

This is the peer reviewed version of the following article:

Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations / Pagano, Livio; Busca, Alessandro; Candoni, Anna; Cattaneo, Chiara; Cesaro, Simone; Fanci, Rosa; Nadali, Gianpaolo; Potenza, Leonardo; Russo, Domenico; Tumbarello, Mario; Nosari, Annamaria; Aversa, Franco; Lessi, Federica; Criscuolo, Marianna; Farina, Francesca; Tisi, Maria Chiara; Turri, Gloria; Barone, Angelica; Spolzino, Angelica; Del Principe, Maria Ilaria; Quinto, Angela Maria; Di Blasi, Roberta; Maracci, Laura; Nabergoj, Mitja; Cambò, Benedetta; Pegoraro, Anna; Marchesi, Francesco; Pascale, Silvia; Passi, Angela; Carlisi, Melania; Polverelli, Nicola; Beggia, Barbara; Rambaldi, Benedetta; Prezioso, Lucia; Sanna, Marco. - In: BLOOD REVIEWS. - ISSN 0268-960X. - 31:2(2017), pp. 17-29. [10.1016/j.blre.2016.09.002]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

25/04/2024 08:02

(Article begins on next page)

25/04/2024 08:02

Accepted Manuscript

Risk Stratification for Invasive Fungal Infections in Patients with Hematological Malignancies: SEIFEM recommendations

Livio Pagano, Alessandro Busca, Anna Candoni, Chiara Cattaneo, Simone Cesaro, Rosa Fanci, Gianpaolo Nadali, Leonardo Potenza, Domenico Russo, Mario Tumbarello, Annamaria Nosari, Franco Aversa, Federica Lessi, Marianna Criscuolo, Francesca Farina, Maria Chiara Tisi, Gloria Turri, Angelica Barone, Angelica Spolzino, Maria Ilaria Del Principe, Angela Maria Quinto, Roberta Di Blasi, Laura Maracci, Mitja Nabergoj, Benedetta Cambò, Anna Pegoraro, Francesco Marchesi, Silvia Pascale, Angela Passi, Melania Carlisi, Nicola Polverelli, Barbara Beggia, Benedetta Rambaldi, Lucia Prezioso, Marco Sanna

PII: S0268-960X(16)30075-3
DOI: doi:[10.1016/j.blre.2016.09.002](https://doi.org/10.1016/j.blre.2016.09.002)
Reference: YBLRE 455

To appear in: *Blood Reviews*

Please cite this article as: Pagano Livio, Busca Alessandro, Candoni Anna, Cattaneo Chiara, Cesaro Simone, Fanci Rosa, Nadali Gianpaolo, Potenza Leonardo, Russo Domenico, Tumbarello Mario, Nosari Annamaria, Aversa Franco, Lessi Federica, Criscuolo Marianna, Farina Francesca, Tisi Maria Chiara, Turri Gloria, Barone Angelica, Spolzino Angelica, Del Principe Maria Ilaria, Quinto Angela Maria, Di Blasi Roberta, Maracci Laura, Nabergoj Mitja, Cambò Benedetta, Pegoraro Anna, Marchesi Francesco, Pascale Silvia, Passi Angela, Carlisi Melania, Polverelli Nicola, Beggia Barbara, Rambaldi Benedetta, Prezioso Lucia, Sanna Marco, Risk Stratification for Invasive Fungal Infections in Patients with Hematological Malignancies: SEIFEM recommendations, *Blood Reviews* (2016), doi:[10.1016/j.blre.2016.09.002](https://doi.org/10.1016/j.blre.2016.09.002)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Risk Stratification for Invasive Fungal Infections in Patients with Hematological Malignancies: SEIFEM recommendations

Livio Pagano¹, Alessandro Busca², Anna Candoni³, Chiara Cattaneo⁴, Simone Cesaro⁵,
Rosa Fanci⁶, Gianpaolo Nadali⁷, Leonardo Potenza⁸, Domenico Russo⁹, Mario
Tumbarello¹⁰, Annamaria Nosari¹¹, Franco Aversa¹² on behalf of **SEIFEM (Sorveglianza
Epidemiologica Infezioni Fungine nelle Emopatie Maligne) Group.**

Other Authors:

Federica Lessi¹³, Marianna Criscuolo¹, Francesca Farina¹⁴, Maria Chiara Tisi¹, Gloria
Turri⁷, Angelica Barone¹⁵, Angelica Spolzino¹², Maria Ilaria Del Principe¹⁶, Angela Maria
Quinto¹³, Roberta Di Blasi¹, Laura Maracci¹⁷, Mitja Nabergoj¹³, Benedetta Cambò¹², Anna
Pegoraro⁵, Francesco Marchesi¹⁸, Silvia Pascale¹⁹, Angela Passi⁴, Melania Carlisi²⁰,
Nicola Polverelli^{9,21}, Barbara Beggia²², Benedetta Rambaldi⁹, Lucia Prezioso¹², Marco
Sanna²³

¹ Istituto di Ematologia, Università Cattolica S. Cuore, Roma.

² Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Turin, Italy.

³ Clinica Ematologica, Azienda Ospedaliero-Universitaria Santa Maria Misericordia, Udine.

⁴ Ematologia, Spedali Civili, Brescia.

⁵ Oncoematologia Pediatrica, Azienda Ospedaliera Universitaria Integrata, Verona.

⁶ Unità Funzionale di Ematologia, Azienda Ospedaliero-Universitaria Careggi e Università di Firenze.

⁷ Unità Operativa Complessa di Ematologia, Azienda Ospedaliera Universitaria Integrata di Verona.

⁸ UOC Ematologia, Dipartimento di Scienze Mediche e Chirurgiche Materno Infantili e dell'Adulto, Università degli Studi di Modena e Reggio Emilia, Modena.

⁹ Cattedra di Ematologia, Unità di Malattie del Sangue e Trapianto di Midollo Osseo, Dipartimento di Scienze Cliniche e Sperimentali, Università di Brescia e ASST Spedali Civili, Brescia.

¹⁰ Istituto di Malattie Infettive, Università Cattolica S. Cuore, Roma.

¹¹ Divisione di Ematologia e Centro Trapianti Midollo, ASST Grande Ospedale Metropolitano Niguarda, Milano.

¹² Hematology and BMT Unit, Department of Clinical and Experimental Medicine,

University of Parma.

¹³ Dipartimento di Medicina- Unita' Operativa di Ematologia Azienda Ospedaliera di Padova Padova.

¹⁴ Clinica Ematologica, Ospedale San Gerardo, ASST Monza, Università Milano Bicocca.

¹⁵ Pediatria e Oncoematologia, Azienda Ospedaliero-Universitaria, Parma.

¹⁶ Cattedra di Ematologia, Dipartimento di Biomedicina e Prevenzione, Università degli studi di Roma "Tor Vergata".

¹⁷ Clinica di Ematologia, Azienda Ospedaliero-Universitaria, Ospedali Riunti di Ancona, Ancona.

¹⁸ Hematology and Stem Cell Transplant Unit Regina Elena National Cancer Institute Rome.

¹⁹ U.O. Ematologia Clinica Dipartimento di Ematologia Medicina Trasfusionale e Biotecnologie Ospedale Civile Spirito Santo Pescara.

²⁰ Cattedra ed U.O. di Ematologia con trapianto, Dipartimento di Medicina interna e specialistica, Università degli Studi di Palermo.

²¹ Institute of Hematology and Clinical Oncology "L. and A. Seràgnoli", Department of Experimental, Diagnostic and Specialty Medicine (DIMES), St.Orsola-Malpighi University Hospital Bologna.

²² Divisione di Ematologia, AO San Giovanni Addolorata, Roma.

²³ Divisione di Ematologia, Università di Cagliari.

ABSTRACT

Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in immunocompromised patients. Patients with hematological malignancies undergoing conventional chemotherapy, autologous or allogeneic hematopoietic stem cell transplantation are considered at high risk, and *Aspergillus* spp. represents the most frequently isolated micro-organisms. In the last years, attention has also been focused on other rare molds (e.g., Zygomycetes, *Fusarium* spp.) responsible for devastating clinical manifestations. The extensive use of antifungal prophylaxis has reduced the infections from yeasts (e.g., candidemia) even though they are still associated with high mortality rates.

This paper analyzes concurrent multiple predisposing factors that could favor the onset of fungal infections. Although neutropenia is common to almost all hematologic patients, other factors play a key role in specific patients, in particular in patients with AML or allogeneic HSCT recipients. Defining those patients at higher risk of IFIs may help to design the most appropriate diagnostic work-up and antifungal strategy.

Keywords: molds; yeast; leukemia; hematopoietic stem cell transplantation; risk factors.

1. INTRODUCTION

Hematologic disorders comprise a great variety of malignant diseases requiring treatment strategies that may differ significantly from one another. In this respect, conventional chemotherapy treatments have recently been joined by alternative therapies. In patients with acute leukemia, chemotherapy and stem cell transplantation are regularly curative in a consistent number of cases; however, monoclonal antibodies (MoAbs) and cellular therapies are now becoming a valid alternative option. Likewise, lymphoproliferative and myeloproliferative disorders have witnessed the development of novel chemo-immunotherapy regimens, MoAbs and biologic agents [1,2]. According to these considerations, we might expect that the inclusion of novel agents in standard treatment combinations would result in consistent benefits for patients with hematologic malignancies. On the other hand, the real immunologic effects of these new treatment modalities are largely undetermined, raising the possibility of infectious complications.

Invasive fungal infections (IFIs) are opportunistic diseases that can develop because of the concurrence of multiple predisposing factors. Among all immunocompromised hosts, those considered at higher risk for developing IFIs are patients affected by hematological malignancies (HMs) and, above all, acute leukemias and those undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [3,4].

Risk factors for yeast and mold infections may differ significantly from each other; however, it should be emphasized that the epidemiology of IFIs in hematologic patients has shifted in the most recent years, and mold, in particular *Aspergillus* spp., have become the predominant pathogens. In fact, yeasts and, above all, *Candida* spp. have historically been the most common causative organisms [5]; however, recent epidemiological studies clearly demonstrated that invasive candida infections, probably due to effective current antifungal prophylaxis, represent a rare event in HMs [6]. In contrast, the most frequent

and dangerous IFIs observed in HMs are those caused by molds, in particular those caused by *Aspergillus* spp. [7]. Based on these observations, the majority of recently published studies have defined the overall risk of IFIs in HMs [7-10]. Similarly, the present review will consider the risk factors for IFIs, assuming that *Aspergillus* spp. represent the most common pathogen.

While remaining a major cause of death from infectious complications, IFIs represent one of the significant causes of expense in the management of HMs [11,12]. Over the past decade, the cost of antifungal strategies (imaging, microbiology and antifungal agents) have increased dramatically, as has the risk of antifungal resistance [13-15]. Furthermore, the drug-drug interactions between antifungal agents, chemotherapy and immunosuppressive agents remain a major concern [16, 17].

The aim of this review is to analyze the risk of developing an IFI among different HMs and HSCT procedures, with particular emphasis on the phases of treatment of the underlying malignancy. In fact, it seems of the utmost importance for clinicians to have a model that can serve as a guide to categorize the risk for IFI among different hematologic malignancies. The choice of antifungal prophylaxis, diagnostic testing, kind of antifungal approaches (i.e. empirical or pre-emptive) are outside of the scope of this consensus and on-going efforts are underway for these information.

