1000/μL with a predicted decline to <500/μL within 48 hours.[4]
- Candidemia: At least 1 positive blood culture for *Candida* spp.
- Invasive Pulmonary Aspergillosis (IPA): Classified as possible, probable, or proven according to

  European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) definitions.[5]

- Mortality was defined as all-cause 30-day mortality after IFI diagnosis.

Diagnostic Procedures

- Blood cultures for fungemia were obtained. Also, respiratory tract sampling (sputum, endotracheal aspirate, bronchoalveolar lavage [BAL]) was performed when indicated. Tissue samples from suspected foci (e.g., skin, sinuses) were collected for culture and pathology.
- For IPA, GM testing was performed twice weekly on serum samples using the Platelia Aspergillus EIA kit (Bio-Rad Laboratories, France). A threshold of ≥0.5 optical density index (ODI) in 2 consecutive tests was considered positive.
- High-resolution computed tomography (HRCT) was used as an imaging method.

Microbiological Evaluation

Blood culture samples were processed using an automated system (BacT/Alert; BioMérieux, France). Positive cultures were Gram-stained and subcultured on Sabouraud dextrose agar (Oxoid, UK). Yeasts were identified using CHROMagar Candida (CHROMagar Candida, France), germ tube testing, and the API 32C identification kit (bioMérieux, France). Molds were identified based on macroscopic and microscopic morphology in lactophenol cotton blue preparations.

Statistical Analysis

Statistical analyses were performed using the SPSS 16.0 program (SPSS Inc., Chicago, IL, USA). Findings were summarized using descriptive statistics (numbers and percentages).

Results

During the study period, 727 patients with hematological malignancies were hospitalized. A total of 168 febrile neutropenic patients with clinical suspicion of IFIs were included in the analysis. The median age was 47.3 years (range: 18-74), 64.3% (n = 108/168) were male, and 56% (n = 96/168) had acute leukemia. Patient characteristics are summarized in Table 1.

During follow-up, 100 out of 168 patients (59.5%, n = 100/168) were diagnosed with IFI. When based on hospitalized patients, the overall incidence of IFIs was determined to be 13.8% (N = 100/727) in this study period. The defining algorithm of IFIs is presented in Figure 1. Mold infections accounted for 86% (n = 86/100), and yeast infections for 14% (n = 14/100). Based on EORTC/MSG 2008 criteria, 40% (n = 40/100) of IFI cases were classified as possible IPA, 43% (n = 43/100) as probable IPA, and 17% (n = 17/100) as proven IFIs. Candidemia was the leading cause of proven IFI at 76.4% (n = 13/17).

Microbiological findings are summarized in Table 2. Notably, *Fusarium* spp. were isolated from 2 patients, *Aspergillus* spp. from 1, *Trichosporon* spp. from 1, and *P. jirovecii* was identified by direct fluorescent antibody in BAL samples from 2 patients. Galactomannan antigen test was found positive in 51.8% (n = 43/83) of patients with HRCT findings. Figure 2 presents the ODI values in serum samples from patients with positive galactomannan test.

The 30-day mortality rate was 54% (54/100). Case fatality rates were 22.5% (n = 9/40) in possible IPA, 76.7% (n = 33/43) in probable IPA, and 70.5% (n = 12/17) in proven IFIs.

Discussion

Incidence and Mortality

This study demonstrated an overall IFIs incidence of 13.8% in patients with hematological malignancies, with mold infections,

Table 1. Characteristics of Febrile Neutropenic Patients with Clinical Suspicion of Invasive Fungal Infections

Median age, years (min-max)	47.3 (18-74)	
Sex (F/M)	60/108	
Mean duration neutropenia, days (min-max)	24.3 (5-210)	
Underlying diseases	Patient no.	%
Acute leukemia	96	56
Lymphoma	32	18
Multiple myeloma	20	12
Chronic lymphocytic leukemia	9	5
Others	11	6.5
HSCT/Autologous	14	8
HSCT/Allogeneic	15	9
Total	168	100

HSCT, hematopoietic stem cell transplantation.

