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Risk factors and prophylaxis against invasive fungal disease for haematology and stem cell transplant recipients: an evolving field

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Abstract

Introduction: Due to increasing intensity and complexity of therapies and longer survivorship, many patients with haematologic malignancy (HM) are at risk of invasive fungal disease (IFD). Mortality from IFD is high and treatment of an episode of IFD results in an excess length of hospital stay and costs and delays delivery of curative therapy of the underlying haematologic condition. Therefore, prevention and early recognition and treatment of IFD are crucial.

Areas covered: Risk factors particular to certain HMs and haematopoietic stem cell transplantation, as well as those risk factors universal to all HM groups are examined.

Expert commentary: Risk stratification identifies those patients who would benefit most from mould active versus yeast active prophylaxis and those who can be safely managed with monitoring and clinically driven interventions for IFD. This approach aids in antifungal stewardship.

Keywords:

Antifungal prophylaxis, haematologic malignancy, stem cell transplantation, risk factors, moulds

1.0 Introduction

With increasing intensity and complexity of cancer therapies and longer survivorship through multiple lines of therapy, many haematology patients are at risk of invasive fungal disease (IFD). Without antifungal prophylaxis, IFDs occur in up to 30% of acute leukemias and 15% of allogeneic haematopoietic stem cell transplant (alloHSCT) recipients [1,2]. Mortality from IFD is high and delays in treatment increase mortality [3,4]. Treatment for an episode of IFD is costly and results in an excess length of hospital stay [5,6]. Importantly, these infections impact on cancer-specific treatment, with delayed delivery of curative therapy and poorer outcomes of the underlying haematologic condition [7]. Therefore, prevention and early treatment of IFD are crucial, and institution of mould active prophylaxis is recommended for those at high risk of IFD.

Conversely, the overuse of antifungal prophylaxis could have detrimental effects, with cost, toxicities and emergent antifungal resistance resulting in potential adverse outcomes [8]. Therefore, knowledge of risk factors to establish risk stratification can aid in antifungal stewardship and avoid the negative effects of overuse of antifungal agents.

New developments in treatment of HM and in HSCT continue to impact risk and timing of IFD. For example, the emergence of reduced-intensity (non-myeloablative) conditioning (RIC) regimens as an alternative to conventional (myeloablative) regimens prior to alloHSCT has reduced duration of neutropenia pre-engraftment[9]. RIC use has increased dramatically from 2000 to 2011[10], and although IFD rates seem similar[11] infection occurs later with RIC[12]. Furthermore, there has been an evolution in the timing of alloHSCT. Where once transplant was used predominantly as a rescue therapy after failing multiple lines of chemotherapy, today, HSCT is frequently used early after achievement of first complete remission. Therefore, alloHSCT recipients may have fewer risks for IFD at time of transplant than in the past. Use of alternate donors such as haploidentical, mismatched and cord blood transplants are also likely to change the risk profile and temporal pattern of IFD in alloHSCT. It is thus timely to review risk stratification in light of new developments in management of both HM and HSCTs.

We aim to review the literature for factors that have been found to impart risk of IFD, with a focus on invasive mould infection, and discuss how risk stratification informs the approach to antifungal prophylaxis in patients with haematologic malignancy and stem cell transplantation.

2.0 Risk stratification

A patient's risk level is a result of multiple factors including those relating to the underlying malignancy status and treatment, factors intrinsic to the patient (for example, comorbidities and performance status) and the environment (inside of

the hospital and externally)[13]. We will examine these factors in turn in the following discussion (table 1).

Importantly, risk factors for IFD are dynamic and risk status can evolve in an individual patient, shifting those from a low or intermediate risk into a high risk category [14]. For instance, lymphoma patients may be classified initially as low risk, however with prolonged therapies and corticosteroid use, they become at much higher risk for IFD.

3.0 Universal risk factors

There are some factors that appear to confer risk of IFD independent of the underlying condition. These are examined in the following section.

3.1 Patient factors

3.1.1 Age

Age >40 years has been found by a small number of groups to be a risk factor for IFD[4,15,16], however recent multivariate analyses have not found this to be a significant predictor [17,18].

3.1.2 Nutritional and metabolic status

Diabetes mellitus and hyperglycaemia are well-described risk factors for invasive mucormycoses, particularly of the rhinosinoorbital variety [19]. There is also an increased risk of invasive Fusariosis in this group [20] and it has been described as a risk for invasive mould disease in an allogeneic HSCT cohort [21]. Whilst case reports of invasive Aspergillosis in diabetic patients exist,

hyperglycaemia is not widely reported or supported by multivariate analyses of risk for invasive aspergillosis.

Hypoalbuminaemia was found to be a statistically significant risk factor of IFD in alloHSCTs in one study, and further analysis into the strength and validity of this relationship is required [2].

3.1.3 Genomics

An individual's genetics can influence risk of fungal infection, as seen in a recent study of a family with autosomal recessive CARD9 mutations who displayed various phenotypes including chronic mucocutaenous candidiasis, cutaneous and deep dermatophytosis and invasive candidiasis with stroke[22].