Improved knowledge of the actual risk (low, intermediate or high) of developing an IFI can allow physicians to reduce the administration of antifungal drugs (prophylaxis and empirical treatment) in patients where the risk of IFIs is negligible and may help to initiate timely antifungal treatment in those where the risk of IFI is high.

2. METHODS

A systematic literature review was performed using PubMed database listings

through September 2015 for the following MeSH terms: neutropenia, treatment, HMs, stem cell transplantation, fungal infection, aspergillosis, candidemia, risk factors.

The attention was focused on the epidemiology and risk factors for IFIs.

The co-authors reviewed all the publications identified and prepared a slide set comprising evidence-based statements and recommendations presented to the plenary session on the annual SEIFEM Group meeting 2015. After revision according to the results of the plenary discussion, a summary report was made.

3. RISK FACTORS IN HEMATOLOGICAL DISORDERS

The identification of risk factors predisposing to IFIs in HMs may be extremely complex in clinical practice. Beyond the well-known characteristics that favor the development of IFIs, systematic studies on a large series of patients outside of an AML or allograft setting are lacking. The patients' medical history, including the home environment, previous lifestyle, actual HMs and disease stage, and the role of leukocytes (neutrophils, monocytes, lymphocytes) are still of great significance in predicting the onset of IFIs [3,4,18]. Moreover, in the era of new drugs, a great deal has changed in terms of therapeutic approaches and antifungal treatments. On one hand, a growing number of patients is being treated with chemotherapy-free regimens with a prevalent immunomodulating action [19,20]. On the other hand, the introduction of mold-active antifungal prophylaxis (i.e., posaconazole or voriconazole) has changed the epidemiology, clinical and laboratory manifestation and timing of fungal infections [21].

3.1 RISK FACTORS IN ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is the hematologic disease with the highest rate of

IFIs, with an incidence ranging from 10 to 25% according to SEIFEM epidemiologic studies [7,22,23,24]. The overall outcome of AML has improved in recent years, mainly thanks to improvements in supportive care. In fact, the chemotherapy protocols have changed very little, while new antibiotics and new diagnostic methods have become available. For this reason, although the incidence of the IFIs is still very high in AML, particularly during the remission induction phase, the IFI-attributable mortality has decreased progressively, going from 60-70% in the past to the current 20-30% [4,25-27]. However, AML is a very heterogeneous disease, and the incidence of IFIs is highly variable depending on the type of leukemia, the patient's characteristics and the fungal exposure [3,4,25-31]. For example, acute promyelocytic leukemias (APLs) have a documented lower incidence of IFI complications than other AML subtypes, probably due to the mild induction chemotherapy and the short duration of severe neutropenia. Indeed, patients with APL receiving a chemotherapy-free treatment could be considered at low risk for IFIs, and thus, a diagnostic work-up for IFIs as well as any antifungal prophylaxis protocol should be reviewed [23].

In a recent, prospective epidemiologic study by SEIFEM (including more than 1000 AML cases), the following pre-treatment variables were identified in multivariate analysis as high risk factors of IFIs after the first course of chemotherapy: performance status of 2 or greater; chronic obstructive pulmonary disease; recent house renovation; and job with high exposure, such as construction work, farming and gardening [18,25].

Overall, on the basis of the more recent published papers, the risk factors for IFIs in AML can be classified in four main categories: leukemia-related factors (advanced stage of the disease, failure to enter CR), host-related factors (performance status, comorbidities, older age, organ dysfunction, unfavorable genetic pattern), treatment-related factors (deep and prolonged neutropenia, severe mucositis-associated chemotherapy), and fungal exposure-related factors (patient rooms without HEPA filters, previous IFI). These factors

are reported in Table 1 [4,18,25,27-29].

The definition of risk factors for IFI might allow the identification of three main groups of AML patients (High risk, Intermediate risk and Low risk) and contribute to designing their diagnostic, prophylactic and therapeutic approaches. Indeed, risk stratification may be considered a useful tool for defining high-risk patients who might benefit from avoiding the overtreatment of low-risk patients.

A careful assessment of pre- and post-treatment risk factors for IFIs should become part of our routine evaluation of patients at the time of the diagnosis of AML and over the course of the disease [4,25,29,31]. A delay in bone marrow blast clearance after induction chemotherapy along with additional risk factors contribute to favor infection complications [25]. This so-called “dynamic adapted antifungal strategy” may enable clinicians to select the best patient-tailored antifungal strategy and may improve the management of IFIs in all phases of AML [25,29].

3.2 MYELOYDYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDSs) are associated with a risk of severe infections due to quantitative and qualitative granulocytic defects, such as impaired bactericidal and fungicidal activities; reduced expression of the CD11b/CD18 complex; and functional anomalies of myeloperoxidase, lysozyme, superoxide anion lactoferrin and antibiotic proteases such as elastase and cathepsin G [32,33]. Other immunological abnormalities include impaired B, T, T-reg and NK (NK G2D) cell functions [34,35].

In addition, advanced age, the presence of comorbidities and iron overload are significant additional risk factors for MDS. Iron is an essential factor for both the growth and virulence of most microorganisms. Iron overload, which is frequently observed in MDS due to red blood cell transfusions, increases the risk of bacterial infections and IFIs, such as mucormycosis or aspergillosis, through complex mechanisms including the inhibition of

IFN-gamma, TNF-alpha, and IL-2 and the impairment of macrophage, neutrophil and T-cell functions [36-38].

In a recent review, it was emphasized that despite these risk factors [39], the incidence of IFIs in MDS is not frequently reported even in more recent prospective clinical trials [40,41]. In some prospective registries of IFIs, the incidence of proven/probable IFIs in MDS is lower than that reported in AML [42-45].

Patients with transformed MDS can be treated with either AML-like chemotherapy protocols or hypomethylating agents. In a prospective multicenter observational study on decitabine treatment in 101 MDS patients (47.5% high-risk), the rate of infectious events was significantly higher during the first 3 courses, with an IFI incidence of 12% during 97 febrile episodes [46]. In another retrospective multicenter study in 157 high-risk MDS patients treated with azacitidine, the incidence of IFIs was 4.8%; in univariate analysis, the most important risk factors for infections were low hemoglobin level, low platelet count, unfavorable cytogenetics and low neutrophil count; additionally, in this study, the rate of infections decreased gradually along with the progression and probable efficacy of therapy [47]. In contrast, the risk of IFIs significantly increased in MDS patients treated with azacitidine as salvage therapy after intensive chemotherapy (IC) compared to patients who received front-line azacitidine (risk difference of 22.4%) and in those treated with azacitidine at a standard dose (75 mg/m² for 7 days) compared to short-schedule treatment (75 mg/m² for 5 days) [48,49].

Data reported in these recent clinical trials indicate that the most relevant risk factors of IFIs in MDS patients receiving hypomethylating agents seem to be: 1) High IPSS risk (> 1.5) 2) Type of azacitidine treatment (salvage after IC or conventional dosage of 75 mg/m² for 7 days); and 3) Number of azacitidine or decitabine cycles, with a higher risk during the first 2-3 cycles.

3.3 ACUTE LYMPHOBLASTIC LEUKEMIA

The risk of developing IFIs in acute lymphoblastic leukemia (ALL) patients has not yet been fully elucidated. Most epidemiological studies report data concerning heterogeneous series, mainly represented by AML patients. However, some retrospective studies also demonstrated a not irrelevant IFI incidence in ALL patients, which was 6.5% in the SEIFEM study [7], with a predominance of mold infections (4.3%), particularly during induction/reinduction treatment; the incidence of aspergillosis was even higher (6.8%) in a French cohort doing construction work [50]. There are some discrepancies regarding the incidence of IFIs in two different studies on prophylaxis in a well-defined setting, such as in acute leukemia (AL) induction patients. In a randomized (casposfungin vs. investigator's choice) prospective study in AML/ALL induction patients, only one case of proven/probable IFIs was reported among 37 patients (2.7%) [51]; in a larger and more recent study comparing liposomal amphotericin B to placebo, the percentage of IFIs was higher, with a 7.9% and 11.7% incidence in the two arms, respectively. This high incidence may reflect a more aggressive schedule of treatment given to adult ALL patients, which was recently introduced with the aim of improving the percentage of long-term survivors; still, this value is disappointing if compared to observations made with a pediatric population [52].

Indeed, the more intensive, pediatric-like schemes demonstrated better results in younger adults, with a low incidence of infections [53,54], while this approach exhibited elevated toxicity, mainly due to infectious complications during induction treatment, among older ALL patients, resulting in lower event-free survival (EFS) and overall survival (OS) [55]. In fact, the incidence of non-fatal IFIs was 8.3% during induction in a Dutch-Belgian study for patients above 40 years [56]; in the United Kingdom Medical Research Council (MRC) cohort, IFIs were reported in 9-10% of patients above 55 years during phase 1 and 2 induction, respectively [57].

High doses of dexamethasone were also associated with a relevant incidence of IFIs during the induction phase. Eleven cases (mainly mold infections) were observed in 60 patients (18.3%) enrolled in the GRAAL-SA1 study [58], and similar results were reported in elderly patients in the phase 2 GRASPAAL/GRAAL-SA2-2008 study (23% IFIs during induction phase 1) [59].

Few studies reporting data on IFI incidence are available in relapsed/refractory ALL, which is considered a category at high risk for infections. IFIs were responsible for death in 6.5% of relapsed/refractory ALL patients in the PETHEMA group study [60]. In a recent study conducted at the M.D. Anderson Cancer Center, the incidence of proven IFIs was 10.8% (4/37) in relapsed/refractory ALL patients treated with chemotherapy and high doses of dexamethasone (MOpAD regimen), with yeast being the most frequently involved despite fluconazole prophylaxis [61].

Tyrosine kinase inhibitors (TKIs) significantly improved the outcome of Philadelphia-positive (Ph+) ALL. Infectious complications due to IFIs were relatively low when TKIs were associated with standard or reduced-intensity chemotherapy as a first-line treatment (3% and 3.8% in the PETHEMA and NILG studies, respectively) [62,63]. Infectious events were even lower in patients treated with TKIs alone, and, in this setting, IFIs were not reported at all, both in first-line and in salvage therapy [64,65].

Few or no data are available on the incidence of IFIs during monoclonal antibody-containing regimens or new treatment options, such as blinatumomab or chimeric antigen receptor (CAR) T-cell therapy. Although cases of fatal *Candida* spp. infections have been reported in relapsed patients treated with blinatumomab [66], further studies are warranted in order to clarify the role of new treatments as immunosuppressive agents.

ALL can be considered a risk factor for IFIs in elderly patients, particularly those over 55 years, receiving intensive (pediatric-like) induction therapy or reinduction for relapsed ALL including high cumulative doses of corticosteroids. Younger adults, patients in

complete remission and those receiving less intensive regimens, including TKI inhibitors, are associated with a low risk for IFIs. Adverse biological features may also be helpful in the early identification of a proportion of poorly responsive ALL patients who should be considered susceptible to IFI [25].