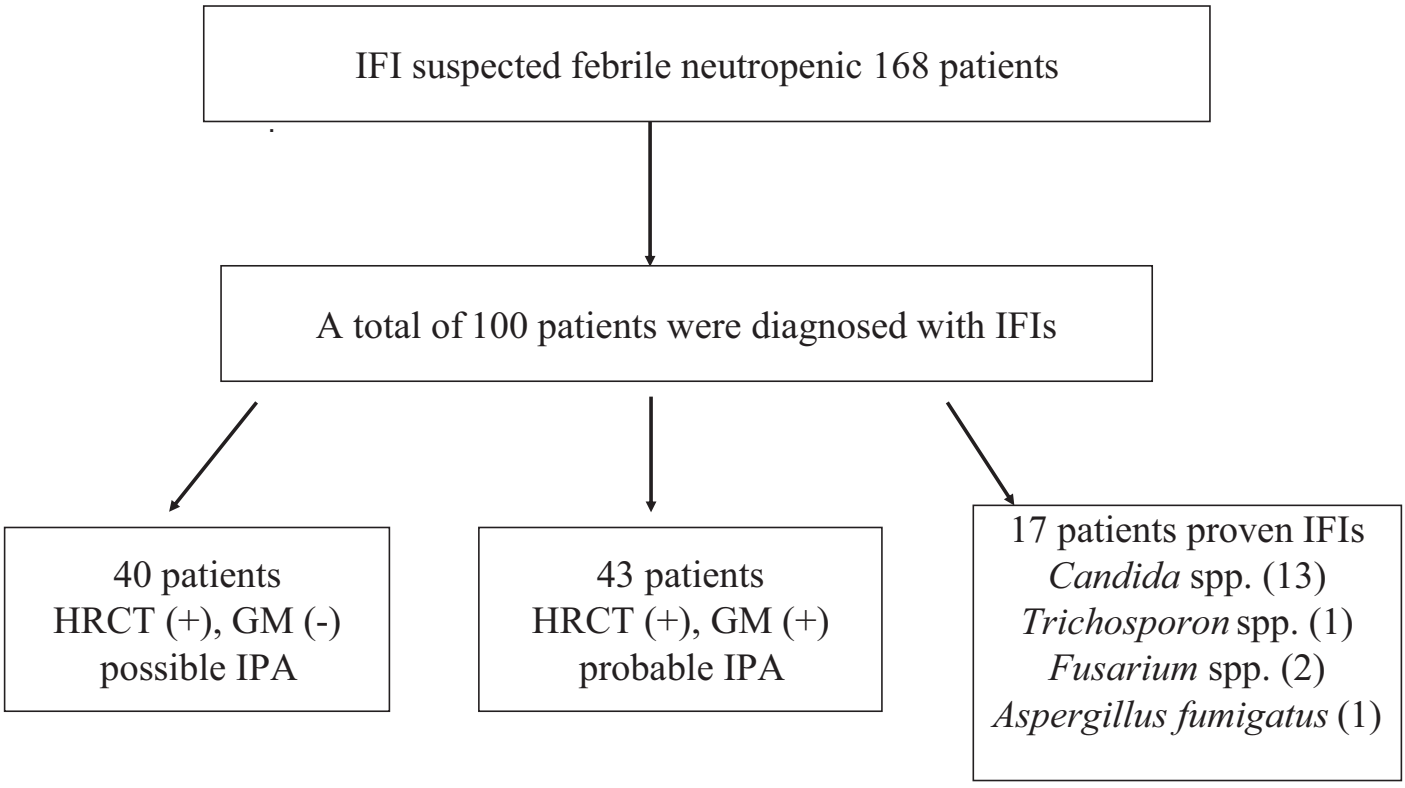

Figure 1. Flow chart of patients with invasive fungal infection.

particularly invasive aspergillosis, predominating. Mortality remained high at 54%.

