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Delphi-based study and analysis of key risk factors for invasive fungal infection in haematological patients

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ABSTRACT

Introduction. Mortality caused by invasive fungal infections due to filamentous fungi (IFI-FF) is high. Predisposing factors to IFI-FF are multiple and should be stratified. The objective of this study was to identify key risk factors for IFI-FF in onco-haematological patients in different clinical settings.

Methods. Prospective national Delphi study. Risk factors for IFI-FF in patients with onco-haematological diseases were identified by a systematic review of the literature. An anonymous survey was sent by e-mail to a panel of experts. A key risk factor was defined when at least 70% of the surveyed participants assigned a "maximal" or "high" risk.

Results. In allogenic stem cell transplantation, 18 of the 42 risk factors analyzed were classified as key risk factors, including neutropenia, previous IFI-FF, grade III/IV acute or extensive chronic graft-versus-host disease (GVHD), umbilical cord blood transplantation, HLA mismatching transplantation, graft failure, absence of HEPA filters, absence of laminar air flow, diagnosis of acute myeloid leukaemia, haploidentical transplantation, anti-TNF-α drugs, alemtuzumab, anti-thymocyte globulin, immunosuppressive prophylaxis for GVHD, lymphocytopenia, cytomegalovirus infection, and proximity to construction areas. In acute leukaemia/myelodysplastic syndrome (AL/MDS), 7 of 25 risk factors were defined as key risk factors, including neutropenia, consolidation therapy without response, induction therapy, antifungal prophylaxis with azoles, proximity to construction areas, and absence of HEPA filters. In lymphoma/multiple myeloma (MM), the five key risk factors among 21 analyzed were use of steroids, neutropenia, progressive disease, anti-CD52 therapies, and proximity to construction areas.

Conclusions. The Delphi method was useful for the classification and stratification of risk factors for IFI-FF in patients with onco-haematological diseases. Identifying key risk factors will contribute to a better management of IFI-FF in this group of patients at high or changing risk.

Key words: Delphi method, invasive fungal infection, risk factors, stratification.

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Análisis de los factores de riesgo clave para infecciones fúngicas invasoras en pacientes onco-hematológicos: estudio Delphi

RESUMEN

Introducción. La mortalidad por infecciones fúngicas invasoras por hongos filamentosos (IFI-HF) es elevada. Los factores predisponentes de IFI-HF son múltiples y deben ser estratificados. El objetivo de este estudio fue identificar factores de riesgo clave para IFI-HF en pacientes onco-hematológicos en diversos contextos clínicos.

Métodos. Estudio Delphi, nacional y prospectivo. Mediante revisión sistemática de la literatura se identificaron los factores de riesgo de IFI-HF en pacientes con patología onco-hematológica. Se envió por correo electrónico una encuesta anónima a un panel de expertos. Se definió factor de riesgo clave cuando al menos el 70% de los encuestados le asignaba un riesgo "máximo" o "alto".

Resultados. Los factores de riesgo considerados clave fueron: en trasplante alogénico de progenitores hematopoyéticos 18/42 analizados (neutropenia, IFI-HF previa, enfermedad injerto contra huésped aguda III-IV o crónica extensa, trasplante de cordón umbilical, trasplante HLA incompatible, fracaso del injerto, ausencia filtros *HEPA*, ausencia flujo laminar, diagnóstico de leucemia aguda mieloblástica, trasplante haploidéntico, anti-

TNF-α, alemtuzumab, globulina antitimocítica, profilaxis inmunosupresora para enfermedad injerto contra huésped, linfocitopenia, citomegalovirus y proximidad a construcciones). En LA/SMD 7/25 (neutropenia, consolidación sin respuesta, IFI-HF previa, inducción, profilaxis con "*azoles*", proximidad a construcciones y ausencia filtros HEPA). En linfoma/MM 5/21 analizados (esteroides, neutropenia, enfermedad en progresión, terapias anti-CD52 y proximidad a construcciones).

Conclusiones. El método Delphi ha demostrado ser útil para clasificar los factores de riesgo de IFI-HF en pacientes con patología onco-hematológica. La identificación de factores de riesgo clave permitirá adecuar el manejo de IFI-HF en este grupo de pacientes con riesgo alto o cambiante.

Palabras Clave: Método Delphi, infecciones fúngicas invasoras, factores de riesgo, estratificación.

INTRODUCTION

Advances in onco-haematology have allowed prolonging survival in severely immunosuppressed patients with haematological disorders. With the improvement of the control of bacterial infections and fungal infections caused by yeasts, filamentous fungi (FF) have become highly relevant, both for the frequency and severity of presentation of invasive fungal infections (IFI) due to FF (IFI-FF)[1-3].

Onco-haematological diseases are the most common predisposing conditions for IFI-FF accounting for about 90% of host-related primary risk factors[4,5]. The incidence of IFF-FF is variable, ranging between 2% and 24% in subjects diagnosed with acute leukaemia (AL) and/or undergoing allogenic hematopoietic stem cell transplantation (allo-HSCT), and between 0.4% and 3% in patients with lymphoma or multiple myeloma (MM)[4,6-11].

Despite advances in diagnostic techniques and the introduction of new treatment modalities, mortality caused by IFI-FF continues to be high, reaching up to 80% in patients on induction chemotherapy or undergoing allo-HSCT[4,11-15]. This high mortality rate is probably due to both the virulence of the microorganism and the vulnerability of the host, as well as difficulties in the diagnosis and the possibility of developing antimicrobial resistance[6,16,17].

A correct definition of the risk level of IFI-FF is the first step for optimizing preventive and therapeutic strategies. In recent years, new predisposing factors have been recognized, such as the presence of comorbidities, immunosuppressive treatment, and the level of airborne pollution. Multiplicity of risk factors generates the need of stratification to be able to define the probability of IFI-FF in each particular patient and, therefore, to establish more individualized preventive and therapeutic approaches. On the basis of assessment of the individual risk for IFI-FF, surveillance and diagnostic strategies could be improved and therapeutic measured optimized[10].

The objective of this study was to identify and stratify key risk factors for the development of IFI-FF (especially *Aspergillus* spp.) in onco-haematological patients in different clinical settings.

MATERIALS AND METHODS

A prospective national multicenter study using the Delphi method was carried out in November 2014, in order to reach a consensus regarding key risk factors for IFI-FF in patients with onco-haematological diseases.

A scientific committee was created based on their experience on IFI in oncohematologic patients and the Delphi method. The scientific committee developed the questionnaires and selected the panel of experts. Firstly, a list of risk factors associated with IFI in different groups of patients with onco-haematological diseases (AL/myelodysplastic syndrome [MDS], lymphoma/multiple myeloma [MM], and allo-HSCT recipients) was established on the basis of systematic review of the literature and discussion with specialists in haematology and infectious diseases.