3.4 CHRONIC LYMPHOPROLIFERATIVE DISORDERS

In chronic lymphoproliferative disorders, the incidence of IFIs varies from 0.5 to 10.8% and seems to have increased in the last few years, probably due to more widespread use of new targeted treatments.

For non-Hodgkin Lymphoma (nHL), from 2005 to 2015, 7800 patients have been enrolled in 7 prospective [29,67] and 5 retrospective [7, 68-71] studies. The incidence of IFIs rose from 1.6% in 2006 [7] to 4.3% in 2014-2015 [69]. The average incidence was 2.6%. Risk factors were analyzed in 5 studies [29, 67-70], and multivariate analysis showed that severe and prolonged neutropenia, the status of the disease (advanced versus the diagnosis), and prior IFI were factors independently associated with the occurrence of IFIs.

In the same period, 5 studies have evaluated the incidence of IFIs among 4846 patients with Hodgkin's Lymphoma (HL) [7, 67-69, 72]. The incidence of IFIs ranged from 0.3% [72] to 1.2% [69], although no definite risk factors were identified, except severe and prolonged neutropenia [67-69]. Consequently, patients with HL may not be considered at risk for IFIs, and in this setting, screening for IFIs should not be performed routinely, but only when clinically required. However, particular attention must be paid when patients receive very aggressive treatment (e.g., "*escalating* BEACOPP") [71].

For multiple myeloma (MM), 9 studies were retrieved, evaluating 4025 patients [25,29,69,71,73-77]. The incidence of IFIs ranged from 0.4% to 14% in the most recent studies. The multivariate analysis of risk factors identified severe neutropenia, use of

bortezomib, three or more lines of treatment and a previous history of IFI as the main factors affecting the occurrence of IFIs [29,76,77].

Five studies, including 1847 patients, were identified evaluating the incidence and risk factors for IFIs in patients with chronic lymphocytic leukemia (CLL) [25,29,71,78,79]. The incidence of IFIs ranged from 0.5% [25] in the early 2000s to 7.8% in the most recent study [55]: univariate analysis showed that neutropenia, prior IFI, lymphocytopenia, the stage and state of the underlying malignancy, CD38 expression, genetic analysis (p53, ATM or 12+), and IgVH mutation status were all factors associated with the presence of IFIs.

In all the other chronic lymphoproliferative disorders, severe and prolonged neutropenia, the stage and state of the underlying diseases and more than two therapeutic lines were the most important risk factors for IFIs when multivariate analysis was considered. The possibility that novel drugs, and in particular the proteasome inhibitor bortezomib, may increase the risks of such infections should be further investigated.

However, the vast majority of the studies were retrospective, and the analyses performed were extremely heterogeneous. Epidemiologic prospective studies are urgently needed to assess the current incidence and risk factors of IFIs in this setting in order to identify the most appropriate clinical monitoring for those patients who appear in new categories of subjects at risk.

3.5 MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative neoplasms (MPNs) include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) [80].

Data regarding the epidemiology of infectious complications in MPN are scanty and mainly related to outdated treatment modalities. In the last ten years, the availability of new targeted drugs has significantly modified the therapeutic landscape in MPNs, improving

survival and disease-related symptoms [81-83]. However, some concerns regarding the immunosuppressant activity of these drugs were raised after the documentation of opportunistic infections during treatment [84-87].

Most patients affected by CML are diagnosed in the chronic phase (CP); a minority may present after progression to the blastic phase (BP), which is comparable to acute leukemia. The survival of CML patients has been dramatically improved with the availability of TKIs targeting the BCR-ABL1 oncoprotein, leading to disease control in the great majority of patients.

In-vitro studies have demonstrated that tyrosine kinase inhibition affects the cell-mediated immune-response, possibly creating a permissive microenvironment for opportunistic infections [88-91]. Additionally, a non-negligible rate of neutropenia is observed during treatment, especially during the first months of therapy. Despite these relevant findings, registrative trials, IRIS (imatinib vs. interferon plus low-dose cytarabine), DASISION (dasatinib vs. imatinib), ENESTnd (nilotinib vs. imatinib), BELA (bosutinib vs. imatinib) and PACE (ponatinib) did not report IFIs in CP CML patients [92-95].

The majority of currently approved kinase inhibitors are significantly affected by CYP3A4 inhibitors/inducers. Although fungal infections are uncommon in patients with CML, caution is required when TKIs are used with azole antifungals, which are moderate or strong CYP3A4 inhibitors.

ET and PV are chronic pro-thrombotic diseases with favorable prognosis and no increased incidence of infections. Conversely, infections are one of the main causes of morbidity and mortality in MF, with approximately 10% of patients dying from infections and sporadic cases of fungal complications [96-101]. The increased infectious risk in MF depends on intrinsic immune deregulation but also on treatment strategies [102].

Targeted therapy with JAK (Janus kinase) inhibitors has shown promising activity in controlling constitutional symptoms and splenomegaly in MF and PV. Ruxolitinib, the first

approved JAK1/JAK2 inhibitor, was recently associated with the occurrence of opportunistic fungal infections, namely *Cryptococcus neoformans* and *Pneumocystis jiroveci* pneumonia, nodal and lung involvement by *Talaromyces marneffe* and sino-orbital mucormycosis [103-106].

More recently, a multicenter Italian study in 507 MF patients on infectious complications in MF reported 112 cases of grade 3-4 infections. Among these complications, only 2 cases of IFIs were detected [107]. In that cohort, disease status in terms of IPSS risk score and massive splenomegaly were found to correlate with an increased risk of infection, but this effect was not specific for IFIs.

Overall, fungal infections represent a rare but potentially fatal complication in MF. No evidence has been found of specific risk factors for IFIs in these subsets of patients.

3.6 AUTOLOGOUS STEM CELL TRANSPLANTATION

The number of autologous stem cell transplantations (ASCTs) reported in the EBMT (European Bone Marrow Transplantation) and GITMO (Gruppo Italiano Trapianti Midollo Osseo) registries over the last 10 years has progressively increased to approximately 20,000/year [108,109], with more than 80% of the patients receiving ASCT for the treatment of lymphomas and myelomas and less than 5% of the patients receiving ASCT for AMLs [110]. Overall, the incidence of IFIs in patients receiving ASCT for HMs ranges from 3% to 8% [8,73,75,111-115].

Data from the literature do not allow us to fully understand the reasons for the great variability of IFI incidence reported in the last decade. Most published articles are based on retrospective studies, and only a few of them included a consistent high number of patients with lymphoma and myeloma [75,112]. Along this period of observation, an apparent reduction of the mortality correlated with IFIs has been reported, as has a prevalence of mold infections [8,111].

The local epidemiology or the specific antifungal use in different centers may have an impact on the incidence of IFIs. However, some independent risk factors emerged from the reported studies, including prior fungal infection, *Candida* colonization, the duration of neutropenia, the duration of steroid treatment, the use of fludarabine and the advanced status of disease [75,115-117]. To date, there is not stringent evidence that either the prior use of fludarabine ASCT in patients with lymphoma or the use of IMiDs in MM patients may induce an increased risk of fungal infections.

From this analysis, we can conclude that patients who undergo ASCT and have one or more risk factors should be considered at intermediate risk of fungal infections [111].

3.7 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Allogeneic HSCT recipients represent one of the categories of patients at high risk of developing IFIs [4]. According to the most recent epidemiological studies including a large number of patients, the reported incidence of IFIs ranges between 7% and 15% [9,113,115,118]. Nevertheless, there is now ample evidence showing that vulnerability to IFIs appears to be multifactorial, including standard, well-known clinical risk factors and other new factors that can impact antifungal defenses. A better understanding of the risk factors potentially for IFIs would improve our ability to discriminate high-risk patients who might benefit from more aggressive therapeutic strategies. In this respect, it is of utmost importance to discriminate between risk factors already present at the time of HSCT and unpredictable variables that might occur during the post-transplant clinical course (table 2).

Age is a well-recognized risk factor, even among allogeneic HSCT recipients, although a specific threshold has not been defined [111,119-121].

There is no doubt that the patient's history, the type of underlying malignancy (MDS/AML, lymphomas) and the presence of active hematologic disease will certainly predict vulnerability to infection during conditioning and transplantation [10,122,123].

Iron overload (IO) has been identified as an independent risk factor for invasive aspergillosis [119, 124-127], although two major drawbacks limit its applicability in the clinical practice. First, the estimation of the iron burden is primarily based on serum ferritin as a surrogate for IO; however, many confounding factors, particularly in HSCT recipients (GVHD, liver damage, inflammation), may result in potential ferritin overestimation. Second, a specific threshold of serum ferritin defining the risk for IFD has not been identified.

A consistent number of studies have documented that patients receiving transplants from alternative donors are at a high risk for IFIs, while those receiving grafts from matched sibling donors in the absence of additional risk factors should not be considered a risky procedure [9,10,111,115,119,122]. The presence of polymorphisms in genes such as TLR-4, dectin-1 or pentraxin have been reported to significantly influence the occurrence of post-HSCT IFIs when associated with high-risk transplants (MUD, haplo), although it should be emphasized that a large number of potential genetic risk factors for IFIs have been described [128-132].

We know that neutropenia is no longer the only primary risk factor for IFIs after HSCT. In fact, many IFIs develop when neutrophil counts have been normalized, months or even years after the transplant, when abnormalities in lymphocyte counts and functions remain the main risk factor. [133,134].

The crucial role of GVHD and immunosuppressive treatments (ISTs) in the development of IFI has been documented by several studies [9,10,118-121,123]. In this respect, the Seattle group showed that patients with moderate-to-severe GVHD who were treated with high-dose corticosteroids had a significantly increased incidence of IFIs [135]. Corticosteroids compromise the neutrophil and monocyte-macrophage activity as well as immunity to fungi by inducing lymphopenia, decreasing lymphokine production and inducing Th1/Th2 dysregulation [136]. Similarly, the use of other ISTs, including

basiliximab, alemtuzumab, ATG and infliximab, dramatically increases the rate of IFIs [9,115,118,119,123,137,138].

CMV infection is a well-documented predisposing factor for IFI in allo-HSCT. In fact, CMV itself modulates the immune response by suppressing the function of antigen-specific CTLs and by impairing neutrophil activity and macrophage respiratory burst. Notably, treatment of CMV infection commonly includes ganciclovir, which in turn may be considered an additional worsening factor due to the drug-related neutropenia [139].

Lastly, high environmental *Aspergillus spp.* spore counts represent a significant risk factor for IFI in HMs and particularly among HSCT recipients [140].

Taken as a whole, the defective recovery of both innate and adaptive immunity after HSCT may be considered as a condition shared by all risk factors, ultimately favoring the development of IFIs. As a result, novel strategies to enhance post-HSCT immune reconstitution are currently in clinical development.