Although the data reflect the 2008-2010 period, it is noteworthy that more recent studies report significantly lower IFI incidence (<5%) due to widespread use of antifungal prophylaxis.[2,6] These findings are consistent with earlier reports from the same decade, prior to the widespread implementation of mold-active prophylaxis.[7-9]

At the beginning of the century, IFIs-related mortality was as high as 50% in neutropenic patients and reached up to 90% in hematopoietic stem cell transplantation recipients.[10,11] In this cohort, the overall mortality rate was 54%, while mortality among patients with probable or proven IFIs reached 75%. These findings are consistent with outcomes reported during that period, when limited diagnostic tools and restricted antifungal treatment options were considered to contribute to poor survival.[8,11] In contrast, recent data suggest a notable reduction in invasive aspergillosis-related mortality, most likely due to earlier diagnosis and the availability of more effective and better-tolerated antifungal agents.[12,13]

The incidence and mortality estimate from this study should be interpreted in the context of uncommon mold-activated prophylaxis and limited diagnostic tools (no access to β-D-glucan, fungal PCR) during 2008-2010.[8,10,11] Recent studies conducted in centers with routine implementation of mold-active prophylaxis and rapid diagnostic tools report markedly lower IFI incidences (<5%) and reduced mortality rates (17.6%-37%).[12,14-16] This historical dissimilarity explains the discrepancy between these findings and the current literature. This improvement in the historical course of the IFI is indicative of advances in antifungal therapy, diagnostic modalities, and preemptive treatment strategies.

Table 2. Microbiological Results of Clinical Samples

Samples	Agent
Blood culture	*Aspergillus* spp.* (1) *Fusarium* spp. (1) *C. albicans* (4) Non-albicans *Candida* (9) *Trichosporon* spp. (1)
Tissue culture	*Fusarium* spp.[#] (2)
Respiratory tract samples (sputum (11), endotracheal aspiration (1), bronchoalveolar lavage (2))	*Aspergillus* spp. (12) *Pneumocystis jirovecii* [$](2)

*Aspergillus spp. was cultured from the blood, sputum, and urine of 1 patient.
[#]Fusarium sp. was cultured from both the blood and tissue of 1 patient.
[$]Coinfection, it was determined in bronchoalveolar lavage by direct fluorescent antibody staining assay.

Microbiological Data

Proven IFIs cases were mainly due to candidemia, with non-albicans *Candida* species predominating. This is consistent with both historical and recent surveillance data, suggesting a shift in epidemiology related to antifungal prophylaxis practices.[17,18]

In the patient with acute myeloid leukemia (AML), *Aspergillus fumigatus* was isolated from blood, sputum, and urine cultures. The isolation of Aspergillus from blood cultures is an occurrence of great rarity. In instances where it is observed, it is indicative of profound immunosuppression with a high fungal burden. In AML and post–hematopoietic stem cell transplantation, intensive chemotherapy–related, deep and prolonged neutropenia is the principal risk factor for invasive aspergillosis. *Aspergillus* fungemia has been documented in medical literature, albeit infrequently.[19,20] The contemporaneously grown *A. fumigatus* from multiple different