There have been several lines of investigation into a potential genetic predisposition to IFD in patients with HM or undergoing transplantation. Detection of fungal pathogens by innate immune cells occurs by a series of pattern recognition receptors (PRRs)[23]. There are at least three families of PRRs involved in fungal detection, and single nucleotide polymorphisms in some of these PRRs have been linked to an increased risk of IFD[23]. These include Toll Like Receptor 4 (TLR4)[24,25], Dectin-1[26,27] and the soluble PRR long pentraxin 3 (PTX3)[28]. Cunha et al's study revealed that the receipt of an alloHSCT from a donor with homozygous haplotype (h2/h2) of PTX3 was associated with a hazard ratio (HR) of 3 for invasive Aspergillosis [28]. Functionally, it was shown that this haplotype led to impaired phagocytosis and clearance of fungus. These associations require further validation with large scale studies that account for clinical as well as genetic factors to confirm a true risk exists with each polymorphism. In the future, information about genetic risk

factors could augment clinical risk factors to improve risk assessment for IFD to more accurately target antifungal prophylaxis.

In the context of a rapidly decreasing cost of next-generation sequencing and the increased interest in the human microbiome, there has been some early work on assessing the effect of the microbiome on the risk of IFD. Shelburne et al found that a patient who developed invasive mucormycosis had a dysbiotic microbiome with low alpha-diversity, potentially predisposing to the infection [29]. There is an increasing appreciation of how the human micriobiome can protect against fungal invasion via mechanisms such as competition for surfaces and substrates, and secretion of substances that inhibit fungal adhesion and growth [30]. Furthermore, there is developing evidence that our commensal bacteria can modulate the host antifungal immune response [30]. This is an emerging area with more research needed to understand how this knowledge and technology may be applied to clinical practice.

3.2 Treatment-related factors

3.2.1 Neutropenia

Neutropenia is a universally recognised risk factor for IFD, with the duration of neutropenia being the key factor [13,31,32]. Patients with HM are at high risk (>10% incidence of IFD) if neutrophils are <0.1 X 10^9/L for more than 3 weeks[33] or <0.5 X 10^9/L for more than 5 weeks. An intermediate risk (~10% incidence if IFD) is observed with neutrophils 0.1-0.5 X 10^9/L for 3 to 5 weeks or neutrophils of 0.1-0.5 X 10^9/L for less than 3 weeks with concomitant

lymphopenia (lymphocytes <0.5 X 10^9/L)[34]. This last caveat recognises the role that lymphopenia plays in IFD risk[21] (see below).

3.2.2 Corticosteroids

Corticosteroids are an important universal risk factor for IFD[4,21,35,36] and are commonly used to treat graft versus host disease (GVHD) after HSCT. Corticosteroids exert this effect by inhibiting neutrophil chemotaxis and oxidative bursts and suppressing the ability of monocytes/macrophages to kill conidia[37]. Both the dose and the duration of steroids are important [3], with >1mg/kg prednisolone equivalent in the setting of neutrophils of <1 X 10^9/L for > 1 week, and >2mg/kg prednisolone equivalent for >2 weeks regarded as high risk in one study. Even lower doses of steroid are considered high risk by some groups [38] however there is no consensus on the dose threshold for risk. Cumulative doses of steroids may also be an important risk predictor; with a recent study finding that ≥ 55 mg/kg of prednisolone during the first 4 weeks of treatment for GVHD was associated with an increased risk of fungal disease (hazard ratio, 3.65; P = .03)[39].

3.2.3 Chemotherapy agents

Cytarabine has been associated with increased risk of IFD in a small number of studies [40,41], however this has not been replicated in other studies [42]. Cornely et al found that cytarabine chemotherapy was a strong risk factor for recurrent IFD following an initial episode of IFD (odd ratio 3.92)[41]. In a study comparing cytarabine-containing remission induction regimens, it was shown that the high-dose cytarabine-containing regimen (AML-87) was at a much

higher risk of IFD, with an incidence of 36% and a HR of 27 compared to low-dose cytarabine and cytarabine-free regimens[40]. The high-dose cytarabine regimen was associated with more severe gut mucositis, which may at least partly explain the mechanism behind this association. Two small studies have observed an intermediate risk of IFD during cytarabine consolidation for AML (3-7%)[43,44], however these small studies have large margins for error and larger studies would be required to further examine this association.

A recent study examining incidence of IFD in AML/MDS patients treated with azacytadine found low rates of IFD (0.21% per treatment cycle and 1.6% per patient throughout treatment course), and even in a higher risk subgroup of those with severe neutropenia incidence was still low (0.73% per treatment cycle and 4.1% per patient throughout treatment course)[45]. Based on these results, antifungal prophylaxis would not be recommended for this group, however findings should be confirmed in other centres.

There has been an exponential increase in the use of targeted therapies and immunotherapies for both haematologic and oncologic malignancies. For many of these therapies, the IFD risk profile is poorly characterised. Some of these agents, such as the B-cell lymphoma-2 inhibitor ABT-199, have potential interactions with azole antifungals and risk of QT prolongation, which provide potential barriers to the future use of antifungal prophylaxis and treatment, should they be required [46].

The area of chemotherapy agents and IFD risk would benefit from more contemporary investigation of regimens currently used and their risks.

3.3 Environmental factors

Moulds are found in soil and decaying plant matter, as well as contaminated water and building materials. Moulds are commonly spread by the airborne route when aerosolised, with inhalation and pulmonary colonisation as the portal of entry. Environmental factors that increase the ambient spore count have been associated with an increased risk of invasive mould infection. Studies have shown links between dry weather with high temperatures and a higher incidence of IA [47,48]. Environmental mould spore counts from the period 28-42 days preceding infection was significantly associated with admissions due to IA in a Spanish study[49]. In an isolated study, living in the country was found to be a risk of IFD [50]. Having an occupation or hobbies that place the patient at high risk of exposure to dirt, soil and decaying plant matter (such as farming, construction, gardening, floristry and forestry) has been shown in a small number of studies to be at significant risk [17,50,51]. It has been well documented in the literature that building works at hospitals is a risk for increasing spore counts and invasive mould infection [52-59].

