Defining Invasive Fungal Infection Risk in Hematological Malignancies: A New Tool for Clinical Practice

Keywords: Hematological Malignancy; Fungal Infections; Infection Risk.

Dear Editor,

Invasive fungal infections (IFIs) represent an important cause of morbidity and mortality in patients affected by hematological malignancies (HMs), particularly those with an immunocompromised status.\(^1,2\) In this setting, IFIs still represents a major clinical problem also for the high costs related to the antifungal prophylaxis and treatment.\(^3,4\) When considering the high clinical heterogeneity of these patients, the risk of IFIs may be remarkably different. Accordingly, if such a risk is not appropriately evaluated, the possibility of an overtreatment in some or an undertreatment in other patients is very likely.

Pagano et al., on behalf of SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne) group, recently published a systematic review of the literature on the risk and incidence of IFIs in the setting of HMs with the aim to consider the main predisposing factors and to suggest practical strategies for prevention and treatment of IFIs.\(^5\) In this review, specific IFI predisposing factors are summarized for each disease class. Depending on the risk of developing IFIs, patients are then divided into three groups: high, intermediate, low-risk group. Briefly, patients with acute myeloid leukemia (AML) or treated with an allogeneic hematopoietic stem cell transplantation (HSCT) have per se an increased risk of IFI. Moreover, some conditions predispose a high risk of IFI, independently of the underlying disease, like neutropenia, relapse/refractory disease, previous history of IFI, salvage therapy and a high dose of steroids.

To facilitate the reading of this analysis and to estimate in each patient the IFI specific risk, we here propose a practical consultation tool composed of a table where risk categories, their related risk factors, and the HMs, are reported and matched (Table 1, part 1 and 2). This estimated risk stratification was developed correlating each disease class with the variables risk factors, categorized according to patient’s features, underlying comorbidities, immunity status, environmental factors, neutropenic status, disease and therapy or transplant’s procedures.

By this approach, each box of the table represents a matching of a specific disease with a specific risk factor. Red boxes, expressing a high risk (HR) of IFI, are used to indicate a reported incidence of IFI above 5%; yellow boxes, expressing an intermediate risk (IR) of IFI, are used to indicate a reported incidence of IFI of 2-5%; green boxes, expressing low risk (LR) of IFI, are used to indicate a reported incidence of IFI minor of 2%. In the case of lacking data, the boxes are white.

Looking at the colored boxes, people can read this table from two different points of view, by focusing on the risk categories or vice versa on the specific HM. In general, the horizontal reading of the table highlights the principal IFI risk factors, regardless of the underlying disease. In particular, red boxes appear to be associated with a long history of HM, with a relapse or refractory disease, a prolong neutropenia, older age, predisposing polymorphisms, pulmonary comorbidities, intense chemotherapy and prolong used of steroids. Some of these risk factors are routinely screened in the clinical practice, others, like predisposing genetic polymorphisms, are used only in experimental setting, but look promising. On the other hand, the vertical reading of the table highlights the disease mostly associated with IFI, in particular, AML and patients undergoing HSCT.

It should be underlined that each disease may present one or more risk factors and that the risk factors may vary during the course of illness and due to the type of treatments. For this reasons, it is important to follow the patient over time, with a dynamic score,
evaluating the presence or absence of risk factors, with the aim to start or withdrawn an appropriate antifungal prophylaxis or treatment. In this setting, this table allows a rapid consultation in the clinical practice.

In conclusion, this IFI’s risk table may represent a useful and simple tool to assess over time the risk of developing IFI in patients with HMs and may help to plan an appropriate antifungal stewardship.

Table 1 (part 1). IFI risk table: risk categories and their related risk factors are reported in the first and second column of the table, respectively; the HMs are listed in the first row of the table.