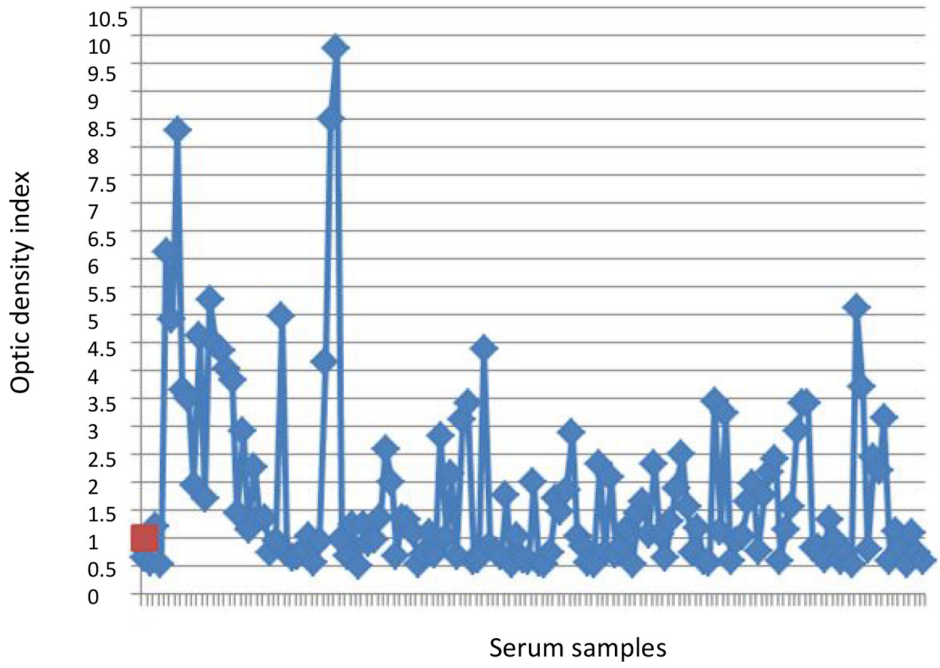

Figure 2. Galactomannan antigen test optical density index distribution.

samples gives rise to significant concern regarding disseminated disease as opposed to colonization.

Previous studies have reported the sensitivity of the GM assay to range between 0.48 and 0.79, depending on the selected cut-off value, with values between 0.78 and 0.79 when the threshold was set at ≥0.5.[21] At the time this study was initiated in 2008, the GM test had only recently been introduced, and no consensus existed regarding the optimal cutoff. Therefore, the manufacturer's recommended threshold of 0.5 was adopted. In this cohort, the rate of GM positivity was relatively low (51.8%), which was primarily attributed to the empirical antifungal treatment approach in patients suspected of having IFIs in the center. This likely reduced fungal burden and consequently lowered the diagnostic yield of the assay. Although these findings support the utility of GM antigen testing and HRCT in IFIs diagnosis. Also, incorporating β-D-glucan assays and fungal PCR, as recommended in recent guidelines, may enhance diagnostic sensitivity and specificity.[3,22,23]

This study has several limitations that should be acknowledged. First, it was conducted at a single center, which may limit the generalizability of the findings to other institutions with different patient populations, treatment protocols, and antifungal prophylaxis strategies. Second, the study period (2008-2010) reflects an earlier era in antifungal therapy; therefore, these results may not fully represent the current epidemiology and clinical outcomes of IFIs in hematological malignancies. Third, the sample size was relatively small, which may have reduced the statistical power to detect outcomes. Fourth, diagnostic tools available during the study period were limited, as fungal PCR and β-D-glucan assays were not routinely performed, possibly leading to underdiagnosis or misclassification of IFIs cases. Finally, the observational design precludes establishing causal relationships between risk factors and outcomes.

The current findings, based on data collected between 2008 and 2010, underscore the substantial burden and high mortality associated with IFIs in patients with hematological malignancies. Although significant advances in recent years have led to improved outcomes, IFIs remain an important clinical challenge in this vulnerable population.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the İstanbul University-Cerrahpaşa, Faculty of Medicine, Clinical Research Ethical Committee (Approval No.: 9424; Date: April 7, 2008).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.A.; Design – S.A.; Supervision – A.M., R.Ö; Resources – S.A.; Materials – S.A.; Data Collection and/or Processing – S.A.; Analysis and/or Interpretation – S.A.; Literature Search – S.A., R.Ö.; Writing – S.A.; Critical Review – A.M., R.Ö.

Declaration of Interests: The authors have no conflict of interest to declare.

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