In light of the knowledge that high levels of airborne spores are associated with invasive mould infection, there has been investment in technology to reduce ambient spore counts on high-risk wards, namely high-efficiency particulate air (HEPA) filtration and laminar airflow (LAF). Whilst LAF has been shown to be highly effective at reducing spore counts [59-61], it is expensive and has not

been recommended routinely in IFD prevention protocols[62]. HEPA has been shown to be effective at reducing IFD rates[52,63,64] and is recommended for all high-risk wards such as haematology and stem cell transplant wards[62]. In the setting of planned hospital works, it is recommended that air filtration and supply be thoroughly reviewed prior to commencing construction, and to consider using enhanced surveillance for IFD, dust remediation strategies and targeted environmental sampling during this period [65]. Some have reported expanding indications for mould active prophylaxis in response to increased numbers of IFD cases subsequent to building works[66].

Smoking has been shown in a small number of studies to be a risk of IFD [50,67], and for this and many other health reasons, it is recommended that immunosuppressed patients quit smoking.

4.0 Underlying haematologic malignancy/transplant status

The haematologic conditions that have a high incidence of IFD are acute myeloid leukemia/myelodysplastic syndrome (AML/MDS), alloHSCTs and more recently, acute lymphoid leukemia (ALL). We will examine these conditions in turn with respect to IFD incidence and established risk factors.

4.1 Acute myeloid leukemia

AML patients are among some of the highest risk patients for IFD, with the remission-induction phase being particularly high risk [35,68]. The incidence of IFD in AML varies depending on the population examined and the aggressiveness

and thoroughness of the diagnostic approach to IFD in the institution. Without prophylaxis, incidence ranges from 7-11% proven/probable IFD and 24-41% possible IFD [1,69].

Caira et al examined numerous published pre- and post-chemotherapy risk factors for proven/probable IFD in AML patients and found only a small number of factors prevailed in a multivariate analysis[17]. For invasive mould infection, pre-chemotherapy risk factors were a poor performance status (ECOG≥2), house renovation, having a high exposure job (construction, farming, gardening, floristry, forestry) and chronic obstructive pulmonary disease (COPD). Post-chemotherapy risk factors were days of neutropenia and high esophagitis grade (>2 as per WHO scale).

4.2 Acute lymphoid leukemia

The incidence of IFD in ALL has had relatively little examination compared to AML and HSCT [70]. However, it is becoming increasingly apparent that this group are at high risk of IFD, particularly in the setting of prolonged survivorship, aggressive therapies and issues with providing routine prophylaxis due to interaction between vinca alkaloids and triazoles [71]. Incidence of proven/probable IFD in ALL patients without prophylaxis is 12-21%[72-75], with another study finding 8.8% of febrile neutropenic episodes in ALL attributable to IFD [76].

Risk stratification in ALL is still in its infancy, however some early observations of risk factors include increased risk with relapsed disease, prolonged neutropenia and the BFM95 treatment protocol [73,76].

4.3 Other lymphoproliferative disorders

Until recently, little was known of the incidence of IFD in lymphoproliferative disorders other than ALL. However recent publications have found a low but not insignificant rate of IFD in these disorders. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and diffuse large B cell lymphoma have been shown to have an IFD rate of 7.8% and 4.3% respectively in one study[72]. Non-Hodgkin lymphomas as a group have IFD rates of 0.3-1.6% [77,78], and Hodgkin's lymphoma between 0.7-3.6% [72,77,78]. Multiple myeloma has between 0.5-3.3% rate of IFD [72,77-80], with a recent study showing that those who have received multiple lines of therapy (3 or more) are at significant risk (15% IFD rate) [79]. This finding highlights the importance of pre-treatment and that treatment-experienced patients may have cumulative risks for IFD. Assessment of traditional risk factors of corticosteroid use, neutropenia and lymphopenia should be utilised in these patients, as those who may not be at high-risk early in their malignancy, may evolve into higher risk with the cumulative effects of treatment.

Newer agents coming into use such as idelalisib and venetoclax (ABT-199) have unknown potential IFD risks. These agents may be used in patients who have failed multiple lines of therapy, putting these patients in a higher risk group due to cumulative effects of prior regimens. Idelalisib has been associated with a

higher risk *Pneumocystis jiroveci* pneumonia[81] and CMV disease[82], which raises the possibility of increased IFD risk. We must be vigilant for possible infections in such patients as there is much still to learn about the adverse effects of novel therapies.

4.4 Autologous HSCT

Autologous HSCT has been consistently shown to be a moderate risk of IFD, with rates between 0.4 and 4% seen in many studies [38,77,83]. This places these patients in an intermediate risk group and prophylaxis is prescribed accordingly (see below).

4.5 Allogeneic HSCT

Risk factors of IFD in alloHSCT have been extensively examined and will be discussed in detail in the following section, divided into transplant, pre-transplant, post-transplant and treatment related factors.