3.8 RISK FACTORS IN SEVERE APLASTIC ANEMIA (SAA)

SAA is bone marrow failure characterized by the reduction of hematopoietic stem cells, leading to a severe pancytopenia. Profound and persistent neutropenia is the major risk factor for the development of IFIs in patients with SAA, although there are significant differences between the immune impairment of SAA patients and that of patients with neutropenia secondary to chemotherapy treatment [141]. In addition, the different treatments of SAA may influence the risk of IFIs. Immunosuppressive therapy typically includes ATG and cyclosporin, resulting in profound T-cell depletion and dysfunction. For patients eligible for HSCT, the transplant procedure may be considered an additional risk factor. Very few data are available regarding the incidence of IFI in patients with SAA. Valdez et al. reported a significant reduction in the incidence of IFIs in SAA, from 49% during 1989-1996 to 8% in the most recent years (2002-2008) [142]. This reduction was

predominantly related to a decrease in the frequency of invasive pulmonary aspergillosis. Indeed, *Candida* spp. are not frequently observed in patients with SAA, while *Aspergillus* spp. are among the most common infections reported in the literature.

3.9 RISK FACTORS IN PEDIATRIC PATIENTS

Although children are less exposed than adults to risk factors for fungal diseases, such as environmental or living habits (i.e., smoke, drug addiction, job or hobbies in dusty places), they are equally prone to developing fungal complications when a chemotherapy-based approach is required to treat their hematological diseases. We identified 11 papers published from 2005 onwards that analyzed the incidence of IFIs in pediatric patients [143-154]. In 4 studies, patient enrollment started before the 2000s [143,146,147,151], whereas in the remaining studies, the patients were recruited after the 2000s. Six papers considered IFIs in patients affected by acute leukemia or treated for malignancy [144,147-150, 152], whereas 5 papers considered only patients who underwent HSCT, for a total of 3674 patients assessed [143,145,146,151,155]. Overall, the reported incidence of IFI was < 5% in one study only [152], ranged between 5% and 10% in 3 studies [146-148] and was > 10% in 7 studies [143-145,149-151,155]. From a methodological point of view, 3 studies were prospective [145,150,152], 7 studies were retrospective [143,146-149,151, 155], and one was a case-control study [144]; moreover, 4 studies included also patients with possible IFIs in the analysis of risk factors [143,146,147,152]. All studies considered IFIs by *Aspergillus* spp, *Candida* spp. and other fungal etiologies, except one study, which considered *Aspergillus* spp. infection only [146]. The significant risk factors for IFIs in multivariate analysis are shown in Table 3. In HSCT patients, acute and chronic GVHD, high-dose steroid treatment at ≥ 2 mg/kg/day, older age at transplant, and a priori TRM risk $\geq 20\%$ on the basis of the EBMT risk score [153] were significant risk factors. In one study, other factors were significantly associated with IFI in univariate analysis, including

the diagnosis of severe aplastic anemia or Fanconi anemia, severe neutropenia lasting more than 10 days, and adolescence or teenage years [143].

The risk factors associated with IFIs in patients treated with chemotherapy were related mostly to the need for intensive treatment [155-158] and included ALL at high risk of relapse or relapsed ALL, AML, and prolonged and deep neutropenia. The use of a central venous catheter and admission to pediatric intensive care were risk factors, especially for *Candida* infection. Moreover, the risk of IFIs was associated with persistent fever lasting 4 days or more, severe monocytopenia, and elevated C-reactive protein [152].

4. DISCUSSION

The identification of factors influencing the onset of IFIs in patients with HM undergoing chemotherapy or bone marrow transplantation procedures is one of the most important strategies in current clinical practice. Knowledge of these parameters is useful for the better identification of patients to be considered at the highest risk and for defining the most appropriate surveillance procedures or preventive strategies [3,4]. More importantly, in patients with HMs, these factors can be frequently upgraded due to the frequent changes in clinical practice (e.g., introduction of posaconazole prophylaxis in AML with a consequent reduced incidence of IFI in the induction therapy phase) and treatment approaches that continuously modify the host condition [154,159].

Risk stratification of IFI is extremely complex because outside of patients with AML or undergoing allografts, systematic studies on large series are lacking. Experts, often on behalf of different scientific societies, have long tried to identify specific risk factors in different categories of HMs [3,4,]. The 5th European Conference on Infections in Leukemia (ECIL) suggested that HMs other than AML or HSCT require some antifungal prophylaxis, although they did not analyze the risk factors in each subgroup in order to identify those at higher or lower risk (except for allo-HSCT) [160]

It is clear that the patient's history, environment and lifestyle prior to the onset of malignancy, the diagnosis of malignancy, and a disease stage beyond the first complete remission will certainly predict vulnerability to IFIs during conventional chemotherapy and transplantation procedures [4,18].

In addition to well-known risk factors common to all patients (e.g., neutropenia, neutrophil dysfunction, lymphocytopenia, monocytopenia, steroid use, hospital air control) [32,33,137,161-164] new entities were included over time and linked to more aggressive treatment of the underlying disease.

In the past decade, new drugs (i.e., immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, PI3K inhibitors, tyrosine-kinase inhibitors) have been introduced for the treatment of HMs. The price for improved control of the underlying diseases is a higher risk of IFI in this non-neutropenic cohort of patients. The corollary appears to be a lowered resistance to infection, which is rather surprising in patients who did not usually present this type of complication. One consequence of this immunodeficiency, unlike the neutropenia alone that is prevalent in AL, is a higher incidence of opportunistic infections; with increasing frequency, a higher-than-expected risk for IFIs has been reported with the administration of immunotherapies such as monoclonal antibodies [165]. In this category of patients, in whom the presence of IFIs is rather underestimated, diagnosis may also be difficult because the radiologic findings are often nonspecific, possibly due to the immunosuppression that is different from neutropenia [166,167]. Accordingly, in these symptomatic immunosuppressed patients, the concomitant presence of atypical radiologic features and well-defined risk factors recommend rapid and invasive diagnostic procedures to exclude the presence of a fungal disease.

Another important point not well defined by the current literature is whether the risk can vary with the underlying malignancy state. In AML, which is the more studied hematological malignancy regarding IFI, few data on the incidence rate, for example, in the

consolidation or resistant phases have been published.

Thus, after a comprehensive analysis of current epidemiological data and risk factors reported in the literature, we established that the risk stratification reported in Table 4 can be considered at present the most reliable for the evaluation of the potential risks for IFIs in patients with HMs according to diagnosis, phase and type of treatment.

A possible algorithm that takes into account the dynamic risk and all cofactors that may influence the onset of IFI is depicted in Figure 1. Although this approach designed for AL is the best, it may not be easily transferred to all the categories of HM patients due to the lack of data and studies on large series that would allow researchers to validate the actual correctness of this methodology.

5. CONCLUSION

IFIs remain a major problem in HMs despite the availability of new appropriate multidisciplinary diagnostic approaches that make an “in vivo” diagnosis feasible [164]. However, given these emerging categories of patients "at risk", one would expect increasing costs of antifungal drugs (more efficient but more expensive) and the appearance of resistance, in particular to azoles because they are also used in agriculture [1-17,168].

In this literature review, we analyzed the current data regarding the epidemiology of and risk factors for IFIs in patients with HMs. In agreement with other recent reports, at present, the risk stratification for IFI should take into consideration the “non-static level of risk” for IFI. For instance, the risk of IFI could be low in patients at the time of diagnosis of the underlying hematological malignancy, while in the following months, during the management of HM, the same patient could be considered at high risk in the case of non-responsiveness to the anti-neoplastic treatment. The present review might offer a useful tool for designing future studies with the aim of optimizing the diagnostic procedures and

therapeutic strategies for preventing and treating IFIs in patients with HMs.

6. PRACTICE POINTS

Why is a risk stratification of IFIs necessary?

- High costs for diagnostics procedures and antifungal treatments
- Increased antifungal resistance
- Drug-drug interactions between antifungal, antineoplastic and immunosuppressive agents
- Need for a risk-adapted antifungal prophylaxis, diagnostic work-up and treatments (empiric vs. pre-emptive antifungal therapy)

7. RESEARCH AGENDA

- Improved knowledge of the risk factors for IFIs in HMs other than AMLs and HSCTs.
- Identification of the risk factors in different phases of treatments (i.e., AML in consolidation or resistant-relapse).
- Develop a new strategy based on risk factor identification (do not forget that IFI risk may change day-to-day).

Conflict of interest statement

L.P. has received honoraria from Gilead Sciences, Janssen, Basilea, Merck and Pfizer Pharmaceuticals and has been a speaker for Gilead Sciences, Merck, and Basilea.

A.C. has received honoraria from Gilead Sciences, Merck and Pfizer Pharmaceuticals and has been a speaker for Gilead Sciences, Merck, and Pfizer.

R.F. has received honoraria from Merck and has been a speaker for Merck

C.C. no disclosures

LePo has received research funds and honoraria from Gilead Sciences, Merck Sharp and Dohme and Pfizer Pharmaceuticals.

G.N. has been a speaker for Pfizer and Merck.

D.R. no disclosures.

A.B. has received honoraria from Gilead Sciences, Merck, Pfizer Pharmaceuticals, Basilea, Jazz Pharmaceuticals and Hospira; he has been speaker for Gilead Sciences, Merck, Pfizer Pharmaceuticals, Astellas Pharma, and Novartis.

S.C. has received speaker honoraria from Gilead Sciences and Merck Sharp and Dohme

A.N. has received honoraria from Gilead Sciences and speaker honoraria from Merck Sharp and Dohme

M.T. has received honoraria from MSD and Pfizer and has been a speaker for Gilead Sciences, MSD, and Pfizer.

F.A. has received honoraria from Gilead Sciences, Basilea, Merck, Roche and Pfizer Pharmaceuticals and has been a speaker for Gilead Sciences, Merck, Pfizer and Roche.

All other authors declare no conflict of interest.

REFERENCES

1. Teo EC, Chew Y, Phipps C. A review of monoclonal antibody therapies in lymphoma. *Crit Rev Oncol Hematol*. 2016; 97:72-84.
2. Stein BL, Gotlib J, Arcasoy M, et al. Historical views, conventional approaches, and evolving management strategies for myeloproliferative neoplasms. *J Natl Compr Canc Netw*. 2015;13:424-34
3. Herbrecht R, Bories P, Moulin JC, Ledoux MP, Letscher-Bru V. Risk stratification for invasive aspergillosis in immunocompromised patients. *Ann N Y Acad Sci*. 2012;1272:23-30
4. Pagano L, Akova M, Dimopoulos G, Herbrecht R, Drgona L, Blijlevens N. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *J Antimicrob Chemother*. 2011;66 Suppl 1:i5-14.
5. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis*. 1999;28:1071-9
6. Cornely OA, Gachot B, Akan H, et al. Epidemiology and outcome of fungemia in a cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). *Clin Infect Dis*. 2015;61:324-31.
7. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006;91:1068-75
8. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001-2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis*. 2010;50:1091-100.
9. Omer AK, Ziakas PD, Anagnostou T, et al. Risk Factors for Invasive Fungal Disease

after Allogeneic Hematopoietic Stem Cell Transplantation: A Single Center Experience. *Biol Blood Marrow Transplant* 2013;19:1190-96

10. Girmenia C, Raiola AM, Piciocchi A, et al. Incidence and Outcome of Invasive Fungal Diseases after Allogeneic Stem Cell Transplantation: A Prospective Study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Biol Blood Marrow Transplant* 2014;20:872-80

11. 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. *Antimicrob Agents Chemother.* 2011;55:1953-60

12. Heimann SM, Vehreschild MJ, Cornely OA et al. A cost and resource utilization analysis of micafungin bridging for hemato-oncological high-risk patients undergoing allogeneic stem cell transplantation. *Eur J Haematol.* 2015;94:526-31

13. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole Resistance in *Aspergillus fumigatus*: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? *Clin Infect Dis.* 2016;62:362-8.

