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Letters to Editor

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

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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	HSCT	ASCT	AML	MDS	ALL	MPN	NHL HL	CLL	MM
Patient	Age > 65									
	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	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
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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

Table 1 (part 2). 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	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									

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

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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