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

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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 MYELODYSPLASTIC 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/m^2 for 7 days) compared to short-schedule treatment (75 mg/m^2 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/m^2 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 (caspofungin 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 DISORDES

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 marneffei* 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 $\geq$ 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, Jannsen, 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

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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.

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FIGURE 1. Possible dynamic risk stratification.

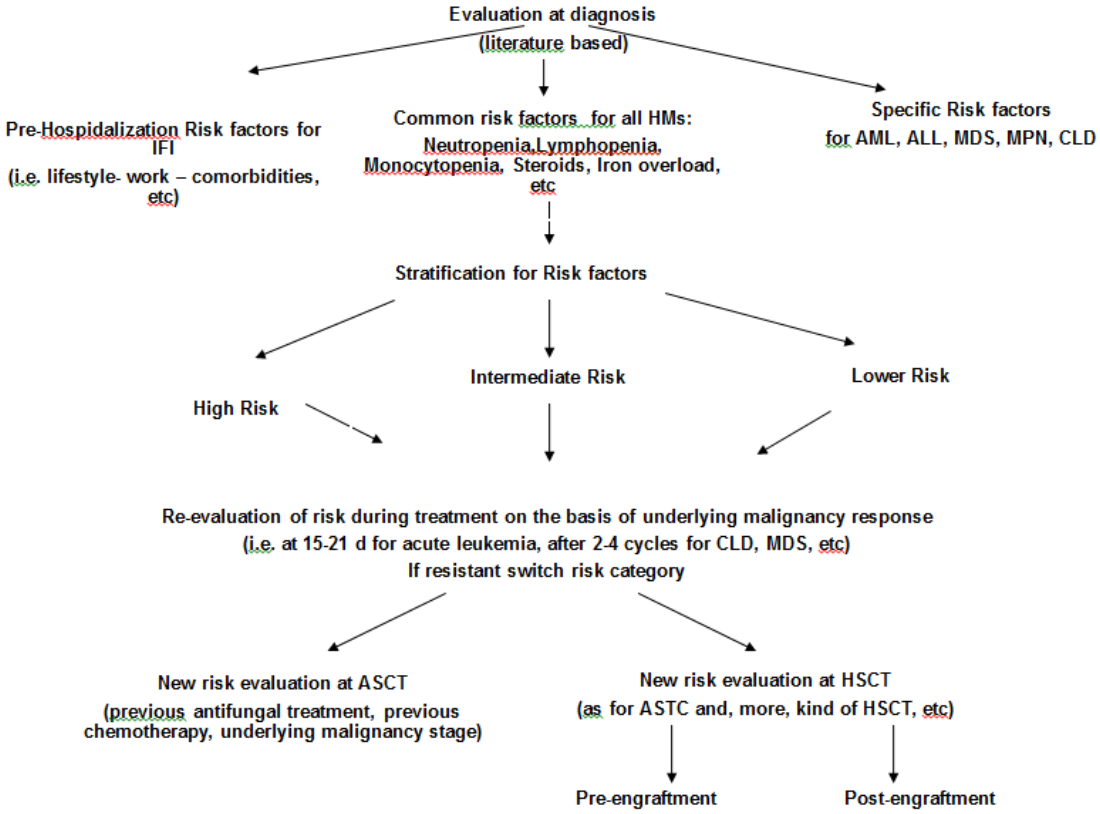

TABLE 1.Risk Factors for IFIs in AML according to Leukemia, Host, Treatment and Fungal Exposure.

Leukemia Related	Host Related	Treatment Related Factors	Fungal Exposure
Lower Probability of CR (Adverse Cytogenetic/gene mutation profiles; WBC > 50.000/µL; Secondary AML	Age > 65 yrs	Expected treatment related severe and prolonged neutropenia (ANC < 100/µL for > 10 d)	Rooms without HEPA filtration; Building constructions or renovations/ recent house renovation
Baseline neutropenia with ANC <500/µL 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 Pulmunary Disease. Active Smoking	Mucositis grade ≥ 3 for > 7 days, especially if involving lower gut.	Prior Aspergillosis
Persistance 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, contruction work)