Once all risk factors were identified, a survey was designed for the assessment of the relevance of each of them. The survey was divided into three questionnaires: one addressed patients diagnosed with lymphomas/MM in which the relevance of 21 risk factors was evaluated, one addressed patients undergoing allo-HSCT in which the importance of 42 risk factors was assessed, and the third questionnaire addressed patients diagnosed with AL/MDS in which 25 risk factors were included. In each of the questionnaires, five possible closed and mutually

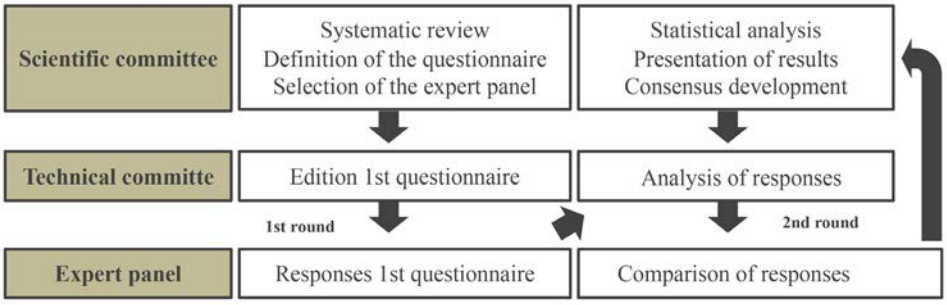

Figure 1 | **Consensus preparation process**

Table 1 Risk factors for IFI-FF in patients with multiple myeloma and lymphomas (level of risk)

Item	Median	IQR	% against[b]
Neutropenia[a]	5 (maximal)	4-5	14.29
Alterations of cellular immunity	4 (high)	3-4	32.14
Break in mucocutaneous barriers	4 (high)	2-4	46.43
COPD chronically treated with GC	4 (high)	3-4	42.86
Advanced liver disease	3 (medium)	2-3	50.00
Progression of haematological disease[a]	4 (high)	4-5	21.43
Renal failure	2 (low)	2-3	46.42
Use of antacids	2 (low)	2-3	32.14
Advanced age	3 (medium)	2-3	50.00
COPD greater than 2	3 (medium)	2-3	57.14
CD4+ lymphocytopenia	4 (high)	3-4	35.71
Use of anti-CD52 biological therapies[a]	4 (high)	4	21.43
Use of anti-CD20	2 (low)	2	21.43
Use of bortezomib	2 (low)	1-2	14.29
Use of lenalidomide	2 (low)	2	21.43
Use of purine analogues	3 (medium)	3-4	50.00
Use of high doses of GC[a]	5 (maximal)	4-5	7.14
Functional or anatomic hyposplenism/anesplenia	3 (medium)	2-3	53.57
Proximity to construction or remodelling areas[a]	4 (high)	3-4	28.57
Seasonality (winter season)	3 (medium)	2-3	60.71
Work or leisure activities at risk of exposure	3 (medium)	3-4	42.86

[a]Key risk factor; [b]Proportion of panellists against; IFI-FF: invasive fungal infection caused by filamentous fungi; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; GC: glucocorticoids. ECOG: Eastern Cooperative Oncology Group.

exclusive responses (5-point ordinal Likert scale) were considered, including "minimal relevance", "low", "medium", "high", or "maximal" (see Supplementary Material).

The scientific committee was responsible for the definition of the content of the Delphi questionnaire and for the selection of the participant panel, which included experts of recognized experience and professional prestige. The survey was anonymous and questionnaires were sent by e-mail. A key risk factor was defined when at least 70% of the experts assigned a "maximal" or "high" risk in their responses (figure 1).

Identification and selection of risk factors associated to IFI. In October 2014, relevant articles focused on risk factors for IFI in onco-haematological patients were searched in the MEDINE and PubMed database. Two different series of key words were combined to ensure a comprehensive review of the literature. The search was limited to cohort studies, clinical trials, systematic reviews, and meta-analysis published in English and Spanish.

Full text relevant articles were independently reviewed by researchers of the scientific committee. Then, both researchers compared their findings and disagreements were solved by a third reviewer. Also and besides the initial literature search, a consultation was made with experts in haematology and infectious diseases with the aim of identifying additional risk factors. A total of 42 risk factors for IFI-FF in allo-HSCT recipients were detected, 25 for IFI-FF in patients with AL/MDS, and 21 in patients diagnosed with lymphoma/MM.

Stratification of risk factors associated to IFI. Stratification of risk factors was carried out in November 2014 using a formal consensus process based on a two-round Delphi method. The Delphi method is a research survey technique the purpose of which is to reflect a scenario of higher or lower agreement among experts regarding a specific topic. Surveys were addressed to a group of experts in haematology. A structures questionnaire was sent by e-mail to all participants. In the initial part of the questionnaire, the design and objectives of the study were fully explained. At the same time, the questionnaire was divided into three sections: 1) Lymphoma/MM; 2) AL/MDS; and 3) allo-HSCT recipients. Different risk factors were listed in each category (21 for lymphoma/MM, 25 for AL/MDS, and 42 for allo-HSCT). Participants were questioned regarding the importance of each risk factor for the overall IFI risk stratification, and items were evaluated using a 5-point ordinal Likert scale. Possible responses were grouped into 5 closed and mutually exclusive categories as follows: "minimal", "low", "medium", "high", or "maximal" relevance. Responses to the questionnaires were anonymously analyzed.

Statistical analysis and interpretation of results. In order to establish the level of agreement for each of the factors analyzed. The five possible responses were grouped into three regions [1-2], [3], and [4-5]. It was considered that there was agreement among the experts when two third of the panel scored in the region in which the median was included, disagreement when scores of one third or more of the panel were in the [1-2] region and of other one third or

Table 2 Risk factors for IFI-FF in patients with multiple myeloma and lymphomas (level of agreement)

Item	Mean	Level of agreement[b]
Neutropenia[a]	4.3	Concordance
Alterations of cellular immunity	3.6	Concordance
Break in mucocutaneous barriers	3.5	Indeterminate
COPD chronically treated with GC	3.6	Indeterminate
Advanced liver disease	2.7	Indeterminate
Progression of haematological disease[a]	4.0	Concordance
Renal failure	2.5	Indeterminate
Use of antacids	2.3	Concordance
Advanced age	2.9	Indeterminate
COPD greater than 2	2.8	Indeterminate
CD4+ lymphocytopenia	3.6	Indeterminate
Use of anti-CD52 biological therapies[a]	3.9	Concordance
Use of anti-CD20	2.1	Concordance
Use of bortezomib	1.9	Concordance
Use of lenalidomide	2.0	Concordance
Use of purine analogues	3.5	Indeterminate
Use of high doses of GC[a]	4.5	Concordance
Functional or anatomic hyposplenism/anesplenia	2.9	Indeterminate
Proximity to construction or remodelling areas[a]	3.9	Concordance
Seasonality (winter season)	2.8	Indeterminate
Work or leisure activities at risk of exposure	3.2	Indeterminate

[a]Key risk factor; IFI-FF: invasive fungal infection caused by filamentous fungi; COPD: chronic obstructive pulmonary disease; GC: glucocorticoids; ECOG: Eastern Cooperative Oncology Group.
[b]Level of agreement: concordance: when experts scoring outside the region in which the median value is included are fewer than one third of the panel, discordance: when scores of one third or more of the panellists are in the region [1-2] and of another one third or more in the region [4-5];

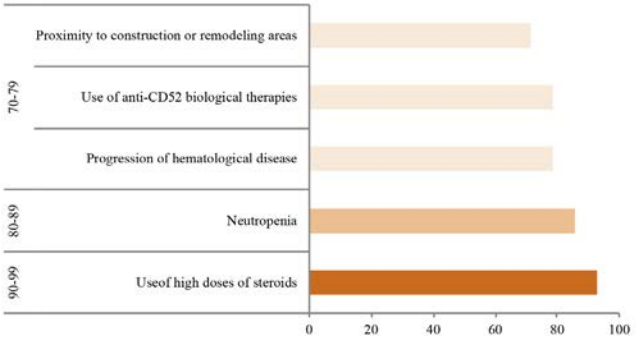

Figure 2 Key risk factors for IFI-FF in patients with multiple myeloma and lymphomas (level of agreement)

more in the [4-5] region, and an indeterminate level of agreement when the distribution of responses did not meet neither agreement nor disagreement criteria. The proportion of panellists against each item was defined as those who scored outside the region in which the median was included.