14. van der Linden JW, Arendrup MC, Melchers WJ, Verweij PE. Azole Resistance of *Aspergillus fumigatus* in Immunocompromised Patients with Invasive Aspergillosis. *Emerg Infect Dis.* 2016;22:158-9

15. Wang E, Farmakiotis D, Yang D, et al. The ever-evolving landscape of candidaemia in patients with acute leukaemia: non-susceptibility to caspofungin and multidrug resistance are associated with increased mortality. *J Antimicrob Chemother.* 2015;70:2362-8

16. Brüggemann RJ, Alffenaar JW, Blijlevens NM et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents *Clin Infect Dis.* 2009;48:1441-58.

17. Niwa T, Imagawa Y, Yamazaki H. Drug interactions between nine antifungal agents and drugs metabolized by human cytochromes P450. *Curr Drug Metab.* 2014;15:651-79

18. Caira M, Candoni A, Verga L, et al. Pre-chemotherapy risk factors for invasive fungal

diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study). *Haematologica* 2015; 100:284-92.

19. Wang Y, Yang F, Shen Y et al. Maintenance Therapy With Immunomodulatory Drugs in Multiple Myeloma: A Meta-Analysis and Systematic Review. *J Natl Cancer Inst.* 2015;108(3): pii: djv342. doi: 10.1093/jnci/djv342.

20. Vallabhaneni S, Chiller TM. *Curr Rheumatol Rep.* Fungal Infections and New Biologic Therapies 2016;18:29

21. Maccioni F, Vetere S, De Felice C et al. Pulmonary fungal infections in patients with acute myeloid leukaemia: is it the time to revise the radiological diagnostic criteria? *Mycoses.* 2016;59:357-64

22. Pagano L, Caira M, Valentini CG, Posterano B, Fianchi L. Current therapeutic approaches to fungal infections in immunocompromised hematological patients. *Blood Reviews* 2010;24:51-61.

23. Pagano L, Stamouli M, Tumbarello M, et al. Risk of invasive fungal infection in patients affected by acute promyelocytic leukaemia. A report by the SEIFEM D registry. *Br J Haematol* 2015;170:434-9.

24. Pagano L, Caira M, Candoni A, et al. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. *Haematologica* 2010; 95:644-50.

25. Nucci M, Anaissie E. How we treat invasive fungal diseases in patients with acute leukemia: the importance of an individualized approach. *Blood* 2014;124:3858-3869.

26. Neofytos D, Lu K, Seung AH, et al. Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy. *Diagn Microbiol Infect Dis* 2013;75:144-9.

27. Nicolle MC, Bénet T, Thiebaut A, et al. Invasive aspergillosis in patients with hematologic malignancies: incidence and description of 127 cases enrolled in a single institution prospective survey from 2004 to 2009. *Haematologica.* 2011;96:1685-91.

28. Hoenigl M, Strenger V, Buzina W, et al. European Organization for the Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) host factors and invasive fungal infections in patients with haematological malignancies. *J Antimicrob Chemother* 2012;67:2029-33.
29. Mühlemann K, Wenger C, Zenhäusern R, Täuber MG. Risk factors for invasive aspergillosis in neutropenic patients with hematologic malignancies. *Leukemia* 2005;19:545-50.
30. Stanzani M, Lewis RE, Fiacchini M, et al. A Risk Prediction Score for Invasive Mold Disease in Patients with HMs. *PLoS ONE* 2013; 8:1-9.
31. Berthelot P, Loulergue P, Raberin H, et al. Efficacy of environmental measures to decrease the risk of hospital-acquired aspergillosis in patients hospitalised in haematology wards. *Clin Microbiol Infect* 2006; 12:738-44.
32. Fianchi L, Leone G, Posteraro B, et al. Impaired bactericidal and fungicidal activities of neutrophils in patients with myelodysplastic syndrome. *Leuk Res* 2012;36:331-33.
33. Kontoyiannis DP, Georgiadou SP, Wierda WG, et al. Impaired bactericidal but not fungicidal activity of polymorphonuclear neutrophils in patients with chronic lymphocytic leukemia. *Leuk Lymphoma*.2013;54:1730-33
34. Kotsianidis I, Bouchliou I, Nakou E, et al. Kinetics, function and bone marrow trafficking of CD4+CD25+FOXP3+ regulatory T cells in myelodysplastic syndromes (MDS). *Leukemia* 2009;23:510-8.
35. Kiladjian JJ, Bourgeois E, Lobe I, et al. Cytolytic function and survival of natural killer cells are severely altered in myelodysplastic syndromes. *Leukemia* 2006;20:463-70
36. Weinberg ED. Microbial pathogens with impaired ability to acquire host iron. *Biometals* 2000;13:85-9.
37. Pieracci FM, Barie PS. Iron and the risk of infection. *Surg Infect* 2005; 6(Suppl 1):S41-6.

38. Álvarez F, Fernández-Ruiz M, Aguado JM. Iron and invasive fungal infection. *Rev Iberoam Micol.* 2013;30:217-25.
39. Toma A, Fenaux P, Dreyfus F, Cordonnier C. Infections in myelodysplastic syndromes. *Haematologica* 2012;97:1459-70
40. Musto P, Maurillo L, Spagnoli A, et al. Azacitidine for the treatment of lower risk myelodysplastic syndromes: a retrospective study of 74 patients enrolled in an Italian named patient program. *Cancer* 2010;116:1485-94.
41. Garcia-Manero G. Myelodysplastic syndromes: 2015 Update on diagnosis, risk-stratification and management. *Am J Hematol.* 2015 ;90:831-41
42. Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005-2007). *Clin Microbiol Infect* 2011;17:1882-89.
43. Shiada A, Pagano L, Groll A, et al. European Confederation of Medical Mycology Working Group on Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. *Clin Microbiol Infect.* 2011;17:1859-67
44. Herbrecht R, Caillot D, Cordonnier C, et al. Indications and outcomes of antifungal therapy in French patients with haematological conditions or recipients of haematopoietic stem cell transplantation. *J Antimicrob Chemother.* 2012;67:2731-38.
45. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006;24:3895-3903.
46. Lee JH, Jang JH, Park J, et al. A prospective multicenter observational study of decitabine treatment in Korean patients with myelodysplastic syndrome. *Haematologica.* 2011;96:1441-47.
47. Merkel D, Filanovsky K, Gafter-Gvili A, et al. Predicting infections in high-risk patients

with myelodysplastic syndrome/acute myeloid leukemia treated with azacitidine: a retrospective multicenter study. *Am J Hematol.* 2013;88:130-4.

48. Falantes JF, Calderón C, Márquez-Malaver FJ, et al. Patterns of infection in patients with myelodysplastic syndromes and acute myeloid leukemia receiving azacitidine as salvage therapy. Implications for primary antifungal prophylaxis. *Clin Lymphoma Myeloma Leuk.* 2014;14:80-6.

49. Ofran Y, Filanovsky K, Gafter-Gvili A, et al. Higher infection rate after 7- compared with 5-day cycle of azacitidine in patients with higher-risk myelodysplastic syndrome. *Clin Lymphoma Myeloma Leuk.* 2015;15:e95-9.

50. Chabrol A, Cuzin L, Huguet F, et al. Prophylaxis of invasive aspergillosis with voriconazole or caspofungin during building work in patients with acute leukemia. *Haematologica.* 2010;95:996-1003.

51. Cattaneo C, Monte S, Algarotti A, et al. A randomized comparison of caspofungin versus antifungal prophylaxis according to investigator policy in acute leukaemia patients undergoing induction chemotherapy (PROFIL-C study). *J Antimicrob Chemother.* 2011 ;66:2140-5

52. Cornely O, Leguay T, Maertens J, et al. A Double-Blind, Multicentre, Randomised, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Prophylactic Liposomal Amphotericin B (AmBisome®) for the Prevention of Invasive Fungal Infections in Subjects Receiving Remission-Induction Chemotherapy for Acute Lymphoblastic Leukaemia (AmBiGuard trial). *Blood* 2014; suppl124: Abstr 3646.

53. Ribera JM, Oriol A, Sanz MA, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Español de Tratamiento en Hematología pediatric-based protocol ALL-96. *J Clin Oncol.* 2008;26:1843-9.

54. Rijneveld AW, van der Holt B, Daenen SM, et al. HOVON Cooperative group. Intensified chemotherapy inspired by a pediatric regimen combined with allogeneic transplantation in adult patients with acute lymphoblastic leukaemia up to the age of 40.

Leukemia. 2011;25:1697-703.

55. Storing JM, Minden MD, Kao S, et al. Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. *Br J Haematol.* 2009;146:76-85.

56. Daenen S, van der Holt B, Dekker AW, et al. Intensive chemotherapy to improve outcome in patients with acute lymphoblastic leukaemia over the age of 40: a phase II study for efficacy and feasibility by HOVON. *Leukemia.* 2012;26:1726-9.

57. Sive JI, Buck G, Fielding A, et al. Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. *Br J Haematol.* 2012;157:463-71.

58. Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. *Haematologica.* 2011;96:245-52.

59. Hunault-Berger M, Leguay T, Huguet F, et al. A Phase 2 study of L-asparaginase encapsulated in erythrocytes in elderly patients with Philadelphia chromosome negative acute lymphoblastic leukemia: The GRASPALL/GRAALL-SA2-2008 study. *Am J Hematol.* 2015;90:811-8.

60. Barba P, Sampol A, Calbacho M, et al. Clofarabine-based chemotherapy for relapsed/refractory adult acute lymphoblastic leukemia and lymphoblastic lymphoma. The Spanish experience. *Am J Hematol.* 2012;87:631-4.

61. Kadia TM, Kantarjian HM, Thomas DA, et al. Phase II study of methotrexate, vincristine, pegylated-asparaginase, and dexamethasone (MOpAD) in patients with relapsed/refractory acute lymphoblastic leukemia. *Am J Hematol.* 2015;90:120-4.

62. Ribera JM, Oriol A, González M, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. *Haematologica.* 2010;95:87-95.