4.5.1 Transplant factors and the incidence of IFD

For alloHSCTs, overall rates of IFD are between 5 and 19%, with the majority of estimates around 10-11% [2,77,84-86]. It has been repeatedly demonstrated that the type of transplant predicts the risk of IFD in this population [4,87-89]. Cord blood, haploidentical and mismatched transplants are at particularly high risk, and matched related donors confer the lowest risk [4,11,89,90]. In a snapshot across the US of patients receiving alloHSCT [38], the observed incidence of IFD was 5.8% for matched related donors, 7.7% for matched unrelated donor and 8.1% for mismatched donor transplants. However

incidence varied considerably between centres and the impact of antifungal prophylaxis was not examined. The widespread use of antifungal prophylaxis may have decreased IFD incidence. Further, there are several common risk factors that elevate these patients into high-risk categories as elaborated below.

Increasingly alternative donors such as haploidentical or cord blood donors are used in HSCT and immune reconstitution post-transplant may be delayed in the recipients [91]. There is a lack of an accurate marker of immune reconstitution to indicate that fungal infection risk is declining. Recently however, there has been promising research into developing several monitoring assays detecting fungal specific T-cell immune reconstitution[91]. Although not yet translated into clinical practice, this may lead to advances in our ability to characterise fungal-specific immune reconstitution in the various donor types and better individualise fungal prophylaxis.

4.5.2 Pre-transplant factors

Pre-transplant IFD as risk for further IFD

Several groups have found that an IFD pre-transplant puts a patient at higher risk of IFD in the post-transplant period [11,18,92]. Fukuda et al [92] found that those with IA prior to transplant had lower overall survival and higher transplant-related mortality. Importantly however, if the patient had received >1 month of antifungal treatment and had radiologic resolution of changes, their probability of post-transplant IA and survival was the same as those without pre-transplant IA [92].

Control of underlying condition prior to transplant

It has been observed in several studies, including multivariate analyses [11,18], that patients who are not in complete remission pre-transplant are at higher risk of IFD post-transplant.

4.5.3 Post-transplant factors

4.5.3.1 Graft versus host disease

Both high-grade acute and chronic extensive GVHD have been shown to be strong risk factors for IFD post alloHSCT [11,12,21,89,90]. In a multivariate analysis, Fukuda et al [12] found high grade (grade III or IV) acute GVHD had a hazard ratio of IFD of 2.8 (p=0.04), and chronic extensive GVHD a hazard ratio of 3.7 (p=0.04) for IFD. Furthermore, the requirement for increased immunosuppression to manage GVHD confers an added risk of IFD (see section on corticosteroids).

4.5.3.2 Cytomegalovirus (CMV) disease

Some groups have found CMV disease to be associated with IFD post alloHSCT, with adjusted HRs of between 7 and 21 reported [12,21,93,94]. However, Girmenia et al [11] did not find CMV disease to be significant in their multivariate analysis. Interestingly, one study found that ganciclovir, rather than CMV disease itself, was a strong risk factor for IFD [3], which may be related to the myelosuppressive nature of the ganciclovir. CMV viraemia without disease has not been shown to be a risk factor for IFD although a recent retrospective study indicates that a CMV viral load of $\geq$250 IU/ml was independently associated with increased risk death day 0-60 after HSCT(HR 19.8, 95%CI 9.6-41

by multivariable cox proportional hazards modelling)[95]. Many of these deaths resulted from infection including IFD [95]. In light of these findings, further investigation of the role of CMV viraemia in IFD should be undertaken.

4.5.3.3 Viral respiratory tract infections

A small number of groups have identified respiratory viral infections as a risk factor for IFD post alloHSCT [4,49,96] . There may be some measurement bias in these studies however, as when patients have fever and respiratory symptoms, patients are more likely to be tested for respiratory viruses and hence be detected. However, Garcia-Vidal et al [49] found a temporal relationship between higher rates of circulating respiratory syncytial virus, influenza A (H1N1) and adenovirus and higher rates of IFD, lending plausibility to the findings from other studies.

4.5.4 Treatment-related factors

4.5.4.1 Lymphopenia and monocytopenia

In addition to the well-documented risk factor of neutropenia, lymphopenia has been shown in several studies to be of importance in IFD[4,21] and a risk prediction score produced by Stanzani et al found lymphocytopenia and lymphocyte dysfunction as a key predictor of IFD[18]. Monocytopenia was found to be a risk factor in alloHSCT in several multivariate analyses, although the importance of absolute count versus duration of monocytopenia requires further study [21,97].

4.5.4.2 Monoclonal antibodies

Alemtuzumab (Anti-CD52 monoclonal antibody) has been shown to be a risk factor for IA [98]. This risk is likely due to the profound lymphopenia that occurs for up to 9 to 12 months [99,100], and also may in part be related to the neutropenia seen in some patients for 2-12 weeks[101,102]. With newer treatment options in lymphoproliferative disorders becoming available, the use of alemtuzumab appears to have waned, with the exception of T cell lymphomas. Vigilance is required in this group for fungal infection complications.

Anti-CD20 monoclonal antibodies may be associated with increased IFD risk, with several reports in the literature, mostly in the setting of HSCT [103]. In a prospective observational study of autologous HSCT patients who had received rituximab prior to transplant, a univariate analysis found rituximab to be associated with IFD, however a multivariate analysis did not [104]. There were two recently published cases of IFD following receipt of obinutuzumab[105], which has more potent CD20-positive B cells depletion effects than rituximab[106]. Given that obinutuzumab is not yet widely used, we are yet to quantify its risk for IFD.