A key risk factor was defined when at least 70% of the surveyed participants assigned a "maximal" or "high" risk. Also, key risk factors were further divided into four groups if the proportion of agreement was 100%, 99-90%, 89-80%, and 79-70%.

Items for which consensus was reached on the first round, were reconsidered in a second round previous information of the preliminary results to the experts. The same criteria used in the first round were applied to the second round. Results were expressed as mean and median with interquartile range (25th-75th percentile). Descriptive statistics are reported.

RESULTS

The panel was composed on 42 experts in haematology from different autonomous communities. All of them agreed to participate in the Delphi-based consensus survey, and 28 (66.7%) completed the questionnaire.

In the group of patients diagnosed with lymphoma/MM, 21 risk factors associated with IFI-FF were identified. After two evaluation rounds, consensus was achieved in 10 of the 21 items (47.6%), with agreement (concordance) in all of them. Five of the 10 items (50%) fulfilled criteria for the definition of key risk factor. In none of the items, unanimity among experts was attained but there was a wide consensus in considering the use of high doses of steroids (more than 1 mg/kg/day) for more than 2 weeks (92.9%) and the presence of neutropenia (85.7%) as key factors. Also, a percentage of agreement between 79-70% was also obtained for three risk factors: progression of the haematological disease, use of biological therapies anti-CD52 (alemtuzumab), and the proximity to construction, demolition or remodelling areas (tables 1 and 2, figure 2). In patients undergoing allo-HSCT, the relevance of 42 risk factors associated with IFI-FF was evaluated. After two rounds, consensus was achieved in 24 of the 42 items (57-1%): agreement (concordance) in 23 and disagreement (discordance) in 1. Of the 23 items in which agreement was obtained, 18 (78.3%) met the definition of key risk factor. Experts unanimously agreed (100%) in considering the following risk factors: profound neutropenia (absolute neutrophil count [ANC] < 100 cells/mL) or prolonged neutropenia (> 14 days), history of previous IFI-FF, and current treatment with immunosuppressive drugs/corticoids because of grade III/IV acute or extensive chronic graft-versus-host disease (GVHD). A high percentage of agreement (99-90%) was also obtained for allo-HSCT using umbilical cord blood, HLA mismatching allo-HSCT, graft

Table 3 Risk factors for IFI-FF in allo-HSCT recipients (level of risk)

Item	Median	IQR	% against[b]
Diagnosis of AML[a]	4-5 (high-maximal)	4-5	10.71
Diagnosis of ALL	4 (high)	3-4	39.29
Diagnosis of MDS	4 (high)	3-4	32.14
Profound and prolonged neutropenia[a]	5 (maximal)	5	0.00
Monocytopenia	3 (medium)	3-4	62.96
Lymphopenia	3 (medium)	3-4	62.96
COPD chronically treated with GC	4 (high)	3-4	35.71
Renal failure	3 (medium)	2-3	42.85
Uncontrolled hyperglycaemia	3 (medium)	3-4	57.14
Malnutrition	3 (medium)	3-4	57.14
Obesity	2-3 (low-medium)	2-3	7.14
Break in mucocutaneous barriers	4 (high)	3-4	35.71
Advanced age	3 (medium)	2-4	57.14
COPD greater than 2	3 (medium)	3-4	46.43
Allo-HSCT related donor, identical HLA	3 (medium)	3-4	64.29
Allo-HSCT unrelated donor, identical HLA	4 (high)	3-4	32.14
Allo-HSCT HLA mismatched[a]	5 (maximal)	4-5	3.57
Hematopoietic cell transplantation using umbilical cord cells[a]	5 (maximal)	4-5	3.57
Haploidentical hematopoietic cell transplantation[a]	4 (high)	4-5	17.86
Graft failure[a]	5 (maximal)	4-5	7.14
Prophylaxis against GVHD with IS drugs[a]	4 (high)	4-5	21.43
Grades III-IV GVHD on treatment with IS and GC[a]	5 (maximal)	4-5	0.00
Extensive chronic GVHD on treatment with IS and GC[a]	5 (maximal)	4-5	0.00
Anti-TNFα (infliximab, adalimumab, etanercept)[a]	4 (high)	4-5	14.29
Alemtuzumab[a]	4 (high)	4-5	14.29
CD4+ lymphocytopenia[a]	4 (high)	4	21.43
Anti-thymocyte globulin[a]	4 (high)	4	21.43
Genetic polymorphisms (MBL, TLR4-2, etc.)	3 (medium)	3-4	46.43
Previous IFI-FF[a]	5 (máximo)	4-5	0.00
Iron overload	3 (medium)	3-4	53.57
Infection by CMV or other herpes group viruses[a]	4 (high)	3-4	28.57
Parvovirus B19 infection	3 (medium)	2-3	53.57
Respiratory viruses infection	3 (medium)	3-4	53.57
Antifungal prophylaxis with "azoles"	4 (high)	3-5	32.14
Antifungal prophylaxis with "candins"	3-4 (medium-high)	3-4	10.71
Prophylaxis with polyene antifungals	4 (high)	3-4	42.85
Proximity to construction or remodelling areas[a]	4 (high)	4-5	17.86
Living with pets	3 (medium)	2-4	78.57
Work or leisure activities at risk of exposure	4 (high)	3-4	46.43
Rooms without HEPA filters[a]	4 (high)	4-5	7.41
Rooms without laminar air flow[a]	4 (high)	4	18.52
Seasonality (winter season)	3 (medium)	2-3	51.85

[a]Key risk factor; [b]Proportion of panellists against; IFI-FF: invasive fungal infection caused by filamentous fungi; AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; MDS: myelodysplastic syndrome; GVHD: graft-versus-host-disease; HEPA: high efficiency particle arrestance; COPD: chronic obstructive pulmonary disease; GC: glucocorticoids; IS: immunosuppressant drugs. ECOG: Eastern Cooperative Oncology Group.

failure, and stay in rooms not equipped with high-efficiency particulate arrestance (HEPA) filters. Finally, and with a lower agreement proportion but higher than 70%, other key risk factors included diagnosis of acute myeloid leukaemia (AML), haploidentical transplant recipient, proximity to construction areas and stay in rooms without laminar air flow, treatment with anti-tumor necrosis factor [TNF]-α drugs, use of anti-CD52 (alemtuzumab) agents, use of anti-thymocyte globulin, prophylaxis against GVHD with immunosuppressant drugs, lymphocytopenia (CD4+ < 200 cells/mL), and infections caused by cytomegalovirus (CMV) or by other herpes group viruses (tables 3 and 4, figure 3).

In patients diagnosed with AL/MDS, 25 risk factors were identified. After two rounds of assessment, consensus was obtained in 8 items (32%), with agreement (concordance) for all them. Seven of the 8 items (87.5%) fulfilled the definition of key risk factors. In this group of patients, experts agreed unanimously (100%) in considering the presence of profound or prolonged neutropenia, consolidation chemotherapy without response, and previous IFI-FF as maximal or high risk factors. The percentage of agreement was also high (99-90%) for current induction chemotherapy, which was rated as maximal or high risk factor. Finally, with a lower percentage of agreement but greater than 70%, the following key risk factors were established: prophylactic treatment with extended-spectrum azoles, proximity to construction or remodelling areas, and stay in rooms without HEPA filters (tables 5 and 6, figure 4).