63. Bassan R, Rossi G, Pogliani EM, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. *J Clin Oncol*. 2010;28:3644-52.
64. Foà R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2011;118:6521-8.
65. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood*. 2002;100:1965-71.
66. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16:57-66.
67. Sun Y, Huang H, Chen J, et al. Invasive fungal infection in patients receiving chemotherapy for hematological malignancy: a multicenter, prospective, observational study in China. *Tumour Biol*. 2015;36:757-67.
68. Kurosawa M, Yonezumi M, Hashino S, et al. Epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. *Int J Hematol*. 2012;96:748-57.
69. Nosari AM, Pioltelli ML, Riva M, et al. Invasive fungal infections in lymphoproliferative disorders: a monocentric retrospective experience. *Leuk Lymphoma*. 2014;55:1844-8.
70. Takaoka K, Nannya Y, Shinohara A, Arai S, Nakamura F, Kurokawa M. A novel scoring system to predict the incidence of invasive fungal disease in salvage chemotherapies for malignant lymphoma. *Ann Hematol*. 2014;93:1637-44.
71. Teng JC, Slavin MA, Teh BW, et al. Epidemiology of invasive fungal disease in lymphoproliferative disorders. *Haematologica*. 2015;100:e462-6.
72. Wongso D, Fuchs M, Plütschow A, et al. Treatment-related mortality in patients with

advanced-stage hodgkin lymphoma: an analysis of the german hodgkin study group. *J Clin Oncol.* 2013;31:2819-24.

73. Gil L, Kozłowska-Skrzypczak M, Mol A, Poplawski D, Styczynski J, Komarnicki M. Increased risk for invasive aspergillosis in patients with lymphoproliferative diseases after autologous hematopoietic SCT. *Bone Marrow Transplant.* 2009;43:121-6.

74. Offidani M, Corvatta L, Polloni C, et al. Infectious complications in patients with multiple myeloma treated with new drug combinations containing thalidomide. *Leuk Lymphoma.* 2011;52:776-85.

75. Teh BW, Teng JC, Urbancic K, et al. Invasive fungal infections in patients with multiple myeloma: a multi-center study in the era of novel myeloma therapies. *Haematologica.* 2015;100:e28-31.

76. Li J, Li Y, Huang B, Zheng D, Chen M, Zhou Z. Drug-induced modulation of T lymphocytes as a potential mechanism of susceptibility to infections in patients with multiple myeloma during bortezomib therapy. *Cell Biochem Biophys.* 2015;71:457-64.

77. Liu J, Huang H, Li Y, et al. Epidemiology and treatment of invasive fungal diseases in patients with multiple myeloma: findings from a multicenter prospective study from China. *Tumour Biol.* 2016;37:7893-900

78. Francis S, Karanth M, Pratt G, et al. The effect of immunoglobulin VH gene mutation status and other prognostic factors on the incidence of major infections in patients with chronic lymphocytic leukemia. *Cancer.* 2006;107:1023-33.

79. Moreira J, Rabe KG, Cerhan JR, et al. Infectious complications among individuals with clinical monoclonal B-cell lymphocytosis (MBL): a cohort study of newly diagnosed cases compared to controls. *Leukemia.* 2013;27:136-41.

80. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009;114:937-51.

81. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366:799-807.
82. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366:787-98.
83. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994-1004.
84. Daniels JM, Vonk-Noordegraaf A, Janssen JJ, Postmus PE, van Altena R. Tuberculosis complicating imatinib treatment for chronic myeloid leukaemia. *Eur Respir J*. 2009;33:670-72.
85. Heine A, Brossart P, Wolf D. Ruxolitinib is a potent immunosuppressive compound: is it time for anti-infective prophylaxis? *Blood*. 2013;122:3843-44.
86. Ikeda K, Shiga Y, Takahashi A, et al. Fatal hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. *Leuk Lymphoma*. 2006;47:155-57.
87. Mattiuzzi GN, Cortes JE, Talpaz M, et al. Development of Varicella-Zoster virus infection in patients with chronic myelogenous leukemia treated with imatinib mesylate. *Clin Cancer Res*. 2003;9:976-80.
88. Appel S, Boehmler AM, Grunebach F, et al. Imatinib mesylate affects the development and function of dendritic cells generated from CD34+ peripheral blood progenitor cells. *Blood*. 2004;103:538-44.
89. Seggewiss R, Lore K, Greiner E, et al. Imatinib inhibits T-cell receptor-mediated T-cell proliferation and activation in a dose-dependent manner. *Blood*. 2005;105:2473-79.
90. Cwynarski K, Laylor R, Macchiarulo E, et al. Imatinib inhibits the activation and proliferation of normal T lymphocytes in vitro. *Leukemia*. 2004;18:1332-39.

91. Dietz AB, Souan L, Knutson GJ, Bulur PA, Litzow MR, Vuk-Pavlovic S. Imatinib mesylate inhibits T-cell proliferation in vitro and delayed-type hypersensitivity in vivo. *Blood*. 2004;104:1094-99.
92. Jabbour E, Kantarjian HM, Saglio G, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2014;123:494-500.
93. Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol*. 2011;12:841-51.
94. Cortes JE, Kim DW, Kantarjian HM, Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol*. 2012;30:3486-92.
95. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369:1783-96.
96. Palandri F, Catani L, Testoni N, et al. Long-term follow-up of 386 consecutive patients with essential thrombocythemia: safety of cytoreductive therapy. *Am J Hematol*. 2009;84:215-20.
97. Gruppo Italiano Studio Policitemia. Polycythemia vera: the natural history of 1213 patients followed for 20 years. *Ann Intern Med*. 1995;123:656-64.
98. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009;113:2895-901.
99. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115:1703-08.

100. Hultcrantz M, Wilkes SR, Kristinsson SY, et al. Risk and Cause of Death in Patients Diagnosed With Myeloproliferative Neoplasms in Sweden Between 1973 and 2005: A Population-Based Study. *J Clin Oncol*. 2015;33:2288-95.
101. Temeck BK, Venzon DJ, Moskaluk CA, Pass HI. Thoracotomy for pulmonary mycoses in non-HIV-immunosuppressed patients. *Ann Thorac Surg*. 1994;58:333-8.
102. Barosi G. An immune dysregulation in MPN. *Curr Hematol Malig Rep*. 2014;9:331-9.
103. Wysham NG, Sullivan DR, Allada G. An opportunistic infection associated with ruxolitinib, a novel janus kinase 1,2 inhibitor. *Chest*. 2013;143:1478-79.
104. Lee SC, Feenstra J, Georghiou PR. Pneumocystis jiroveci pneumonitis complicating ruxolitinib therapy. *BMJ Case Rep*. 2014;2014. pii: bcr2014204950. doi: 10.1136/bcr-2014-204950.
105. Chan JF, Chan TS, Gill H, et al. Disseminated Infections with *Talaromyces marneffei* in Non-AIDS Patients Given Monoclonal Antibodies against CD20 and Kinase Inhibitors. *Emerg Infect Dis*. 2015;21:1101-06.
106. Stansfield LC, Begna, K, Tosh P, et al. Mucormycosis in a patient treated with ruxolitinib. [e-letter]. *Blood* 2013;122: 3843-3844 (doi:10.1182/blood-2013-10-531103).
107. Polverelli N, Breccia M, Benevolo G, et al. Risk Factors for Infections In Myelofibrosis: Role of Disease Status and Treatment. A Multicenter study On 507 Patients. *Blood* 2015;suppl 126:abs1606.
108. GITMO R. Gruppo Italiano per il trapianto di Midollo Osseo (GITMO). Registries from: <http://www.gitmo.it>
109. Passweg JR, Baldomero H, Barder P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40000 transplants annually. *Bone Marrow Transplant*. 2016. doi: 10.1038/bmt.2016.20. [Epub ahead of print]
110. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic SCT in Europe 2013:

recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. *Bone Marrow Transplant*. 2015;50:476-82.

111. Pagano L, Caira M, Nosari A, et al. Fungal Infections in Recipients of Hematopoietic Stem Cell Transplants: Results of the SEIFEM B-2004 Study "Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne". *Clin Infect Dis*. 2007;45:1161-70.

112. Markowski J, Helbig G, Widziszowska A, et al. Fungal colonization of the respiratory tract in allogeneic and autologous hematopoietic stem cell transplant recipients: a study of 573 transplanted patients. *Med Sci Monit*. 2015;21:1173-80

113. Nucci M, Garnica M, Gloria AB, et al. Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. *Clin Microbiol Infect*. 2013;19:745-51.

114. Srinivasan A, McLaughlin L, Wang C, et al. Early infections after autologous hematopoietic stem cell transplantation in children and adolescents: the St. Jude experience. *Transpl Infect Dis*. 2014;16:90-7.

115. Sun Y, Meng F, Han M, et al. Epidemiology, Management, and Outcome of Invasive Fungal Disease in Patients Undergoing Hematopoietic Stem Cell Transplantation in China: A Multicenter Prospective Observational Study. *Biol Blood Marrow Transplant*. 2015;21:1117-26.

116. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and Outcome of Invasive Fungal Infection in Adult Hematopoietic Stem Cell Transplant Recipients: Analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance Registry. *Clin Infect Dis*. 2009;48:265-73.

117. Gil L, Styczynski J, Komarnicki M. Infectious Complication in 314 Patients after High-Dose Therapy and Autologous Hematopoietic Stem Cell Transplantation: Risk Factors Analysis and Outcome. *Infection*. 2007;35:421-27.

118. Liu Y-C, Chien S-H, Fan N-W, et al. Incidence and risk factors of probable and proven invasive fungal infection in adult patients receiving allogeneic hematopoietic stem

cell transplantation. *J Microbiol Immunol Infect.* 2015.pii:S1684-1182(15)00026-2

119. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of Invasive Mold Infections in Allogeneic Stem Cell Transplant Recipients: Biological Risk Factors for Infection According to Time after Transplantation. *Clin Infect Disease* 2008;47:1041-50.

120. Parody R, Martino R, de la Cámara R, et al. Fungal and viral infections after allogeneic hematopoietic transplantation from unrelated donors in adults: improving outcomes over time. *Bone Marrow Transplant* 2015;50:274-81

121. Montesinos P, Rodríguez-Veiga R, Boluda B, et al. Incidence and risk factors of post-engraftment invasive fungal disease in adult allogeneic hematopoietic stem cell transplant recipients receiving oral azoles prophylaxis. *Bone Marrow Transplant* 2015;50:1465-72

122. Atalla A, Garnica M, Maiolino A, Nucci M. Risk factors for invasive mold diseases in allogeneic hematopoietic cell transplant recipients. *Transpl Infect Dis* 2015;17:7–13.

123. Mikulska M, Raiola AM, Bruno B, et al. Risk factors for invasive aspergillosis and related mortality in recipients of allogeneic SCT from alternative donors: an analysis of 306 patients. *Bone Marrow Transplant* 2009;44:361-70

124. Sucak GT, Yegin ZA, Özkurt ZN, et al. Iron Overload: Predictor of Adverse Outcome in Hematopoietic Stem Cell Transplantation. *Transplant Proc* 2010; 42:1841-48

125. Ozyilmaz E, Aydogdu M, Sucak G, Aki SZ. Risk factors for fungal pulmonary infections in hematopoietic stem cell transplantation recipients: the role of iron overload. *Bone Marrow Transplant* 2010;45:1528-33

126. Sivgin S, Baldane S, Kaynar L, et al. Pretransplant iron overload may be associated with increased risk of invasive fungal pneumonia (IFP) in patients that underwent allogeneic hematopoietic stem cell transplantation (alloHSCT). *Transfus Apher Sci.* 2013;48:103-8.

127. Kontoyiannis DP, Chamilos G, Lewis RE, et al. Increased Bone Marrow Iron Stores Is an Independent Risk Factor for Invasive Aspergillosis in Patients With High-Risk

Hematologic Malignancies and Recipients of Allogeneic Hematopoietic Stem Cell Transplantation. *Cancer* 2007;110:1303-06.

