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Fungal Pneumonia in Patients with Hematologic Malignancy and Hematopoietic Stem Cell Transplantation

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Synopsis

Fungal pneumonias cause unacceptable morbidity among patients with hematologic malignancies (HM) and recipients of hematopoietic stem cell transplantation (HSCT). The high incidence of fungal pneumonias in HM/HSCT populations arises from their frequently severe, complex and persistent immune dysfunction caused by both the underlying disease and its treatment. The cytopenias, treatment toxicities and other immune derangements that make HM/HSCT patients susceptible to fungal pneumonia frequently also complicate its diagnosis by impeding generation of classically recognizable host response patterns and increase the intensity and duration of required antifungal therapy. This manuscript addresses the host factors that contribute to susceptibility, summarizes diagnostic recommendations, and reviews current guidelines for management of fungal pneumonia in HM/HSCT patients.

Keywords

Fungal pneumonia; neutropenia; hematologic malignancy; stem cell transplant; immunocompromised host pneumonia; galactomannan

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Disclosures

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Dr. Evans: S.E.E. is an author on United States patent 8,883,174 entitled

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INTRODUCTION

Immunocompetent hosts are estimated to inhale hundreds of fungal conidia daily, but most fungal pathogens are cleared without development of clinical infection^{1,2}. By contrast, many patients with hematologic malignancies (HM) or those who have received hematopoietic stem cell transplants (HSCT) have impaired antifungal defenses, and account for a disproportionate number of fungal pneumonias in North America and Europe^{3,4}. Despite the use of mold-active prophylaxis since the 1990s, invasive fungal infections (IFI) remain a leading cause of morbidity in HM/HSCT patients, with unacceptably high attributable mortality^{3,5–7}. This review describes the immune deficits that enhance susceptibility to fungal pneumonia in HM/HSCT patients, as well as the diagnosis and management of the fungal pneumonia in this patient population.

MICROBIAL EPIDEMIOLOGY

Most endemic fungal pneumonias in the North America are caused by thermally dimorphic *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*⁸, resulting in IFIs in immunocompetent and immunocompromised hosts⁹. No large epidemiologic registry of endemic fungal pneumonia in HM patients exists, though smaller studies suggest that HM patients develop endemic fungal pneumonias substantially more often than the general population^{4,10}, and that these infections are more likely to be severe and/or lethal⁸. Interestingly, Transplant-Associated Infection Surveillance Network (TRANSNET) data suggest a very low rate of endemic fungal pneumonias in HSCT patients, potentially due to aggressive exposure avoidance during peak vulnerability¹¹.

As in Table 1, several registries of HM/HSCT patients estimate annual incidence of opportunistic IFIs in the range of 1.3% to 10% for patients receiving treatment in tertiary centers, despite widespread use of antifungal prophylaxis^{12–14}. *Aspergillus* spp. account for a substantial majority of the documented events, with *A. fumigatus* identified more than *A. flavus*, while *A. terreus* and *A. ustus* are increasingly noted in severely immunocompromised populations¹⁵. Recent decades have demonstrated increasing pneumonias caused by Mucorales (80% are *Rhizopus*, *Mucor*, *Rhizomucor*, and *Lichtheimia* spp.) and *Fusarium* spp. (primarily *F. solani*, *F. oxysporum* and *F. moniliforme*) in profoundly neutropenic HM/HSCT patients^{5,7,16–18}.

HM/HSCT RISK FACTORS FOR FUNGAL PNEUMONIA

As in the general population, risk factors for endemic fungal pneumonia in HM/HSCT patients primarily relate to exposure to geographically localized biomaterials^{19–21}. Thus, a thorough residential, recreational, travel and occupational history is essential to assessing risk levels in HM/HSCT patients⁸. Interestingly, while neutropenia enhances susceptibility to most endemic fungi, this association is less clear for *H. capsulatum*^{22,23}, possibly because neutrophils are fungistatic, rather than fungicidal, for this endemic pathogen.

In immunocompetent hosts, inhaled fungi initiate immune responses from lung macrophages, dendritic cells and epithelial cells, principally through pattern recognition receptors such as Toll-like receptors and C-type lectins^{22,24,25}. Cytokines from resident cells

drive neutrophilic infiltration and stimulate T cell dependent type 1 and type 17 inflammatory responses that promote clearance of conidia²³ or sequestration within granulomata^{19,21}. Impairment of any of these functions in HM/HSCT may allow opportunistic fungi to evade rapid elimination^{19,22,25} or reactivate from granulomata years after exposure²³. HM/HSCT patients face complex and concurrent immune defects derived both disease^{26,27} and treatment specific insults. Table 2 reports IFI incidence by type of HM and the associated immune impairments are discussed below.

Impaired Mucosal Immune Function

The sinopulmonary epithelium constitutes the first barrier to pathogen translocation and may be disrupted by many HM/HSCT-related processes, including effects of cytotoxic chemotherapy, radiation, preexisting infections, graft-vs.-host disease (GVHD) and placement of nasogastric or endotracheal tubes. Beyond the physical barrier disruption of these processes, these insults may also impair epithelial expression of antimicrobial effectors, such as lactoferrin, lysozyme or cathelicidin²⁵. Alternately, HM may directly impair mucosal immunity, as when AML cells cause alterations of mucosal volatile species generation²⁸.