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

TABLE 2. Risk factors IFI in HSCT

Risk factors associated to IFI Pre-HSCT	Post-HSCT	Reference	Study (No. Patiens)	Comments
Age				
>50 years		Pagano L2007 (111)	Retrosp (1249)	-
		Garcia-VidalC2008(119)	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)	Retrosp (306)	Risk for IA
		Girmenia C 2014 (10)	Prosp (1858)	Risk for early IFI (<40d)
Type of HSCT				
MUD		SunY2015 (115)	Prosp (1053)	-
		Pagano L2007 (111)	Retrosp (1249)	-
		Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
		Girmenia C2014 (10)	Prosp (1858)	Early (<40d)&late (40-100 d) IFI
UCB		Girmenia C2014 (10)	Prosp (1858)	Early (<40d)&late (40-100 d) IFI
Haplos/mismatch		Omer AK2013 (9)	Retrosp (272)	-
		AtallaA2015 (122)	Prosp (345)	Risk for early IFI (>40d)
Iron overload				
Ferritin >500 ng/ml		Sucak GT2010 (124)	Retrosp (250)	-
>1000 ng/ml		Ozyilmaz E2010 (125)	Retrosp (148)	Fungal pulmonary infect
>1550 ng/ml		SivginS2012 (126)	Retrosp (73)	Fungal pulmonary infect
>2000 ng/ml		Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
Score >3		KontoyiannisDP2007 (127)	Retrosp (66)	-
Genetics				
TLR-4 polymorphism		BochudPY2008 (128)	Retrosp (336)	-
SNPs in plasminogen genes		Zaas AK2008 (131)	Retrosp (236)	-
Dectin-1 polymorphism		Cunha C2010 (130)	Retrosp (205)	-
PTX3 deficit		Cunha C2014 (129)	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)	Retrosp (1248)	Risk for IMI
		Sun Y2015 (115)	Prosp (1053)	-
	CMV infection	Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
		ParodyR2015 (120)	Retrosp (434)	-
		Mikulska M2009 (123)	Retrosp (306)	Early IA (<40d)
		AtallaA2015 (122)	Prosp (345)	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	GirmeniaC2014 (10)	Prosp (1858)	Late (40-100d)/very late (>100d) IFI
		Omer AK2013 (9)	Retrosp (272)	-
		Parody R2015 (120)	Retrosp (434)	-
	Acute III-IV	Garcia-VidalC2008 (119)	Retrosp (1248)	Risk for IMI
		Liu YC2015 (118)	Retrosp (421)	-

		Corzo-LeonD2015 (134)	Retros (378)	-
	Chronic	Girmenia C2014 (10)	Prosp (1858)	Very late IFI (>100d)
		MikulskaM2009 (123)	Retrosp (306)	Late IA (>40d)
		ParodyR2015 (120)	Retrosp (434)	-
		Montesinos P 2015 (121)	Retrosp (404)	Risk for IFI >40d
Immunosuppressive Treatments				
Basiliximab		SunY2015 (115)	Prosp (1053)	-
Alemtuzumab		ThurskyK2005 (137)	Retrosp (217)	-
ATG		Garcia-VidalC C2008 (119)	Retrosp (1248)	Risk for IMI
		OmerAK2013 (9)	Retrosp (272)	-
	steroids	Garcia-Vidal C 2008 (119)	Retrosp (1248)	Risk for IMI
		Mikulska M2009 (123)	Retrosp (306)	Late IA (>40 d)
		Liu YC2015 (118)	Retrosp (306)	-
	infliximab	Marty FM 2003 (138)	Retrosp (421)	-
	Immune reconstitution			
	Neutropenia[1]	Sun Y2015 (115)	Prosp (1053)	netropenia >14 d
		Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
		Atalla A2015 (122)	Prosp (345)	Late (>40d) IFI
		Mikulska M2009 (123)	Retrosp (306)	IA
	Monocytopenia[2]	Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
	Lymphopenia[3]	Garcia-Vidal C2008 (119)	Retrosp (1248)	Risk for IMI
		Mikulska M2009 (123)	Retrosp (306)	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		Liu YC2015 (118)	Retrosp (421)	-
	Admission in ICU	Corzo-Leon D2015(134)	Retrosp (378)	-
CVC		Pagano L2007 (111)	Retrosp (1249)	-
Previous IFI		Liu YC2015 (118)	Retrosp (421)	-
		GirmeniaC2014 (10)	Prosp (1858)	Early IFI
Environment			-	-
Geoclimatic factors		WarrisA 2003 (140)	Retrosp (3133)	-
		Panackal AA2010 (158)		

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°CR Relapsed ALL AML PICU admission CVC severe and prolonged neutropenia Persistent fever > 4 days, monocytopenia (≤ 0.1 x 109/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
AML 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. AML with Prior IA AML undergoing salvage regimens for Relapsed/Refractory disease.	AML not meeting criteria for High or Low Risk groups.	AML <45 yrs; Undergoing first remission-induction or consolidation CHT and without ANY Risk Factors for IFI APL treated with ATRA/ATO
Allogeneic Stem Cell transplantation (from donors other than a matched sibling donor, patients active HM, GVHD requiring high-dose steroids and history of previous IFI)	Allogeneic Stem Cell transplantation (from matched sibling donors, patients in complete remission with no evidence of GVHD and no previous IFI)	
MDS/LAM receiving azacitidine as salvage therapy after intensive regimens	MDS with IPSS > 1.5 treated with azacitidine 75 mg/m(2) for 7 days MDS during the first 2-3 cycles of AZA/Decitabine	
Acute Lymphoblastic Leukemia: Elderly patients (≥55y); Intensive pediatric regimens (induction);HD dexametazone; Previously treated (relapsed/refractory)	Acute Lymphoblastic Leukemia: Adults (30-54y); Standard induction chemotherapy; Intensive consolidation treatment; TKI + reduced cht (Ph+ ALL)	Acute Lymphoblastic Leukemia: Younger adults (30y); Maintainance treatment (complete remission); TKI + steroids (Ph+ ALL)
	Autologous Stem Cell Transplantation: 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	MPN (Chronic Myeloid Leukemia, Essential Thrombocitemia, Idiopathic Thrombocytosis, Policytemia Vera)
	CLL treated with multiple lines of CTX Multiple Myeloma in 3 or more lines or during ASCT DLBCL relapsed/refractory HD if treated with “escalating BEACOPP”	Low or high grade NHL, CLL, MM, HD treated with conventional frontline chemotherapy