Table 4 Risk factors for IFI-FF in allo-HSCT recipients (level of agreement)

Item	Mean	Level of agreemnet[b]
Diagnosis of AML[a]	4.4	Concordance
Diagnosis of ALL	3.6	Indeterminate
Diagnosis of MDS	3.9	Concordance
Profound and prolonged neutropenia[a]	4.9	Concordance
Monocytopenia	3.1	Indeterminate
Lymphopenia	3.3	Indeterminate
COPD chronically treated with GC	3.7	Indeterminate
Renal failure	2.7	Indeterminate
Uncontrolled hyperglycemia	3.4	Indeterminate
Malnutrition	3.2	Indeterminate
Obesity	2.5	Concordance
Break in mucocutaneous barriers	3.7	Indeterminate
Advanced age	3.0	Indeterminate
COPD greater than 2	3.0	Indeterminate
Allo-HSCT related donor, identical HLA	3.3	Indeterminate
Allo-HSCT unrelated donor, identical HLA	3.8	Concordance
Allo-TPH mismatch HLA[a]	4.6	Concordance
Hematopoietic cell transplantation using umbilical cord cells[a]	4.6	Concordance
Haploidentical hematopoietic cell transplantationa	4.1	Concordance
Graft failure[a]	4.7	Concordance
Prophylaxis against GVHD with IS drugs[a]	4.2	Concordance
Grades III-IV GVHD on treatment with IS and GC[a]	4.6	Concordance
Extensive chronic GVHD on treatment with IS and GC[a]	4.8	Concordance
Anti-TNF-alpha (infliximab, adalimumab, etanercept)[a]	4.3	Concordance
Alemtuzumab[a]	4.1	Concordance
CD4+ lymphocytopenia[a]	3.8	Concordance
Anti-thymocyte globulin[a]	3.8	Concordance
Genetic polymorphisms (MBL, TLR4-2, etc.)	3.1	Indeterminate
Previous IFI-FF[a]	4.7	Concordance
Iron overload	3.4	Indeterminate
Infection by CMV or other herpes group viruses[a]	3.6	Concordance
Parvovirus B19 infection	2.8	Indeterminate
Respiratory viruses infection	3.3	Indeterminate
Antifungal prophylaxis with "azoles"	3.9	Concordance
Antifungal prophylaxis with "candins"	3.4	Concordance
Prophylaxis with polyene antifungals	3.5	Indeterminate
Proximity to construction or remodelling areas[a]	4.1	Concordance
Pets at home	2.9	Discordance
Work or leisure activities at risk of exposure	3.5	Indeterminate
Rooms without HEPA filters[a]	4.3	Concordance
Rooms without laminar air flow[a]	3.9	Concordance
Seasonality (winter season)	3.0	Indeterminate

[a]Key risk factor; IFI-FF: invasive fungal infection caused by filamentous fungi; AML: acute myeloblastic leukaemia; ALL: acute lymphoblastic leukaemia; MDS: myelodysplastic syndrome; HEPA: high efficiency particle arrestance; COPD: Chronic obstructive pulmonary disease; GC: glucocorticoids; IS: immunosuppressant drugs; ECOG: Eastern Cooperative Oncology Group.
[b]Level of agreement: concordance: when experts scoring outside the region [1-2] [3] [4-5] in which the median value is included are fewer than one third of the panel; discordance: when scores of one third or more of the panellists are in the region [1-2] and of another one third or more in the region [4-5].

DISCUSSION

Profound and prolonged neutropenia, HSCT, and the use of immunosuppressive therapies have been recognized for years as predisposing factors for IFI-FF. Recently, additional risk factors have been identified, such as alteration of innate immunity, presence of comorbidities, and exposure to high levels of airborne fungal spores. The identification of patients at higher risk of IFI-FF is necessary to select those patients, which would obtain the highest benefit from antifungal prophylaxis and which require a more intensive control and early beginning of antifungal treatment[10]. However, this task is difficult given the multiplicity of risk factors described and the synergy between them[4,20]. Definition of key risk factors in different clinical scenarios may be the first step in building a score to assess the risk for each particular patient. Establishing the risk level for each patient would allow the design of individualized surveillance, diagnostic, and therapeutic strategies.

In this study, risk factors for IFI-FF in three clinical scenarios were analyzed, including patients undergoing allo-HSCT, patients diagnosed with AL/MDS, and patients diagnosed with lymphoma/MM. Among risk factors that may be considered "independent" of the onco-haematological disease and its treatment, intrinsic and extrinsic risk factors were evaluated. These included the presence of comorbidities (respiratory disease, liver disease, renal disease, uncontrolled hyperglycaemia, obesity, malnutrition); advanced age; use of antacids (proton pump inhibitors or H2 antagonists); living with pets; proximity to construction or remodelling areas; hospitalization in rooms without HEPA filters or in rooms without laminar air flow; seasonality (winter season); and work or leisure activities at risk of exposure to fungal spores (gardening, jacuzzis, etc.). The only "independent" risk factor of the onco-haematological disease and its treatment, which was considered "key factor" in the three clinical scenarios analyzed, was the proximity to construction or remodelling areas. *Aspergillus* spp., *Zygomycetes* and other filamentous fungi are saprophytic and ubiquitous in air, soil and water. Therefore, exposure to these agents is almost universal[20]. The risk related to proximity of onco-haematological patients to construction or remodelling areas in the hospital and/or at home has been investigated and confirmed in different studies[21,22]. A multicenter study in patients with newly diagnosed AML showed that exposure to house renovation and jobs with high exposure to fungal agents (together with diagnosis of chronic obstructive pulmonary disease [COPD]) were the most important pre-chemotherapy risk factors for IFI-FF (odds ratio [OR] 4.01 and 3.43, respectively)[10].

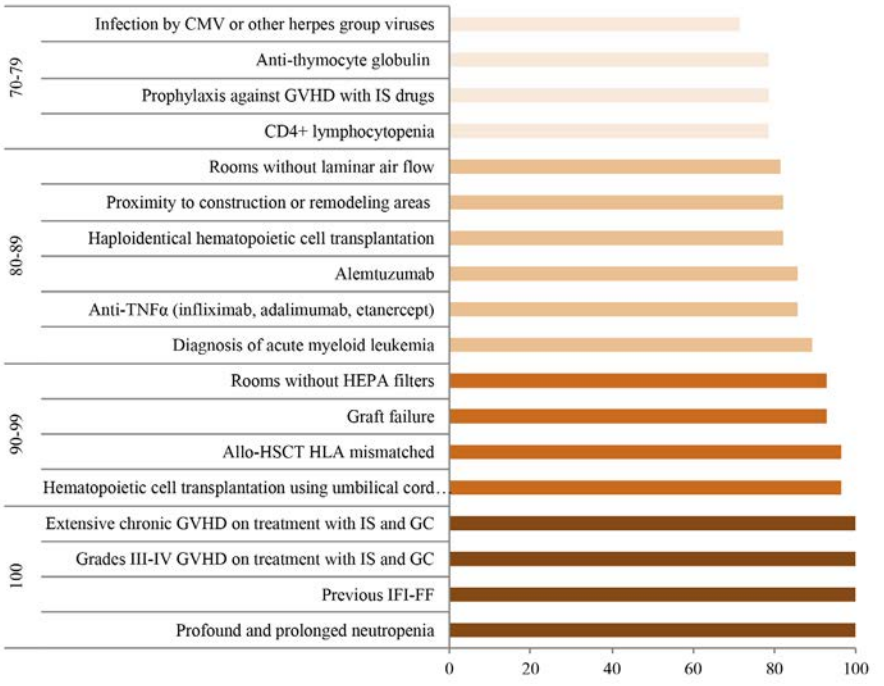

Figure 3 | **Key risk factors for IFI-FF in allo-HSCT recipients (level of agreement)**