128. Bochud P-Y, Chien JW, Marr KA, et al. Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation. *N Engl J Med* 2008;359:1766-77.

129. Cunha C, Aversa F, Lacerda JF, et al. Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell Transplantation. *N Engl J Med* 2014;370:421-32.

130. Cunha C, Di Ianni M, Bozza S, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. *Blood*. 2010;116:5394-402

131. Zaas AK, Liao G, Chien JW, et al. Plasminogen Alleles Influence Susceptibility to Invasive Aspergillosis. *PLoS Genet* 2008;4:e1000101

132. Cunha C, Aversa F, Romani L, Carvalho A. Human Genetic Susceptibility to Invasive Aspergillosis. *PLoS Pathog* 2013;9:e1003434

133. Van den Brink MRM, Velardi E, Perales M-A. Immune reconstitution following stem cell transplantation. *Hematology Am Soc Hematol Educ Program*. 2015;2015:215-9.

134. Corzo-Leon DE, Satin MJ, Soave R, et al. Epidemiology and outcomes of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients in the era of antifungal prophylaxis: a single-centre study with focus on emerging pathogens. *Mycoses* 2015;58:325-36

135. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003;102:827-33.

136. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *Lancet* 2003;362:1828-38

137. Thursky K, Byrnes G, Grigg A, Szer J, Slavin M. Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2004;34: 115-21
138. Marty FM, Lee SJ, Fahey MM, et al. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. *Blood* 2003;102:2768-76
139. Salzberger B, Bowden RA, Hackman RC, Davis C, Boeckh M. Neutropenia in allogeneic marrow transplant recipients receiving ganciclovir for prevention of cytomegalovirus disease: risk factors and outcome. *Blood* 1997;90:2502-08.
140. Warris A, Klaassen CH, Meis JF, et al. Molecular epidemiology of *Aspergillus fumigatus* isolates recovered from water, air, and patients shows two clusters of genetically distinct strains. *J Clin Microbiol.* 2003;41:4101-06.
141. Jessica M. Valdez, Phillip Scheinberg, Neal S. Young, Thomas J. Walsh. Infections in Patients With Aplastic Anemia. *Semin Hematol* 2009, 46:269–276
142. Valdez JM, Scheinberg P, Nunez O, Wu CO, Young NS, Walsh TJ. Decreased Infection-Related Mortality and Improved Survival in Severe Aplastic Anemia in the Past Two Decades. *Clin Infect Dis.* 2011;52:726–735
143. Dvorak CC, Steinbach WJ, Brown JM, Agarwal R. Risks and outcomes of invasive fungal infections in pediatric patients undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2005;36(7):621-9.
144. Hale KA, Shaw PJ, Dalla-Pozza L, MacIntyre CR, Isaacs D, Sorrell TC. Epidemiology of paediatric invasive fungal infections and a case-control study of risk factors in acute leukaemia or post stem cell transplant. *Br J Haematol.* 2010;149:263-72
145. Hol JA, Wolfs TF, Bierings MB, et al. Predictors of invasive fungal infection in pediatric allogeneic hematopoietic SCT recipients. *Bone Marrow Transplant.* 2014;49:95-101.

146. Kobayashi R, Kaneda M, Sato T, Suzuki D, Ichikawa M, Ariga T. Evaluation of risk factors for invasive fungal infection after allogeneic stem cell transplantation in pediatric patients. *J Pediatr Hematol Oncol*. 2007;29:786-91
147. Mor M, Gilad G, Kornreich L, Fisher S, Yaniv I, Levy I. Invasive fungal infections in pediatric oncology. *Pediatr Blood Cancer* 2011;56:1092-7
148. Ozsevik SN, Sensoy G, Karli A, et al. Invasive fungal infections in children with hematologic and malignant diseases. *J Pediatr Hematol Oncol* 2015;37:e69-72
149. Sahbudak Bal Z, Yilmaz Karapinar D, Karadas N, et al. Proven and probable invasive fungal infections in children with acute lymphoblastic leukaemia: results from an university hospital, 2005-2013. *Mycoses* 2015;58:225-32
150. Sano H, Kobayashi R, Suzuki D, Kishimoto K, Yasuda K, Kobayashi K. Bacteremia during neutropenia is a predictive factor for invasive fungal infection in children. *Pediatr Int* 2013;55:145-50
151. Srinivasan A, Wang C, Srivastava DK, et al. Timeline, epidemiology, and risk factors for bacterial, fungal, and viral infections in children and adolescents after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2013;19:94-101
152. Villarreal M, Avilés CL, Silva P, et al. Risk factors associated with invasive fungal disease in children with cancer and febrile neutropenia: a prospective multicenter evaluation. *Pediatr Infect Dis J* 2010;29:816-21
153. Gratwohl A. The EBMT risk score. *Bone Marrow Transplant* 2012;47:749-56
154. Prentice HG, Kibbler CC, Prentice AG. Towards a targeted, risk-based, antifungal strategy in neutropenic patients. *Br J Haematol*. 2000 Aug;110:273-84.
155. Castagnola E, Bagnasco F, Bandettini R, et al. Role of acute graft-versus-host disease in the risk of bacteremia and invasive fungal disease after allogeneic hemopoietic stem cell transplantation in children. Results from a single-center observational study. *Biol Blood Marrow Transplant* 2014;20:1068-73.

156. Stuehler C, Kuenzli E, Jaeger VK, et al. Immune Reconstitution After Allogeneic Hematopoietic Stem Cell Transplantation and Association With Occurrence and Outcome of Invasive Aspergillosis. *J. Infect. Dis.* 2015;212:959-67
157. Bittencourt H, Rocha V, Chevret S, et al. Association of CD34 cell dose with hematopoietic recovery, infections, and other outcomes after HLA-identical sibling bone marrow transplantation. *Blood* 2002;99:2726-33
158. Panackal AA, Li H, Kontoyiannis DP, Mori M, et al. Geoclimatic Influences on Invasive Aspergillosis after Hematopoietic Stem Cell Transplantation. *Clin Infect Dis.* 2010; 50:1588-97.
159. Martino R, Viscoli C. Empirical antifungal therapy in patients with neutropenia and persistent or recurrent fever of unknown origin. *Br J Haematol.* 2006 Jan;132:138-54.
160. Maertens J, Donnelly P, Kibbler C et al. Primary Antifungal Prophylaxis. Proceeding of ECIL 5, September 19-21 2013, Juan Les Pins (France) www.kobe.fr/ecil/telechargements2013/ECIL5antifungalprophylaxis%2020062014Final.pdf
161. Portugal RD, Garnica M, Nucci M. Index to predict invasive mold infection in high-risk neutropenic patients based on the area over the neutrophil curve. *J Clin Oncol.* 2009;27:3849-54.
162. van Burik JA, Carter SL, Freifeld AG, et al. Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. *Biol Blood Marrow Transplant.* 2007;13:1487-98
163. Abdul Salam ZH, Karlin RB, Ling ML, Yang KS. The impact of portable high-efficiency particulate air filters on the incidence of invasive aspergillosis in a large acute tertiary-care hospital. *Am J Infect Control.* 2010; 38:e1-7
164. Ceesay MM, Desai SR, Berry L et al. A comprehensive diagnostic approach using galactomannan, targeted β -d-glucan, baseline computerized tomography and biopsy yields

a significant burden of invasive fungal disease in at risk haematology patients. *Br J Haematol.* 2015;168:219-29

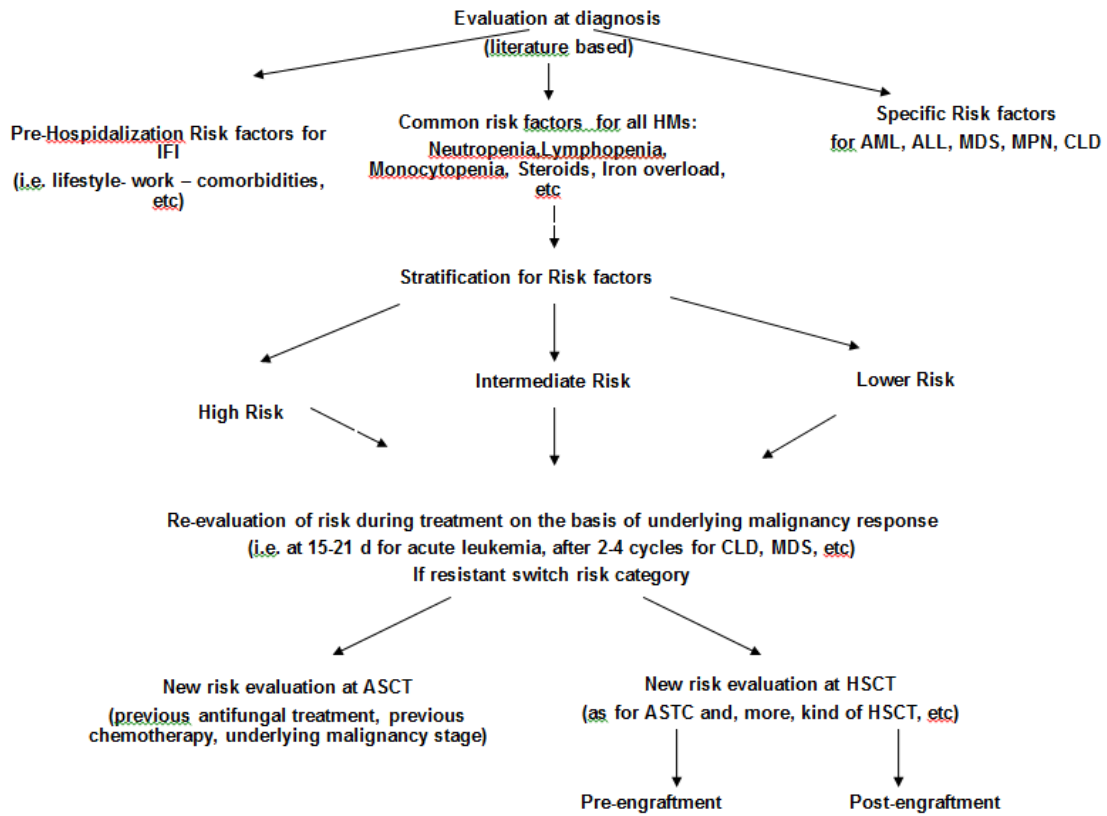
165. Chan JF, Chan TS, Gill H et al. Disseminated Infections with *Talaromyces marneffe* in Non-AIDS Patients Given Monoclonal Antibodies against CD20 and Kinase Inhibitors. *Emerg Infect Dis.* 2015;21:1101-6

166. Nucci M, Nouér SA, Graziutti M, Kumar NS, Barlogie B, Anaissie E. Probable invasive aspergillosis without prespecified radiologic findings: proposal for inclusion of a new category of aspergillosis and implications for studying novel therapies. *Clin Infect Dis.* 2010;51:1273-80

167. Girmenia C, Guerrisi P, Frustaci AM, et al. New category of probable invasive pulmonary aspergillosis in haematological patients. *Clin Microbiol Infect.* 2012;18:990-6.