It is unclear whether the use of tumour necrosis factor alpha (TNF-α) antagonists increases IFD risk. In 2007, the literature of reported cases of IFD in the setting of TNF- α antagonist use for any indication was summarised [107]. Of the 281 IFD cases reported in the literature to that date, concomitant corticosteroids were administered in 98% of cases with information regarding immunosuppression available . The majority of IFDs were histoplasmosis (30%), candidiasis (23%) and aspergillosis (23%). As there was no denominator, an estimate of risk associated with TNF- α antagonists could not be calculated. In a

review of cases of IFD associated with monoclonal antibody use in both autoimmune and HM settings, Nedel et al [103] concluded that infliximab, etanercept and alemtuzumab definitely increase risk of IFD and rituximab, adalimumab and abatacept may increase risk. This is clearly an emerging area and time will reveal the true effect of these agents.

4.5.4.3 Iron overload

A number of studies have found an association between elevated pre-transplant ferritin levels and IFD [21,108]. A study found higher bone marrow iron stores in those who had fungal infection than those without[109] and another found a higher proportion of those with high liver iron stores had IA at autopsy[110]. There has been a link drawn between iron overload and pathogenesis of mucormycosis [111]. However, not all groups have found this association, and given that ferritin is an acute phase reactant, this may be a reflection of underlying disease or inflammation.

5.0 Recent risk prediction tool for IFD in haematologic malignancy patients

It is desirable to have a risk prediction tool for invasive mould disease (IMD) that could be applicable to various HM groups, rather than having separate risk factors for each HM. Stanzani et al sought to develop such a tool in a single centre in Italy [18]. This analysis of 1709 hospital admissions for patients with AML/MDS, allogeneic HSCTs, myeloma and lymphoma found that among 17 risk factors identified in other studies, only 4 factors were independent predictors of IMD across these groups: duration of neutropenia, lymphopenia or lymphocyte dysfunction in alloHSCTs, malignancy status and prior IMD[18]. From this, a risk

prediction tool was developed which was then validated in the same centre prospectively. Their risk prediction tool had high negative predictive value, which would be of use to define patients at low risk of IMD who do not require routine prophylaxis. Limitations of this study are the single centre nature of the study, hence generalizability to other populations has not been established. Furthermore, alloHSCTs only represented a small proportion of the cohort (12%) and thus this study may not be reliably translatable to this complex patient group.

6.0 Antifungal prophylaxis and risk stratification

Assessing the benefit of antifungal prophylaxis is complex. The number needed to treat (NNT), number needed to harm, and the individual patient's IFD risk (see below) are typically utilised to guide clinical decision making. Current expert opinion favours a NNT of around 20 or below for optimal benefit of prophylaxis [112,113].

Clinicians must be aware of their local fungal epidemiology, as there is regional variation in the incidence and aetiology of IFDs, which should influence the decision to use prophylaxis and the subsequent choice of agent [14,38,114-116].

6.1 Efficacy of prophylaxis in AML

Mould active prophylaxis has been shown to significantly reduce the incidence of IFD in AML in comparison to fluconazole [114,117-119]. Not all mould-active azoles are of the same efficacy, with posaconazole shown to be the most effective in several studies [115,116]. Ananda-Rajah et al demonstrated proven/probable

IFD rates in AML patients of 17%, 1.7% and 0% for fluconazole, voriconazole and posaconazole prophylaxis respectively[115]. Pagano et al showed similar results comparing itraconazole to posaconazole with 10.7% and 2.7% proven/probable IFD respectively [120]. Prophylaxis is of course not infallible, with a recent study showing breakthrough IFD rates of 6.4% proven and 17.6% possible IFD in AML patients on posaconazole [121]. There was a higher rate of breakthrough IFD in this study than earlier reports, however this result may be partly explained by the real-life dataset rather than a clinical trial cohort.

Voriconazole prophylaxis has not been well studied in the AML group, although as per the above study by Ananda-Rajah[115], posaconazole did appear to have a small additional benefit over voriconazole. A small open label, randomized trial of intravenous voriconazole versus itraconazole found no difference in IFD between the groups [122] but larger studies are required.

Echinocandins are used in many centres for prophylaxis on account of their tolerability and safety profile. However, they do not have broad spectrum anti-mould activity and may be associated with higher breakthrough IFD rates than voriconazole/posaconazole when used in high risk AML patients [123].

6.2 Efficacy of prophylaxis in ALL

Prophylaxis is difficult in ALL as there are important interactions between mould-active azole antifungals and the vinca alkaloids, which are a key component of chemotherapy regimens for ALL[70,71]. As a consequence, mould-active prophylaxis is either not given or withheld for significant periods of time

during induction and maintenance chemotherapy. Therefore, there is no data on the efficacy of mould active prophylaxis in this group. In those on fluconazole prophylaxis, the observed incidence of proven/probable IFD was 13% in one study[74], compared to 12-21% without prophylaxis[72,73,75].

6.3 Efficacy of prophylaxis in allogeneic HSCT

In studies of alloHSCT patients on fluconazole prophylaxis, incidence ranges from 9-22.5% proven/probable IFD[2,11,89,124,125] compared to 1-5% with mould-active prophylaxis[126]. In a recent breakthrough IFD study in alloHSCTs where prophylaxis was principally posaconazole or micafungin, proven and probable breakthrough IFD rates were 3.4% and 9.0% respectively[121]. The seminal randomised trial by Ullmann et al found that, in comparison to fluconazole, posaconazole had a lower incidence of IA, total IFDs and deaths attributable to fungal infection although overall mortality did not differ[127]. Following this, observational studies of posaconazole prophylaxis have demonstrated good outcomes, with real world experience showing breakthrough IFD rates of 1.9%-7.5%[128,129] and overall IFD mortality of 3.7%[129]. A small observational study comparing posaconazole to itraconazole found less IFDs and higher overall survival in the posaconazole group (0% and 12% breakthrough IFD, and 91% vs 63% overall survival respectively)[130]. Mould-active prophylaxis has also been shown to be protective against IFD in alloHSCTs in a multivariate analysis[11].