Another variable related to environmental exposure that was considered key factor in two of the three clinical scenarios (allo-HSCT and AL/MDS) was hospital stay in rooms without HEPA filters, whereas hospitalization in rooms without laminar flow air was considered a key risk factor only in allo-HSCT. Hospital stay of high risk patients in units with HEPA filters, with or without laminar air flow, has been shown to be a useful measure for preventing hospital-acquired invasive aspegillosis[4,20,23]. Finally, regarding environmental exposure, living with pets was the only risk factors in which there was disagreement among experts. In a study of AML patients, living with pets before induction chemotherapy was not a risk factor for IFI-FF.[10]

In relation to risk factors related to onco-haematological disease and its treatment, the presence of profound and prolonged neutropenia was the only key risk factor selected in all clinical scenarios. In patients undergoing allo-HSCT with a diagnosis of AL/MDS, 100% of participants assigned a high or maximal risk, whereas the proportion of agreement in the lymphoma/MM group was 85.7%. Classic observations have shown that neutropenia is the most important risk factor for invasive aspergillosis (hazard ratio [HR] 2.28-3.0)[21-23]. In onco-haematological patients usually coexist decreased ANC and impaired functioning of polymorphonuclear cells[20]. Impaired cell-mediated immunity is the most prominent defect in the immune system that predisposes individuals to invasive fungal infections. The role of neutrophils in the control of fungal infections is fundamental. These cells are essential in the initiation and execution of the acute inflammatory response and subsequent resolution of infiltrates caused by the fungal infection[20]. The duration and the levels of circulating leukocytes are crucial predictors of the risk of infection. If neutropenia persisted for 3 weeks the risk of developing an infection, including IFI, is 60%, with a further rise to 100% when the neutrophil count dropped to < 100 cells/mL. In a multicenter, prospective, observational study in China (CAESAR study) in which 4,192 patients with different onco-haematological diseases were included, prolonged neutropenia (> 14 days) was an independent risk factor for IFI with an OR of 4.83 (95% confidence interval [CI] 2.44-9.58)[11]. Thus, patients can be classified according to magnitude and duration of neutropenia into individuals at high risk (< 100 cells/mL for more than 14 days), intermediate risk (duration of neutropenia between 7 and 14 days), and low risk (duration of neutropenia of less than 7 days)[24-27].

A previous episode of IFI-FF was another predisposing factor that was considered a key risk factor in patients with allo-HSCT and AL/MDS. Different studies have shown that a previous diagnosis of IFI increases significantly the risk for a further episode[11,24,26,28,29]. However, it is important to define reactivation of a previous infection and *de novo* infection. Reactivation of an invasive aspergillosis during a new episode of neutropenia or during transplantation occurs in 10-30% of cases. However, the risk of reactivation depends on site of the initial infection (being particularly high in patients with sinusitis) and the use of secondary prophylaxis, increasing up to 50% of cases when indication of secondary prophylaxis was inadequate[12]. Reactivation may occur at any time, although it is frequently observed early in the post-transplant period (usually within 100 days) in contrast to *de novo* infection that generally develops at a median of 3 months after transplantation[20,29-32].

Finally, the last risk factor which was considered a key risk variable in two of the three populations analyzed (lymphoma/MMM and allo-HSCT) was the use of anti-CD52 biologic therapy (alemtuzumab). The percentages of agreement were 78.6% in patients diagnosed of lymphoma/MM and 85.7% in allo-HSCT recipients. Current therapeutic regimens that particularly include purine analogues (e.g. fludarabine) and T-cell directed antibodies (e.g. alemtuzumab) generate pancytopenia, which possibly justifies the increased risk of IFI-FF[20,24].

In the group of patients diagnosed with AL/MDS, 7 of the

Table 5 Risk factors for IFI-FF in patients with AL/MSD (level of risk)

Item	Median	IQR	% against[b]
Induction treatment[a]	5 (maximal)	4-5	7.14
Consolidation with haematological response	3 (medium)	3	35.71
Consolidation without haematological response or refractory[a]	5 (maximal)	4-5	0.00
Profound and prolonged neutropenia[a]	5 (maximal)	5	0.00
Monocytopenia	3 (medium)	3-4	60.71
COPD chronically treated with GC	4 (high)	3-4	39.29
Advanced liver disease	3 (medium)	2-3	53.57
Renal failure	3 (medium)	2-3	53.57
Uncontrolled hyperglycaemia	3 (medium)	3-4	46.43
Malnutrition	3 (medium)	3-4	50.00
Obesity	3 (medium)	2-3	50.00
COPD greater tan 2	3 (medium)	2-4	57.14
Advanced age	3 (medium)	3-4	42.86
Antifungal prophylaxis with "azoles"[a]	4 (high)	3-4	25.00
Previous IFI-FF[a]	5 (maximal)	4-5	0.00
CD4+ lymphocytopenia	4 (high)	3-4	32.14
Genetic polymorphisms (MBL, TLR4-2, etc.)	3 (medium)	2-4	53.57
Iron overload	3 (medium)	3-4	53.57
Treatment with purine analogues	4 (high)	3-4	39.29
Treatment with citarabine (high doses)	3-4 (med.-high)	3-4	7.14
Proximity to construction or remodelling areas[a]	4 (high)	4	21.43
Work or leisure activities at risk of exposure	3 (medium)	2-4	75.00
Rooms without HEPA filters[a]	4 (high)	3-5	25.00
Rooms without laminar air flow	4 (high)	3-4	39.29
Seasonality (winter season)	3 (medium)	2-4	71.43

[a]Key risk factor; [b]Proportion of panellists against; IQR: interquartile range; IFI-FF: invasive fungal infection caused by filamentous fungi; COPD: chronic obstructive pulmonary disease; GC: glucocorticoids; ECOG: Eastern Cooperative Oncology Group. HEPA: high efficiency particle arrestance.

25 factors assessed were defined as key risk factors, four of them previously mentioned as they have been also identified in other patient groups. The remaining three key risk factors were consolidation chemotherapy without response (or refractory patients), induction therapy, and antifungal prophylaxis with extended-spectrum azoles. Consolidation treatment without haematological response or refractory patients in which progression of the disease and lack of response require more intensive treatment has been recognized as specific risk factor for invasive aspergillosis[26]. At the same time, prolonged neutropenia due to progression of underlying disease and therapeutic intensification is a predictive factor of mortality associated with invasive aspergillosis[20,33]. In relation to the effect of induction chemotherapy in patients diagnosed of AML, it has been shown a higher incidence of IFI-FF during induction treatment as compared to consolidation treatment. In an open-label, randomized non-inferiority trial that compared an empirical antifungal strategy with a pre-emptive one, IFI due to *Aspergillus* spp. occurred in 1.4% of patients of both empirical and pre-emptive treatment groups during consolidation therapy as compared to 3.8% in the empirical and 9.6% pre-emptive therapy groups, respectively, during the induction therapy[34]. Similar results were reported in a retrospective cohort of 11,802 patients with haematological neoplasms and in the CAESAR prospective study[6,11].