| Categories      | Risk Factors                                                                 |
|-----------------|------------------------------------------------------------------------------|
| **Patient**     |                                                                              |
| Age > 65        | HSCT                           | ASCT | AML | MDS | ALL | MPN | NHL | HL | CLL | MM |
| Age 55-65       |                                |      |     |     |     |     |     |     |     |     |
| Age 30-54       |                                |      |     |     |     |     |     |     |     |     |
| Male sex        |                                |      |     |     |     |     |     |     |     |     |
| **Comorbidities**| PS ≥ 2                         |      |     |     |     |     |     |     |     |     |
| Previous IFI    |                                |      |     |     |     |     |     |     |     |     |
| Iron overload   |                                |      |     |     |     |     |     |     |     |     |
| Diabetes        |                                |      |     |     |     |     |     |     |     |     |
| Prior respiratory disease |                          |      |     |     |     |     |     |     |     |     |
| Hypoalbuminemia |                                |      |     |     |     |     |     |     |     |     |
| Influenza/parainfluenza virus |                        |      |     |     |     |     |     |     |     |     |
| Mucositis ≥ 3 for >7 days |                            |      |     |     |     |     |     |     |     |     |
| Esophagitis >2 (WHO) |                          |      |     |     |     |     |     |     |     |     |
| CMV infection   |                                |      |     |     |     |     |     |     |     |     |
| Candida multiple colonization |                      |      |     |     |     |     |     |     |     |     |
| High e-TRM score |                                |      |     |     |     |     |     |     |     |     |
| **Immunity status** | Toll-like rec. Polymorphism |      |     |     |     |     |     |     |     |     |
|                  | Plasminogen polymorphism      |      |     |     |     |     |     |     |     |     |
|                  | Mannose binding lectin         |      |     |     |     |     |     |     |     |     |
|                  | polymorphism                  |      |     |     |     |     |     |     |     |     |
|                  | Other polymorphism (PTX3,     |      |     |     |     |     |     |     |     |     |
|                  | Dectin-1)                     |      |     |     |     |     |     |     |     |     |
|                  | Lymphocytes dysfunction        |      |     |     |     |     |     |     |     |     |
|                  | Prolong lymphocytopenia (<300 cells/μL) | | | | | | | | | |
| **Environment** |                                                                              |
| Neutropenia at baseline |                                |      |     |     |     |     |     |     |     |     |
| Neutropenia <500/μL for >10gg |                          |      |     |     |     |     |     |     |     |     |

Legend:
- **High**: incidence > 5%, risk factor that put patient at high risk for IFI, reported in previous studies or risk factor in the setting of HSCT.
- **Intermediate**: incidence 2-5%, risk factor known in this setting, but that do not identify a high or low risk for IFI, reported in previous studies.
- **Low**: incidence < 2%, risk factor that put patient at low risk for IFI, reported in previous studies.

*Allogeneic Stem Cell transplantation (HSCT), Autologous Stem Cell Transplantation (ASCT), Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS), Acute Lymphoblastic Leukemia (ALL), Myeloproliferative Neoplasm (MPN), Non Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), Chronic Lymphocytic Leukemia (CLL), Multiple Myeloma (MM).*

*High e-TRM score*: PS (performance status), Age, Platelet, Albumin, secondary AML, WBC, % blast in PB, creatinine (Walter RB, et al. JCO, Oct. 2011)

