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Changes in the Spectrum and Prognosis of Invasive Fungal Diseases in Czech, Slovak, and Croatian Hematology Centers from 2000 to 2023 – FIND Analysis

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Background
Invasive fungal diseases (IFDs) are an important cause of morbidity and mortality in patients with hematological diseases. The epidemiology and prognosis of IFDs in this group of severely immunocompromised patients has changed substantially during the last two decades.

Aims
To map the development of the spectrum and prognosis of IFDs diagnosed at hematology centers in the Czech Republic, Slovakia, and Croatia, and entered into the FIND (Fungal Infection Database) registry, managed by the Czech Leukemia Study Group for Life (CELL).

Methods
A retrospective analysis was conducted on the epidemiology, diagnosis, treatment, and prognosis of invasive aspergillosis (IA), invasive candidiasis (IC), and rare IFDs diagnosed from 2000 to 2023 among hematology patients. Probable and proven IFDs, based on the 2020 EORTC/MSG criteria, were included in the study.

Results

A total of 794 probable and proven IA cases (75% probable IA), 293 IC cases (84% candidemias), and 138 cases of rare IFDs (62% invasive mucormycosis, IM) were documented. Following the introduction of posaconazole (POSA) prophylaxis for high-risk acute myeloid leukemia (AML) patients, the absolute proportion of IA decreased over time, while the relative number of rare IFDs increased in breakthrough infections. The frequency of IA in intensively treated AML patients decreased from 21% to 14%. Breakthrough infections were associated with a higher mortality attributed to IFDs compared to non-

breakthrough infections (43% vs. 28%, p<0.001). Galactomannan (GM) from bronchoalveolar lavage (BAL) fluid maintained a high positivity rate (86%), but the proportion of positive serum GM decreased with POSA prophylaxis (74% to 50%, p<0.001). GM from BAL was performed in 77% of IA cases with negative serum GM (160/208) and proved a high positivity rate in 90% of BAL samples (144/160). In recent years, the rate of Candida non-albicans species, particularly *Nakaseomyces glabratus*, has increased, however, the diagnosis of IC increasingly relied on the 1,3-beta-D-glucan test. The diagnosis of rare IFDs was more frequently based on PCR results (50% of cases recently). For IA, the efficacy of first-line targeted antifungal therapy was 57% with VORI +/- echinocandins. The treatment response rate (RR) for IM improved over time (29% to 65%, p=0.002). Overall mortality attributed to IFDs was 37% for IA, 17% for IC, and 59% for IM, with a decreasing trend in IM mortality over the study period (78% to 36%, p=0.001). Not only in IA cases, RR and mortality were associated with the absolute neutrophil (NEU) count at the end of targeted therapy (NEU ≤0.1 vs. NEU ≥1.0 x 10^9/L: RR: 21% vs. 76% / Mortality: 72% vs. 23%; p<0.001).

Summary/Conclusion

Our study confirmed a shift in the spectrum of causative pathogens towards rare IFDs in relation to POSA prophylaxis and a poor prognosis for breakthrough IFDs. Galactomannan, particularly from bronchoalveolar lavage fluid, remains the gold standard for IA diagnosis. The prognosis of IM has improved, primarily due to the optimization of PCR diagnosis and therapy. Management of neutropenia plays a key role in prognosis.

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