With regard to antifungal prophylaxis with "azoles", candidiasis was the most frequent IFI in onco-haematological patients in the 80s, but lately after the generalized use of fluconazole there was a marked decrease in IFI caused by yeasts[12,35]. These circumstances together with improvement in supportive care measures contributed to current predominant role of filamentous fungi in general, and *Aspergillus* spp. in particular, as the main cause of IFI. On the other hand, infections caused by *Zygomycetes* are resistant to fluconazole, voriconazole, and low-dose posaconazole[25,36]. In 2012, Auberger et al.[37] evaluated the incidence of breakthrough IFIs (bIFIs) and resistance following posaconazole exposure in 90 patients during neutropenia after chemotherapy/HSCT. The incidence of bFIF was 13% (significantly higher than rates historically reported). Species diagnosis exclusively revealed non-*Aspergillus* spp., i.e. mucormycetes in 55% and yeasts in 45%.

In allo-HSCT recipients, consensus was reached in considering 18 of the 42 risk factors evaluated as key risk factors, 6 of which have been previously described as they were also key risk factors in other patient groups. Three of the remaining 12 factors are related to GVHD, which is one of the most common complications in patients undergoing allo-HSCT. Key risk factors included current immunosuppressive treatment (immunosuppressants/glucocorticoids) because of a grade III-IV acute GVHD or an extensive chronic GVHD (both with a proportion of agreement of 100%) and having received prophylaxis for GVHD with immunosuppressants (with a lower proportion of agreement 78.6%). Different studies have shown that GVHD is an independent risk factor for invasive aspergillosis, which is probably due to the need of using high-

Table 6 **Risk factors for IFI-FF in patients with AL/MDS (level of agreement)**

Item	Mean	Level of agreement[b]
Induction treatment[a]	4.5	Concordance
Consolidation with haematological response	3	Indeterminate
Consolidation without haematological response or refractory[a]	4.6	Concordance
Profound and prolonged neutropenia[a]	4.8	Concordance
Monocytopenia	3.1	Indeterminate
COPD chronically treated with GC	3.7	Indeterminate
Advanced liver disease	2.8	Indeterminate
Renal failure	2.7	Indeterminate
Uncontrolled hyperglycaemia	3.3	Indeterminate
Malnutrition	3.1	Indeterminate
Obesity	2.6	Indeterminate
COPD greater tan 2	3.0	Indeterminate
Advanced age	3.1	Indeterminate
Antifungal prophylaxis with "azoles"[a]	3.9	Concordance
Previous IFI-FF[a]	4.6	Concordance
CD4+ lymphocytopenia	3.5	Indeterminate
Genetic polymorphisms (MBL, TLR4-2, etc.)	3.0	Indeterminate
Iron overload	3.3	Indeterminate
Treatment with purine analogues	3.6	Indeterminate
Treatment with citarabine (high doses)	3.5	Concordance
Proximity to construction or remodelling areas[a]	4.0	Concordance
Work or leisure activities at risk of exposure	3.3	Indeterminate
Rooms without HEPA filters[a]	4.0	Concordance
Rooms without laminar air flow	3.5	Indeterminate
Seasonality (winter season)	2.8	Indeterminate

[a]Key risk factor; IFI-FF: invasive fungal infection caused by filamentous fungi; COPD: chronic obstructive pulmonary disease; GC: glucocorticoids; ECOG: Eastern Cooperative Oncology Group. HEPA: high efficiency particle arrestance; [b]Level of agreement.

dose immunosuppressive therapy. Both grade III-IV acute GVHD (HR 2.2, 95% CI 1.4-3.4) and extensive chronic GVHD (HR 2.2, 95% CI 1.3-3.7) as well as steroid-refractory GVHD are major risk factors for opportunistic infections including IFI-FF[26,27,38,39].

Other three key risk factors were related to the type of allo-HSCT, such as the use of umbilical cord blood as the source of hematopoietic stem cells, HLA mismatched allo-HSCT, and haploidentical allo-HSCT (with a lower proportion of agreement than the first two). Umbilical cord stem cells are frequently used in adult patients requiring allo-HSCT, although a delay in haematological recovery, between 21 and 35 days in 90% of the patients, is the main disadvantage[40]. In a study that assessed the risk of invasive aspergillosis among 1,682 patients who received HSCT, cord blood as the stem cell source increased the risk of invasive aspergillosis with a HR of 5.1 (95% CI 1.5-17.2)[38]. Also, in a retrospective study of 434 consecutive allo-HSCTs, umbilical cord blood transplantation was associated with a higher risk of invasive aspergillosis (100-days-cumulative incidence 16% *vs.* 6%, P = 0.04)[41]. On the other hand, various studies have shown that HLA mismatched allo-HSCT also increases the risk of IFI-FF[25,26]. In a retrospective study of 1,248 patients who underwent allo-HSCT, early invasive mold infection was significantly higher in the HLA mismatched group than in the HLA matched group (HR 6.7, 95% CI 2.4-18.3)[35].

Diagnosis of AML prior to allo-HSCT was also considered a key risk factor by the expert panel, with a proportion of agreement close to 90%. In an Italian retrospective cohort study of 11,802 patients with hematologic malignancies, there were 538 proven or probable IFI (4.6%); 373 (69%) occurred in patients with AML. Over half (346/538) were caused by molds (2.9%), in most cases *Aspergillus* spp. (310/346)[6]. Recipients of allo-HSCT or on treatment for AML/MDS have a 20-fold increase in risk for invasive aspergillosis in comparison to patients diagnosed with lymphoma or MM[29,42]. In the prospective Chinese study (CAESAR study), diagnosis of AML/MDS increased the risk of IFI-FF with an OR of 1.82 (95% CI 1.14-2.92)[11].

Graft failure was also considered key risk factors for IFI-FF, with a high proportion of agreement (92.9%). Profound and prolonged neutropenia associated with graft failure increases notably the risk of opportunistic infection including IFI-FF. Neutropenia, lymphopenia, and monocytopenia have been shown to be relevant risk factors for the development of IFI-FF[26,35]. Also, CD4+ lymphocytopenia was selected as key risk factor. In this respect, a retrospective study of 1,248 patients who underwent allo-HSCT, it was found that lymphopenia increased significantly the risk of early (days 1-39 after transplantation) invasive mold infection (HR 6.3, 95% CI 2.1-19.2)[35]. In another study of 840 allo-HSCT recipients, neutropenia/lymphocytopenia or lymphocyte dysfunction was one of the four risk factors for invasive mold infection (HR 2.45, 95% CI 1.39-4.34)[29]. *Aspergillus*-specific CD4+ T cell responses have long been recognized as important in regulating effective pulmonary inflammation and potentially adding antifungal effector activity[35].

Infection with CMV and other viruses of the herpes group were also considered key risk factor with a proportion of agreement close to 70%. CMV infection also increased significantly the risk of invasive aspergillosis in SCHT recipients, with a HR between 2.2 and 7.0[26,27,38]. Infection by CMV has been associated with development

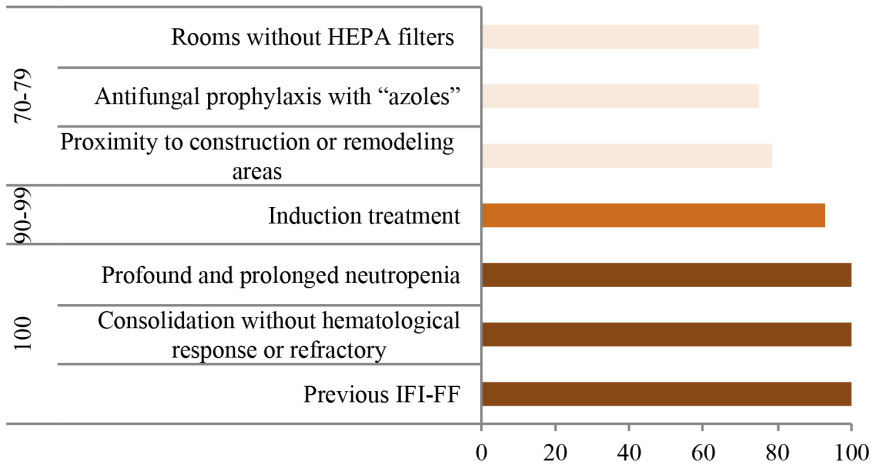

Figure 4 Key risk factors for IFI-FF in patients with AL/MSD (level of agreement)

of both early and late IFI after transplantation. The exact mechanism is not known, although immune modulation of the virus and/or ganciclovir-induced neutropenia probably contribute[35].