*Environment*: intensive care unit admission, building works, tobacco, cannabis, residence, pets, potted plants, gardening, room without HEPA filtration, airways colonization by Aspergillus.
| Categories       | Risk Factors                                                                 | HSCT | ASCT | AML | MDS | ALL | MPN | NHL HL | CLL | MM |
|------------------|------------------------------------------------------------------------------|------|------|-----|-----|-----|-----|--------|-----|-----|
| **Disease**      |                                                                              |      |      |     |     |     |     |        |     |     |
| Active disease†  |                                                                              |      |      |     |     |     |     |        |     |     |
| First Remission  |                                                                              |      |      |     |     |     |     |        |     |     |
| Aggressive disease †† |                                                                              |      |      |     |     |     |     |        |     |     |
| **Therapy**      |                                                                              |      |      |     |     |     |     |        |     |     |
| No Antifungal Prophylaxis |                                                                              |      |      |     |     |     |     |        |     |     |
| Many previous treatment lines |                                                                              |      |      |     |     |     |     |        |     |     |
| High dose Chemotherapy ††† |                                                                              |      |      |     |     |     |     |        |     |     |
| Salvage Regimen  |                                                                              |      |      |     |     |     |     |        |     |     |
| First Induction  |                                                                              |      |      |     |     |     |     |        |     |     |
| Consolidation    |                                                                              |      |      |     |     |     |     |        |     |     |
| Maintenance      |                                                                              |      |      |     |     |     |     |        |     |     |
| High dose of steroid |                                                                              |      |      |     |     |     |     |        |     |     |
| T-cell suppressors* |                                                                              |      |      |     |     |     |     |        |     |     |
| B-cell suppressors** |                                                                              |      |      |     |     |     |     |        |     |     |
| Hypomethylating agents (not as salvage therapy) |                                                                              |      |      |     |     |     |     |        |     |     |
| Total Body Irradiation |                                                                              |      |      |     |     |     |     |        |     |     |
| TKI              |                                                                              |      |      |     |     |     |     |        |     |     |
| Central Venous Catheter |                                                                              |      |      |     |     |     |     |        |     |     |
| Bortezomib       |                                                                              |      |      |     |     |     |     |        |     |     |
| **Transplant related** |                                                                              |      |      |     |     |     |     |        |     |     |
| Type of donor (MMURD>MUD>MRD)*** |                                                                              |      |      |     |     |     |     |        |     |     |
| Stem cell source (UCB > BM > PB) |                                                                              |      |      |     |     |     |     |        |     |     |
| Moderate-severe acute or chronic GVHD |                                                                              |      |      |     |     |     |     |        |     |     |
| > 1 HSCT         |                                                                              |      |      |     |     |     |     |        |     |     |
| Cell manipulations |                                                                              |      |      |     |     |     |     |        |     |     |
| CMV serology status (R+/D- vs R+/D+ vs R-/D+ vs R-/D-) |                                                                              |      |      |     |     |     |     |        |     |     |
| ATG              |                                                                              |      |      |     |     |     |     |        |     |     |
| CD34+ infused (< 3 x 10^6/Kg) |                                                                              |      |      |     |     |     |     |        |     |     |
| EBMT score°     |                                                                              |      |      |     |     |     |     |        |     |     |
| BO score°°     |                                                                              |      |      |     |     |     |     |        |     |     |
| Pre-transplant diagnosis (AML early onset- Lymphoma late onset) |                                                                              |      |      |     |     |     |     |        |     |     |
| Late post-transplant immune recovery |                                                                              |      |      |     |     |     |     |        |     |     |

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- **Tyrosine Kinase Inhibitor (TKI)**: HLA-mismatched unrelated donor unrelated donor (MMURD); matched unrelated donor (MUD); matched related donor (MRD); Umbilical Cord Blood (UCB); Bone Marrow (BM); Peripheral Blood (PB); Cytomegalovirus (CMV); Recipient (R); Donor (D); Anti-thymocyte globulin (ATG).
- **Active disease†**: Day 15 blasts > 5% or No Complete Remission by the end of induction. **Aggressive disease ††**: (lower probability of Complete Remission) Adverse cytogenetic/gene mutation profile, WBC > 50,000/μL, secondary AML. **High dose chemotherapy †††**: for ALL is pediatric conditioning, for HSCT in myeloablative conditioning. **T-cell suppressors***: Fludarabine, Cyclosporine, Tacrolimus, Mycophenolate mofetil, ATG, Alemtuzumab. **B-cell suppressors**: Rituximab. **EBMT score°**: Age, disease stage, time between diagnosis and transplant, donor type, donor/recipient sex (Gratwohl A, et al. Cancer, Oct. 2009). **BO score°°**: bronchiolitis obliterans CT score (de Jong PA, et al. Thorax, 2006 Sep; 61(9): 799-804).
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References:

1. Pagano L, Akova M, Dimopoulos G, Herbrecht R, Drgona L, Bijlevens N. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. Journal of Antimicrobial Chemotherapy 2011: 66: i5-i14. http://jac.oxfordjournals.org/content/66/suppl_1/i5.abstract

2. Herbrecht R, Bories P, Molin J-C, Ledoux M-P, Letscher-Bru Vr. Risk stratification for invasive aspergillosis in immunocompromised patients. Annals of the New York Academy of Sciences 2012:1272: 23-30. http://dx.doi.org/10.1111/j.1749-6632.2012.06829.x

3. Ananda-Rajah MR, Cheng A, Morrissey CO, et al. Attributable Hospital Cost and Antifungal Treatment of Invasive Fungal Diseases in High-Risk Hematology Patients: an Economic Modeling Approach. Antimicrobial Agents and Chemotherapy 201: 55: 1953-1960. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3088208/

4. Heimann SM, Vehreschild MJGT, Cornely OA, et al. A cost and resource utilization analysis of micafungin bridging for hematological high-risk patients undergoing allogeneic stem cell transplantation. European Journal of Haematology 2015: 94: 526-531. http://dx.doi.org/10.1111/ejh.12466

5. Pagano L, Busca A, Candoni A, et al. Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations. Blood Reviews 2016. http://www.sciencedirect.com/science/article/pii/S0268960X16300753