168. Prigitano A, Venier V, Cogliati M, De Lorenzis G, Esposito MC, Tortorano AM. Azole-resistant *Aspergillus fumigatus* in the environment of northern Italy, May 2011 to June 2012. *Euro Surveill.* 2014;19:20747.

FIGURE 1. Possible dynamic risk stratification.



ACCEPT

TABLE 1. Risk Factors for IFIs in AML according to Leukemia, Host, Treatment and Fungal Exposure.

Leukemia Related	Host Related	Treatment Related Factors	Fungal Exposure
Lower Probability of CR (Adverse Cytogenetic/gene mutation profiles; WBC > 50.000/ μ L; Secondary AML	Age > 65 yrs	Expected treatment related severe and prolonged neutropenia (ANC < 100/ μ L for > 10 d)	Rooms without HEPA filtration; Building constructions or renovations/ recent house renovation
Baseline neutropenia with ANC < 500/ μ L for > 7 d; MDS-related phagocytic dysfunction.	Organ dysfunction with High comorbidity index or Poor Performance status (≥ 2)	Highly mucotoxic regimen	Documented Airway Colonization By Aspergillus species
Leukemia Status: Relapse-Refractory > First Induction > Consolidation	Chronic Obstructive Pulmonary Disease. Active Smoking	Mucositis grade ≥ 3 for > 7 days, especially if involving lower gut.	Prior Aspergillosis
Persistence of Day 15 Bone Marrow Blast Cells	Immunity polymorphism		Multisite colonization by Candida species.
No CR by end of induction phase	Pharmacogenomics of antineoplastic drugs		Jobs with high exposure (farming, gardening, construction work)

CR=Complete Remission; ANC=absolute Neutrophils count; WBC= White Blood cells

TABLE 2. Risk factors IFI in HSCT

Risk factors associated to IFI		Reference	Study (No. Patients)	Comments
Pre-HSCT	Post-HSCT			
Age	>50 years	Pagano L2007 (111) Garcia-VidalC2008(119)	Retrosp (1249) Retrosp (1248)	- Risk for IMI
	>30 years	ParodyR 2015 (120)	Retrosp (434)	-
	>40 years	Montesinos P2015(121)	Retrosp (404)	Risk for IFI >40d
Diagnosis	AML	AtallaA 2015 (122)	Prosp (345)	Risk for early IMI (<40d)
	Lymphoma	Atalla A2015 (122)	Prosp (345)	Risk for late IMI (>40d)
Disease status at HSCT		MikulskaM 2009 (123) Girmeria C 2014 (10)	Retrosp (306) Prosp (1858)	Risk for IA Risk for early IFI (<40d)
Type of HSCT	MUD	SunY2015 (115) Pagano L2007 (111) Garcia-Vidal C2008 (119) Girmeria C2014 (10)	Prosp (1053) Retrosp (1249) Retrosp (1248) Prosp (1858)	- - Risk for IMI Early (<40d)&late (40-100 d) IFI
	UCB	Girmeria C2014 (10)	Prosp (1858)	Early (<40d)&late (40-100 d) IFI
	Haplos/mismatch	Omer AK2013 (9) AtallaA2015 (122)	Retrosp (272) Prosp (345)	- Risk for early IFI (>40d)
Iron overload		Sucak GT2010 (124) Ozyilmaz E2010 (125) SivginS2012 (126) Garcia-Vidal C2008 (119) KontoyiannisDP2007 (127)	Retrosp (250) Retrosp (148) Retrosp (73) Retrosp (1248) Retrosp (66)	- Fungal pulmonary infect Fungal pulmonary infect Risk for IMI -
Genetics		BochudPY2008 (128) Zaas AK2008 (131)	Retrosp (336) Retrosp (236)	- -
Dectin-1 polymorphism PTX3 deficit		Cunha C2010 (130) Cunha C2014 (129)	Retrosp (205) Retrosp (268)	- -
Stem cell dose <3 x 10 ⁶ /Kg		Bittencourth2002 (157)	Retrosp (212)	Risk factor in recipients of BM transplantation
Comorbidities	Diabetes	Garcia-VidalC2008 (119) Sun Y2015 (115)	Retrosp (1248) Prosp (1053)	Risk for IMI -
	CMV infection	Garcia-Vidal C2008 (119) ParodyR2015 (120) Mikulska M2009 (123) AtallaA2015 (122)	Retrosp (1248) Retrosp (434) Retrosp (306) Prosp (345)	Risk for IMI - Early IA (<40d) Late IFI (>40d)
	Parainfluenza infection	Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
	Hypoalbuminemia	Corzo-Leon D2015 (134)	Retros (378)	-

	GVHD			
	Acute II-IV	GirmeriaC2014 (10) Omer AK2013 (9) Parody R2015 (120)	Prosp (1858) Retrosp (272) Retrosp (434)	Late (40-100d)/very late (>100d) IFI - -
	Acute III-IV	Garcia-VidalC2008 (119) Liu YC2015 (118)	Retrosp (1248) Retrosp (421)	Risk for IMI -

		Chronic	Corzo-LeonD2015 (134) Girmania C2014 (10) MikulskaM2009 (123) ParodyR2015 (120) Montesinos P 2015 (121)	Retros (378) Prosp (1858) Retros (306) Retros (434) Retros (404)	- Very late IFI (>100d) Late IA (>40d) - Risk for IFI >40d
Immunosuppressive Treatments					
	Basiliximab		SunY2015 (115)	Prosp (1053)	-
	Alemtuzumab		ThurskyK2005 (137)	Retros (217)	-
	ATG		Garcia-VidalC C2008 (119) OmerAK2013 (9)	Retros (1248) Retros (272)	Risk for IMI -
		steroids	Garcia-Vidal C 2008 (119) Mikulska M2009 (123) Liu YC2015 (118)	Retros (1248) Retros (306) Retros (306)	Risk for IMI Late IA (>40 d) -
		infiximab	Marty FM 2003 (138)	Retros (421)	-
	Immune reconstitution				
		Neutropenia ¹	Sun Y2015 (115) Garcia-Vidal C2008 (119) Atalla A2015 (122) Mikulska M2009 (123)	Prosp (1053) Retros (1248) Prosp (345) Retros (306)	netropenia >14 d Risk for IMI Late (>40d) IFI IA
		Monocytopenia ²	Garcia-Vidal C2008 (119)	Retros (1248)	Risk for IMI
		Lymphopenia ³	Garcia-Vidal C2008 (119) Mikulska M2009 (123)	Retros (1248) Retros (306)	Risk for IMI Early IA
		NK ⁴	Stuehler C2015 (156)	Prosp (51)	-
		CD4+ cells ⁵	Stanzani M2013 (30)	-	-
		Neutrophil function (ROS)	Stuehler C2015 (156)	Prosp (51)	-
Miscellaneous					
	EBMT score	Admission in ICU	Liu YC2015 (118) Corzo-Leon D2015(134)	Retros (421) Retros (378)	- -
	CVC		Pagano L2007 (111)	Retros (1249)	-
	Previous IFI		Liu YC2015 (118) GirmaniaC2014 (10)	Retros (421) Prosp (1858)	- Early IFI
	Environment		WarrisA 2003 (140)	-	-
	Geoclimatic factors		Panackal AA2010 (158)	Retros (3133)	-

Abbreviations: IMI, invasive mold infection; AML, acute myeloid leukemia; IA, invasive aspergillosis; d, days; MUD, matched unrelated donor; UCB, umbilical cord blood; SNP, single nucleotide polymorphism; BM, bone marrow; CMV, cytomegalovirus; GVHD, graft-versus-host disease; ATG, antithymocyte globulin; ROS, reactive oxygen species; ICU, intensive care unit; CVC, central venous catheter

TABLE 3. Risk factors in pediatric setting

	Risk factors
Allogeneic stem cell transplantation	Acute GVHD or acute GVHD grave chronic GVHD High-dose of steroid ≥ 2 mg/kg/day A priori TRM risk $> 20\%$ Older age
Malignancy	High-risk ALL in 1 ^o CR Relapsed ALL AML PICU admission CVC severe and prolonged neutropenia Persistent fever > 4 days, monocytopenia ($\leq 0.1 \times 10^9/l$), C-RP ≥ 90 mg/dl

TABLE 4: Risk stratification of HMs for diagnosis, phase and kind of treatment.

HIGH Risk	INTERMEDIATE Risk	LOW Risk
<p><u>AML</u> undergoing Induction CHT with any of the following Risk Factors: Neutropenia at baseline, low CR probability (Adverse K, secondary AML), age > 65 yrs, Significant pulmonary disfunction, high e-TRM score.</p> <p><u>AML</u> with Prior IA</p> <p><u>AML</u> undergoing <u>salvage regimens</u> for Relapsed/Refractory disease.</p>	<p><u>AML</u> not meeting criteria for High or Low Risk groups.</p>	<p><u>AML</u> <45 yrs; Undergoing first remission-induction or consolidation CHT and without <u>ANY</u> Risk Factors for IFI</p> <p><u>APL</u> treated with ATRA/ATO</p>
<p><u>Allogeneic Stem Cell transplantation</u> (from donors other than a matched sibling donor, patients active HM, GVHD requiring high-dose steroids and history of previous IFI)</p>	<p><u>Allogeneic Stem Cell transplantation</u> (from matched sibling donors, patients in complete remission with no evidence of GVHD and no previous IFI)</p>	
<p><u>MDS/LAM</u> receiving azacitidine as salvage therapy after intensive regimens</p>	<p><u>MDS</u> with IPSS > 1.5 treated with azacitidine 75 mg/m² for 7 days</p> <p><u>MDS</u> during the first 2-3 cycles of AZA/Decitabine</p>	
<p><u>Acute Lymphoblastic Leukemia:</u> Elderly patients (≥55y); Intensive pediatric regimens (induction); HD dexametazone; Previously treated (relapsed/refractory)</p>	<p><u>Acute Lymphoblastic Leukemia:</u> Adults (30-54y); Standard induction chemotherapy; Intensive consolidation treatment; TKI + reduced cht (Ph+ ALL)</p>	<p><u>Acute Lymphoblastic Leukemia:</u> Younger adults (30y); Maintenance treatment (complete remission); TKI + steroids (Ph+ ALL)</p>
	<p><u>Autologous Stem Cell Transplantation:</u> Previous IFI; >3 lines of therapy (disease burden); Prolonged neutropenia (ANC <500/mm³ for more than 14 days); corticosteroid therapy; Colonization by Candida spp; Previous Fludarabine treatment</p>	<p><u>MPN</u> (Chronic Myeloid Leukemia, Essential Thrombocitemia, Idiopathic Thrombocytosis, Polycytemia Vera)</p>
	<p><u>CLL</u> treated with multiple lines of CTX</p> <p><u>Multiple Myeloma</u> in 3 or more lines or during ASCT</p> <p><u>DLBCL</u> relapsed/refractory</p> <p><u>HD</u> if treated with “escalating BEACOPP”</p>	<p>Low or high grade <u>NHL</u>, <u>CLL</u>, <u>MM</u>, <u>HD</u> treated with conventional frontline chemotherapy</p>