Two treatment-related variables were also considered key factors. These included having being received anti-TNFα drugs (infliximab, adalimumab, etanercept) and treatment with anti-thymocyte globulin. In a retrospective study of 58 patients with haematological malignancies who developed probable or proven IFI (most of them caused by filamentous fungi) over a 5 year period, T cell suppressive therapy (35/44, 80% vs. 69/116, 59%) were significantly related with development of IFI (HR 7.24, 95% CI 3.58-14.64)[43]. TNFα blockade therapy has been associated with the occurrence of invasive aspergillosis in non-haematological patients who suffer from autoimmune diseases, such as rheumatoid arthritis or Crohn's disease[20]. In a study of 1,248 patients who underwent allo-HSCT, the use of anti-thymocyte globulin in conditioning regimens was a significant risk factor for early IFI (HR 4.9, 95% CI 1.2-19.5)[35]. These agents may not only cause a transitory deep neutropenia, but also induce prolonged lymphocytopenia with an inherent long-lasting impairment of cell-mediated immunity[20].

In the group of patients with lymphoma/MM, 5 of the 21 risk factors evaluated were considered key risk factors, three of them have been previously described and the remaining two were the use of high doses of steroids and progressive disease of the haematological malignancy. The use of corticosteroids is a well-known risk factor for IFI-FF. It has been shown that corticosteroids reduce the immune response of the host through deterioration of the capacity of eliminating fungal conidia engulfed by the alveolar macrophage and decrease the production of proinflammatory cytokines and chemokines by the macrophages, which are important for recruitment of neutrophils and monocytes. In addition, treatment with steroids causes a qualitative alteration in the function of neutrophils. These effects appear to be dependent on both the dose and duration of treatment. Studies have shown that doses from 0.2 mg/kg/day increase mortality associated with invasive aspergillosis independently of the underlying illness of the host (HR 2.8, 95% CI 1.7-4.7)[20,26,33,35]. In addition, the risk associated with corticosteroid treatment increases in the presence of other concomitant risk factors for invasive aspergillosis[12].

Different studies have shown that progression of haematological malignancy increases mortality associated with IFI-HH[29,33]. In a randomized trial of liposomal amphotericin B comparing high-loading dose regimen with standard regimen (AmBiLoad trial), 12-week survival for uncontrolled haematological malignancy was 54% as compared to 81% for controlled malignancy[44].

In this expert consensus a large variety of clinical scenarios were analyzed, which is an advantage of the study. Also, the study has the strengths of anonymity of individual opinions, to allow controlled interaction among group participants, and to provide the opportunity for reconsideration of initial opinions. Limitations of the Delphi method are related to the characteristics of this consensus model, with somewhat structured response options, which do not permit to include additional comments that could be very valuable, particularly in controversial issues. Another limitation is that, it is assessing the perception of the physicians on risk factors rather than assessing the disease-risk factor relationship. But it is important that it reflects an insight based on physician experience and provides stratification. The present study has shown the usefulness of a Delphi-based survey for identifying and classifying key risk factors for IFI-FF in patients with haematological malignancy or in allo-HSCT recipients. Stratification and recognition of key risk factors may improve clinical practice allowing to design preventive and diagnostic strategies, as well as to start early treatment in patients with IFI-FF. Based on these methods, a score with these selected key risk factors may be built and validated for tailoring the best strategy according to the individualized assessment of the patient's risk. However, more studies are needed to validate the risk factors here established by this group of experts in daily practice.

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Supplementary material

Delphi-based study and analysis of key risk factors for invasive fungal infection in haematological patients

QUESTIONNAIRES

A survey study was conducted in which the relevance of different risk factors associated with the development of invasive fungal infection (IFI) caused by filamentous fungi (FF) (IFI-FF) in onco-haematological patients was evaluated. The survey included three questionnaires, a) one addressed to patients diagnosed of multiple myeloma (MM), Hodgkin's lymphoma or non-Hodgkin's lymphoma in which the relevance of 21 risk factors was assessed; b) another questionnaire addressed to patients undergoing allogenic haematopoietic stem cell transplantation (allo-HSCT), in which the relevance of 42 risk factors was evaluated; and c) a third questionnaire addressed to patients diagnosed with acute leukaemia (AL) or myelodysplastic syndrome (MDS), which included 25 risk factors. Five possible closed and mutually exclusive responses were considered for the items of each questionnaire. The five possible responses were: minimal, low, medium, high or maximal relevance. Details of the questionnaires are as follows:

A. MULTIPLE MYELOMA (MM) AND LYMPHOMAS (HODGKIN'S AND NON-HODKIN'S)

1. What degree of relevance do you consider to have neutropenia in risk stratification for IFI?
2. What degree of relevance do you consider to have alterations of cellular immunity in risk stratification for IFI?
3. What degree of relevance do you consider to have breaks in mucocutaneous barriers in risk stratification for IFI?
4. What degree of relevance do you consider to have comorbidity type COPD or structural bronchopneumopathy on chronic treatment with corticoids in risk stratification for IFI?
5. What degree of relevance do you consider to have comorbidity type liver cirrhosis or advanced liver disease in risk stratification for IFI?
6. What degree of relevance do you consider to have progression of haematological disease in risk stratification for IFI?
7. What degree of relevance do you consider to have renal failure in risk stratification for IFI?
8. What degree of relevance do you consider to have the use of antacids or H2 antagonists and proton pump inhibitors in risk stratification for IFI?
9. What degree of relevance do you consider to have advanced age in risk stratification for IFI?
10. What degree of relevance do you consider to have COPD greater than 2 in risk stratification for IFI?
11. What degree of relevance do you consider to have lymphocytopenia (CD4+ < 200 cells/mL) in risk stratification for IFI?
12. What degree of relevance do you consider to have the use of anti-CD52 biological therapies (alemtuzumab or fatumumab) in risk stratification for IFI?
13. What degree of relevance do you consider to have the use of anti-CD20 (rituximab and other) in risk stratification for IFI?
14. What degree of relevance do you consider to have the use of bortezomib in risk stratification for IFI?
15. What degree of relevance do you consider to have the use of lenalidomide in risk stratification for IFI?
16. What degree of relevance do you consider to have treatment with purine analogues (fludarabine) in risk stratification for IFI?
17. What degree of relevance do you consider to have the use of high doses of steroids (1 mg/kg/day for more than 2 weeks) in risk stratification for IFI?
18. What degree of relevance do you consider to have functional or anatomic hyposplenism/anesplenia in risk stratification for IFI?
19. What degree of relevance do you consider to have proximity to construction or remodelling areas (at home or at the hospital) in risk stratification for IFI?
20. What degree of relevance do you consider to have seasonality (winter season) in risk stratification for IFI?
21. What degree of relevance do you consider to have work, hobbies or leisure activities at risk of exposure (gardening, jacuzzis, etc.) in risk stratification for IFI?