Voriconazole was not shown to be different to fluconazole with respect to fungal-free survival and IA incidence in a randomised trial of HSCTs[126], however

there was a non-statistically significant trend to reduced IFD and IA. A randomised, multicentre, open label trial of voriconazole compared to itraconazole also found no difference in IFD rates or survival, although voriconazole was better tolerated [131]. It is important to note, however, that both voriconazole studies were conducted on relatively low risk HSCT populations with neither study having a high rate of patients with mould infection and therefore potentially lacking power to show a benefit in the higher risk transplants.

Similar to the AML group, there is a reluctance to use echinocandin prophylaxis in HSCTs given their lack of broad-spectrum anti-mould activity. A randomized controlled trial compared micafungin 50mg/day to fluconazole 400mg/day as prophylaxis in neutropenic adults and children following HSCT and found micafungin to be superior (success rate 80% vs 73.5%, p=0.03), although invasive mould disease was rare in both arms of the study [132]. Another smaller study (n=104) comparing micafungin 150mg/day to fluconazole 400mg/day found micafungin as effective as fluconazole at 4 weeks follow-up [133]. Micafungin (50mg/day) had similar efficacy and greater tolerability than itraconazole during the neutropenic period post autograft and allograft [134]. A single arm study of caspofungin prophylaxis in HSCTs (35-50mg/day; median duration 73 days) found a breakthrough IFD rate of 7.3%, which is comparable to other prophylaxis used [135]. Neither micafungin nor caspofungin have been compared to posaconazole for prophylaxis in HSCT. Furthermore, given the requirement of intravenous delivery, echinocandins are not as practical as the orally available azoles. In our opinion echinocandins should not be used as first

line antifungal prophylaxis in alloHSCT until comparative studies with the current standard of posaconazole are performed.

7.0 Recommendations based on risk stratification

Based on the abovementioned factors, patients deemed at high risk for IFD (~>10% risk of IFD) should receive mould active prophylaxis [14] with the recommendation of antifungal based on risk strata (guidelines from several authorities summarised in tables 2 and 3)[14,136-141]. Some guidelines including those from ECIL [137] and IDSA [138] are due for an update and publications of these updates are eagerly awaited. Prophylaxis against *Candida* species should be used where neutropenia is less protracted (standard risk as per table 2) but where mucosal integrity may be compromised, such as with mucositis [142]. Where neutropenia is transient, immunosuppression is not extensive (such as standard intensity chemotherapy for lymphoma), and mucosal integrity is not disrupted, patients are at low risk and antifungal prophylaxis is not recommended.

7.1 Timing of commencing prophylaxis

Apart from alloHSCT [143] where prophylaxis is usually commenced at day 0 [126,131], the optimal timing of initiating prophylaxis is unclear. In the original posaconazole prophylaxis study in AML patients, prophylaxis was commenced 24 hours following the last dose of anthracycline or on the first day of chemotherapy if the regimen did not contain an anthracycline [116]. This is in contrast to current practice at many centres, where prophylaxis is commenced at admission for AML induction therapy.

Furthermore, when prophylaxis should be ceased is not clear. Based on early studies, alloHSCT recipients should continue antifungal prophylaxis until at least day 75, in the absence of GVHD [132]. For those with GVHD, prophylaxis duration is guided by expert opinion suggesting it should be continued for 16 weeks or until the corticosteroid dose is less than 10mg/day prednisolone equivalent [3,14]. For treatment of HM including AML, prophylaxis cessation is generally recommended following resolution of risk, for example, cessation of high dose steroids or neutrophil count recovery above 0.5 X 10^9/L [14] (see tables 2 and 3 for recommendations).

7.2 Other considerations during antifungal prophylaxis

Therapeutic drug monitoring of mould-active azole prophylaxis may be beneficial to ensure that adequate levels are achieved [144-146]. However, a recent analysis of levels of voriconazole in HSCT showed no correlation between breakthrough IFD and voriconazole level[147], although low rates of IFD in the voriconazole cohort may have limited ability to detect a difference.

Clinicians must be aware of the impact of antifungal prophylaxis on the utility of diagnostics for IFD. Mould-active prophylaxis (voriconazole and posaconazole) may result in serum galactomannan and Aspergillus PCR testing being less likely to be positive even in presence of invasive mould infection [125,148,149] although likely still useful on bronchoalveolar lavage fluid [150].

8.0 Conclusion

Risk stratification for IFD is complex and can be assessed from a disease-based or a common risk factor-based approach. There has been a move toward recommendations based on common risk factors to streamline the approach, and composite risk scores are in early stages of development. If a patient is deemed to be at high risk for IFD, mould active prophylaxis is recommended. Knowledge of local fungal epidemiology is vital, as recommendations for one population may not translate into the most effective approach for another. As more haematology patients are treated for longer, with novel agents, and with longer survivorship, the epidemiology of fungal infection is likely to change and affect patients outside of the traditional risk groups. Continued surveillance and research into this area will be of great importance. Future research may see addition of genetic and immunological risk factor profiling to enhance risk prediction.

9.0 Expert commentary

Invasive fungal disease remains a lethal and costly infection in patients with HM and HSCT.

Risk stratification to identify patients at risk and to whom mould active prophylaxis should be targeted is complex, impacted by patient, disease and treatment specific factors. Mould active prophylaxis, recommended for traditional high risk groups such as those undergoing AML remission induction and with GVHD requiring immune suppression is imperfect as indicated by breakthrough infection rates. However, increasingly mould infection is

recognised in patients outside of the traditional risk groups not covered by prophylaxis guidelines.

Factors influencing risk and timing of IFD continue to evolve. The rise of mould infections outside traditional risk groups may be due to more aggressive and immune based therapy, the availability of multiple lines of therapy each with differing impacts and duration of effect on the patient's immune system and new approaches to treatment increasing survivorship. Once patients have received multiple lines of therapy and in the presence of active underlying HM it becomes difficult to assess their overall state of immunosuppression and thus risk for IFD.

With the increased use of RIC HSCT reducing duration of neutropenia and alternative donors leading to slower immune-reconstitution IFD may be seen later after transplant when patients are receiving less intensive medical follow-up. Newer targeted therapies used in HM have unknown impacts on the host's immune response and surveillance for opportunistic infection including fungal infection is required.

These findings argue for a need for improved identification of high risk patients. Preliminary work identifying SNPs in PRR as markers for increased risk for IFD as well as the feasibility of assessing an individual's pathogen specific immune responses may lead to better tools to assess risk when combined with clinical risk factors.

Currently prophylaxis guidelines focus on the traditional high risk patient and most authorities recommend mould active prophylaxis with posaconazole for AML type chemotherapy. In the early allogeneic transplant setting mould active prophylaxis is recommended for cord blood transplantation and in the post-engraftment period for graft versus host disease of grade 3-4 severity. The guidelines by Girmenia et al from the GITMO group [136] provide the most granularity around various HSCT scenarios such as mismatch or unrelated donor source and the presence of CMV disease, recurrent reactivation and corticosteroid use that would place a patient into a higher risk for mould infection and can be strongly recommended. However, many other patients outside of AML and HSCT remain at risk for IFD. The challenge is to better identify this diverse group of patients.

10.0 Five year view

Increasingly immunosuppressive and multimodal treatments for lymphomas, multiple myeloma and chronic leukemias will lead to increased rates of IFD in this group, and risk stratification for patients in general will become more complex. Increased use of alternative donors for allogeneic stem cell transplants will also likely increase and change the fungal infections seen in this group.

There will be greater emphasis and developments in immune profiling and pathogen-specific immunity assessment in order to tailor prophylaxis to the at-risk period. Further, there will be increasing emphasis on methods of early detection of fungal infection in at-risk groups.

11.0 Key issues

- As mortality and cost of management of IFD is high, it is highly desirable to prevent IFD
- Risk stratification is used to help target antifungal prophylaxis to those who would most benefit from it
- Key universal risk factors for IFD include high doses of corticosteroids, prolonged neutropenia, prior IFD
- Acute myeloid leukemia/myelodysplastic syndrome during induction-remission chemotherapy is one of the most high risk populations for IFD
- Allogeneic stem cell transplant patients are generally at high risk, with factors such as GVHD, CMV disease, cord blood and haploidentical donors and active leukemia at time of transplant increasing the risk further
- In general, posaconazole is the preferred mould active prophylactic agent, with fluconazole remaining the preferred yeast active prophylactic agent
- There is emerging evidence that other haematologic malignancies (eg ALL and multiple myeloma) are becoming at higher risk of IFD with more aggressive therapies, multiple lines of therapy used and the cumulative effects of these treatments eg corticosteroids
- Novel therapies such as idelalisib and venetoclax have uncharacterised rates of IFD, and vigilance should be maintained in these patients for IFD
- Immune profiling and assessment of fungal-specific immunity may be a more accurate way to risk stratify patients in the near future.

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Reference annotations

* Of interest

** Of considerable interest

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Table 1- Statistically proven risk factors associated with invasive fungal disease in haematological malignancy and stem cell transplant recipients

Consistently associated with risk of IFD	**References**
Disease-related factors	
AML remission-induction chemotherapy	[1,35,68,69,115]

Allogeneic stem cell transplants
• Transplant factors
  ○ cord blood, haploidentical, mismatched transplants
• Pre-transplant factors
  ○ IFD prior to transplant
  ○ Active leukaemia at transplantation
• Post transplant factors
  ○ GVHD (high grade acute and chronic extensive)
  ○ CMV disease
	[2,12,77,84-86]
	
	[4,11,89]
	
	[11, 18,92]
	[11,18]
	
	[4,11,12,15,21,89,96]
	[4,12,21, 93,94]