B. ALLOGENIC HAEMATOPOIETIC STEM CELL TRASPLANTATION

1. What degree of relevance do you consider to have the diagnosis of AML before transplantation in risk stratification for IFI?
2. What degree of relevance do you consider to have the diagnosis of ALL before transplantation in risk stratification for IFI?
3. What degree of relevance do you consider to have the diagnosis of MSD before transplantation in risk stratification for IFI?
4. What degree of relevance do you consider to have profound neutropenia (ANC < 100 cells/mL) and prolonged neutropenia (more than 14 days) in risk stratification for IFI?
5. What degree of relevance do you consider to have monocytopenia in risk stratification for IFI?
6. What degree of relevance do you consider to have lymphopenia in risk stratification for IFI?
7. What degree of relevance do you consider to have comorbidity type COPD or structural bronchopneumopathy on chronic treatment with corticoids in risk stratification for IFI?
8. What degree of relevance do you consider to have renal failure in risk stratification for IFI?
9. What degree of relevance do you consider to have uncontrolled hyperglycaemia in risk stratification for IFI?
10. What degree of relevance do you consider to malnutrition in risk stratification for IFI?
11. What degree of relevance do you consider to have obesity in risk stratification for IFI?
12. What degree of relevance do you consider to have breaks in mucocutaneous barriers in risk stratification for IFI?
13. What degree of relevance do you consider to have advanced age in mucocutaneous barriers in risk stratification for IFI?
14. What degree of relevance do you consider to have COPD greater than 2 in risk stratification for IFI?
15. What degree of relevance do you consider to have an allo-HSCT from a related donor, identical HLA in risk stratification for IFI?
16. What degree of relevance do you consider to have an allo-HSCT from unrelated donor, identical HLA in risk stratification for IFI?
17. What degree of relevance do you consider to have an allo-HSCT mismatch HLA in risk stratification for IFI?
18. What degree of relevance do you consider to have hematopoietic cell transplantation using umbilical cord cells in risk stratification for IFI?
19. What degree of relevance do you consider to have haploidentical hematopoietic cell transplantation in risk stratification for IFI?
20. What degree of relevance do you consider to have graft failure in risk stratification for IFI?
21. What degree of relevance do you consider to have if the patient is on prophylactic immunosuppressive treatment for GVHD in risk stratification for IFI?
22. What degree of relevance do you consider to have if the patient is on treatment with immunosuppressants and steroids because of grades III-IV GVHD in risk stratification for IFI?
23. What degree of relevance do you consider to have if the patient is on treatment with immunosuppressants and steroids because of extensive chronic GVHD in risk stratification for IFI?
24. What degree of relevance do you consider to have the use of anti-TNFα biological therapies (infliximab, adalimumab, etanercept) in risk stratification for IFI?
25. What degree of relevance do you consider to have the use alemtuzumab in risk stratification for IFI?
26. What degree of relevance do you consider to have lymphocytopenia (CD4+ < 200 cells/mL) in risk stratification for IFI?
27. What degree of relevance do you consider to have the use of anti-thymocyte globulin in risk stratification for IFI?
28. What degree of relevance do you consider to have genetic polymorphisms (MLB, TLR4-2, etc.) in risk stratification for IFI?
29. What degree of relevance do you consider to have a previous episode of IFI in risk stratification for IFI?
30. What degree of relevance do you consider to have iron overload in risk stratification for IFI?
31. What degree of relevance do you consider to have infection by CMV or other herpes group viruses in risk stratification for IFI?
32. What degree of relevance do you consider to have parvovirus B19 infection in risk stratification for IFI?
33. What degree of relevance do you consider to have respiratory viruses infection in risk stratification for IFI?
34. What degree of relevance do you consider to have antifungal prophylaxis with extended-spectrum "azoles" (voriconazole, posaconazole) in risk stratification for IFI?
35. What degree of relevance do you consider to have antifungal prophylaxis with "*candins*" in risk stratification for IFI?
36. What degree of relevance do you consider to have antifungal prophylaxis with polyenes (amphotericin formulations) in risk stratification for IFI?

37. What degree of relevance do you consider to have proximity to construction or remodelling areas (at home or at the hospital) in risk stratification for IFI?
38. What degree of relevance do you consider to have living with pets in risk stratification for IFI?
39. What degree of relevance do you consider to have work, hobbies or leisure activities at risk of exposure (gardening, jacuzzis, etc.) in risk stratification for IFI?
40. What degree of relevance do you consider to have staying in rooms without HEPA filters in risk stratification for IFI?
41. What degree of relevance do you consider to have staying in rooms without laminar air flow in risk stratification for IFI?
42. What degree of relevance do you consider to have seasonality (winter season) in risk stratification for IFI?

C. ACUTE LEUKAEMIAS (AL) AND MYELODYSPLASTIC SYNDROMES (MDS)

1. What degree of relevance do you consider to have AL and MDS in induction treatment in risk stratification for IFI?
2. What degree of relevance do you consider to have AL and MDS in consolidation treatment with haematological response in risk stratification for IFI?
3. What degree of relevance do you consider to have AL and MDS in consolidation treatment without haematological response or refractory patients in risk stratification for IFI?
4. What degree of relevance do you consider to have profound neutropenia (ANC < 100 cells/mL) and prolonged neutropenia (more than 14 days) in risk stratification for IFI?
5. What degree of relevance do you consider to have monocytopenia in risk stratification for IFI?
6. What degree of relevance do you consider to have comorbidity type COPD or structural bronchopneumopathy on chronic treatment with corticoids in risk stratification for IFI?
7. What degree of relevance do you consider to have comorbidity such as liver cirrhosis or advanced liver disease in risk stratification for IFI?
8. What degree of relevance do you consider to have renal failure in risk stratification for IFI?
9. What degree of relevance do you consider to have uncontrolled hyperglycemia in risk stratification for IFI?
10. What degree of relevance do you consider to have malnutrition in risk stratification for IFI?
11. What degree of relevance do you consider to have obesity in risk stratification for IFI?
12. What degree of relevance do you consider to have COPD greater than 2 in risk stratification for IFI?
13. What degree of relevance do you consider to have advanced age in risk stratification for IFI?
14. What degree of relevance do you consider to have antifungal prophylaxis with extended-spectrum "*azoles*" (voriconazole, posaconazole) in risk stratification for IFI?
15. What degree of relevance do you consider to have a previous episode of IFI in risk stratification for IFI?
16. What degree of relevance do you consider to have lymphocytopenia (CD4+ < 200 cells/mL) in risk stratification for IFI?
17. What degree of relevance do you consider to have genetic polymorphisms (MLB, TLR4-2, etc.) in risk stratification for IFI?
18. What degree of relevance do you consider to have iron overload in risk stratification for IFI?
19. What degree of relevance do you consider to have treatment with purine analogues (fludarabine, etc.) in risk stratification for IFI?
20. What degree of relevance do you consider to have treatment with citarabine (high doses) in risk stratification for IFI?
21. What degree of relevance do you consider to have proximity to construction or remodelling areas (at home or at the hospital) in risk stratification for IFI?
22. What degree of relevance do you consider to have work, hobbies or leisure activities at risk of exposure (gardening, jacuzzis, etc.) in risk stratification for IFI?
23. What degree of relevance do you consider to have staying in rooms without HEPA filters in risk stratification for IFI?
24. What degree of relevance do you consider to have staying in rooms without laminar air flow in risk stratification for IFI?
25. What degree of relevance do you consider to have seasonality (winter season) in risk stratification for IFI?