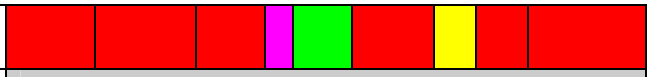
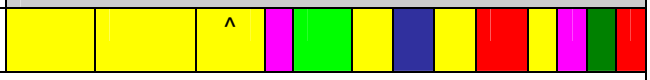
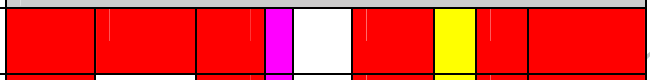
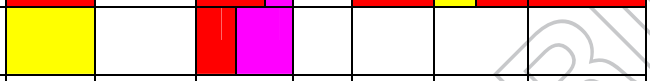
Patient factors	
Diabetes mellitus and hyperglycaemia	[19,20,21]
Treatment-related factors	
Prolonged neutropenia (approx. >3 weeks)	[13,17,31-34]
Corticosteroids	[3,4,35,36,39]
Environmental factors	
Hospital building works	[52-59]
HEPA filtration (protective)	[52, 63,64]
Laminar airflow (protective)	[59-61]
Identified in 1 or more studies as a risk of IFD	
Disease-related factors	
Acute lymphoblastic leukemia	[72-75]
Allogeneic stem cell transplant factors • CMV viraemia • Viral respiratory tract infections • Iron overload	 [95] [4,49,96] [21,108,109]
Patient factors	
Age >40	[4,15,16]
Hypoalbuminaemia	[2]
Genomics	[23-27]
Poor performance status (ECOG ≥2)	[17]
COPD	[17]
Treatment-related factors	
Lymphopenia/lymphocyte dysfunction	[4,18,49]
Monocytopenia	[21,97]
Cytarabine	[40,41,43,44]
Ganciclovir	[3]
Alemtuzumab	[98]
High esophagitis grade (>2 as per WHO scale)	[17]
Environmental factors	

Dry weather with high temperatures	[47,48]
Ambient mould spore counts	[49]
Living in the country	[50]
High risk occupation/activity (farming, construction, gardening etc)	[17,50,51]
Smoking	[50,67]

AML= acute myeloid leukemia; IFD= invasive fungal disease; CMV=cytomegalovirus; HEPA= high-efficiency particulate air; GVHD= graft versus host disease; ECOG= Eastern Cooperative Oncology Group performance status

Table 2- Recommendations from various authorities for primary antifungal prophylaxis- Allogeneic stem cell transplants

Caveat/criteria	GITMO [136]	ANZMIG [14]	ECIL-3 [137]	IDSA [138]	NCCN [139]	Korean [140]	GSHO [141]
Early (days 1-40)							
• High risk							
○ Active leukemia							
○ Cord blood transplant							
○ Grade III or IV a-GVHD							
○ MMRD or UD plus ≥1 of:							
▪ Grade II a-GVHD							
▪ Steroids ≥2mg/kg/day for ≥1 week							
▪ CMV disease							
▪ Recurrent CMV infection							
▪ Prolonged neutropenia (>3 weeks)							
▪ Iron overload							
○ Prior IA							
○ Expected neutropenia >14 days				*			
• Standard risk							
○ All remaining pts not in high risk group							
Late (41-100)							
• High risk							
○ Acute grade III-IV GVHD							
○ MMRD or UD transplant plus ≥1 of:							
▪ Grade II a-GVHD							
▪ Steroids ≥2mg/kg/day for ≥1 week							
▪ CMV disease							
▪ Recurrent CMV infection							
▪ Recurrent neutropenia (>1 week)							
○ Steroid							

refractory/dependent a-GVHD	
• Standard risk	
○ All remaining pts not in high risk group	
Very late (100 +)	
• High risk	
○ Persist. or LO grade III-IV or SR/dependent a-GVHD	
○ Persist. or LO grade II a-GVHD (MMRD or UD)	
• Stndrd risk- Ltd c-GVHD with nonsteroid IS and "de novo c-GVHD"	
• Low risk- Absence of any GVHD and no steroid therapy	

#- ECIL guidelines are being updated and are awaited ^- only when combined with a mould-directed diagnostic approach

*- Including patients with prolonged neutropenia immediately prior to transplant **- receiving immunosuppressive therapy for GVHD

a-GVHD- acute graft versus host disease; c-GVHD- chronic graft versus host disease; LO- late onset; SR- steroid refractory; MMRD- mismatched related donor; UD- unrelated donor; CMV- cytomegalovirus, IA- invasive aspergillosis; Stndrd- standard; Ltd- limited; IS- immunosuppression

Legend

Mould active	Yeast Active
Posaconazole	Voriconazole
Itraconazole	Fluconazole
Micafungin	No prophylaxis

Table 3- Recommendations from various authorities for primary prophylaxis- leukemia, lymphoma and autologous HSCT

Condition	Caveat/criteria	ANZMIG [14]	ECIL-3 [137]	IDSA [138]	NCCN [139]	Korean [140]	German [141]
Leukemia	Induction chemotherapy						
	• AML/MDS						
	• Non-AML/MDS but neutropenia >7 days						
	• Non-AML/MDS but neutropenia <7 days						
	Consolidation chemotherapy						
	• AML/MDS						
	• Non-AML/MDS but neutropenia >7 days						
	• Non-AML/MDS but neutropenia <7 days						
Autologous HSCT	• Mucositis likely					b	a
	• Mucositis unlikely					b	a
	• Prolonged period of neutropenia prior						a
Lymphoma	• Intensive dose-escalated therapy						a
	• Neutropenia>7 days						a

a- patients also received oral fluconazole
b- Based on premise that neutropenia >7 days
AML- acute myeloid leukemia
MDS- myelodysplastic syndrome
HSCT- haematopoietic stem cell transplant
#- ECIL guidelines are being updated and are awaited

Legend

Mould active	Yeast Active
Posaconazole	Voriconazole
Itraconazole	Fluconazole
Micafungin	Lip Amph B (inhaled)