Neutrophil Defects

Neutropenia that is profound (<500 cells/ μ l), prolonged (>10 days), or cyclic increased the risk for fungal pneumonia^{29–31}. In animal models³² and HM autopsies³³, lung tissue from neutropenic hosts demonstrates hyphal growth, angioinvasion, and hemorrhagic infarctions, but minimal inflammation. This is distinct from the high inflammation/low fungal burden seen in non-neutropenic HM patients with GVHD³³ or non-neutropenic HM patients on prolonged corticosteroid therapy³⁴.

Quantitative neutrophil deficits are compounded in HM/HSCT patients by functional defects. Common cancer-related insults such as radiation, corticosteroids, hypovolemia, acidosis and hyperglycemia can impair neutrophil chemotaxis, myeloperoxidase activity³⁵, and neutrophil extracellular trap formation³⁶. These functional impairments may explain in part why up to 40% of HM/HSCT patients do not have documented neutropenia at the time of fungal pneumonia diagnosis³⁷. Relatedly, corticosteroids or colony stimulating factors may increase the neutrophil count to > 500 cells/ μ l without reversing the underlying immune deficits^{38,39}.

Non-neutropenic Leukocyte Defects

T cell depletion or dysfunction contributes substantially to the risk of fungal pneumonia, even in the absence of neutropenia³⁶. T cell depleted HSCT and use of anti-thymocyte globulin place patients at high risk. Radiation, corticosteroids, cyclosporine, azathioprine, tacrolimus, cytotoxic purine analogs (e.g., fludarabine), nucleoside analogue (e.g., cytarabine, gemcitabine, 5-FU), certain monoclonal antibodies (e.g., alemtuzumab), and TNF antagonists can cause profound depletion and dysfunction of T cells that can last many months after treatment is completed^{5,13,17,29,30,40–42}. Moreover, patients with Hodgkin's disease, T-cell lymphoma, and some leukemias have disease-impaired cell mediated

immunity even in the absence of cytotoxic therapy⁴³, possibly due to microenvironment immunosuppressive or exhaustion mechanisms^{44,45}.

Although not historically thought to contribute significantly to antifungal defense, recent studies have identified protective antibodies against *Aspergillus*, *Histoplasma*, and *Pneumocystis* species⁴⁶ that promote complement activation and phagocytosis, and inhibit adhesion and germination. Many HMs are complicated by immunoglobulin dyscrasias, including impaired production, inappropriate class-switching and increased antibody catabolism^{43,47}. These effects appear to reduce host defenses against fungal infections, including invasive pulmonary aspergillosis³⁵.

Memory Defects After HSCT

Near total depletion of the recipients' T- and B-lymphocytes is the goal of pretransplant conditioning. In addition to acute impairments, it largely abrogates immune memory from a lifetime exposure to pathogens, environmental antigens, and vaccines⁴⁸. Even years after successful engraftment, many HSCT recipients experience immune impairment, as passive immunity from the donor provides insufficient protection. This is manifest in abnormal CD4:CD8 T-cell ratios and in immunoglobulin production that is deficient, dysregulated and demonstrates altered kinetics⁴⁹. The regeneration of sufficient quantities of T- and B-lymphocytes takes months to years, and maturation of fungal-specific immune responses takes longer still. Naïve B lymphocytes in HSCT recipients require environmental or vaccine exposure to fungal antigens and interactions with CD4+ T cells to generate fungal-specific antibodies and propagate protective memory B cells.

Graft-vs.-Host Disease

GVHD causes substantial morbidity following allogeneic HSCT, leading to prolonged use of immunosuppressive agents, increased risk of fungal infection, and increased mortality^{50–52}. In addition to impairments caused by GVHD-suppressive agents, chronic GVHD is directly linked to macrophage dysfunction, impaired neutrophil chemotaxis, and immunoglobulin subclass deficiencies⁴⁸. These defects may take years to recover after apparent resolution of GVHD.

Genetic Polymorphisms

Certain HM patient haplotypes are associated with altered immune responses and increased incidence of IFIs, prompting a number novel genetic investigations into host susceptibility to fungal pneumonia^{53–56}. Table 3 lists a select number of polymorphisms in genes encoding mediators of immunity that have been associated with altered risk of fungal disease in HM patients. While these polymorphisms have not yet been incorporated into risk stratification algorithms for the HM/HSCT patients, these genetic associations are likely to enhance understanding of antifungal immunity and may provide improved personalization of fungal prophylaxis and treatment in the future.

DIAGNOSIS OF HM/HSCT FUNGAL PNEUMONIA

Diagnosis of fungal pneumonia in any population can be challenging, due to nonspecific clinical presentations, slow growth rates in culture, and cross-reactions in fungal antigen testing²⁰. These issues are amplified in HM/HSCT patients, as the above described immune defects frequently result in atypical presentations. Fever, fatigue, or exertional dyspnea may be the only presenting symptoms, while sputum and radiographic consolidations may be absent^{43,57}. Many of the cardinal clinical features of pneumonia depend on robust immune responses that may be impaired in HM/HSCT patients, thus a high clinical suspicion is key to making the correct diagnosis.

Chest Radiography

Chest radiography is routinely performed in HM/HSCT patients with new fever or respiratory complaints. Chest x-ray is sufficient to detect some nodular or cavitary lesions, but up to 10% of patients with invasive pulmonary aspergillosis present with a normal x-ray. Consequently, CT imaging is the modality recommended by European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group in HM/HSCT patients²⁹. EORTC/MSG criteria list three chest CT findings as highly suspicious for fungal pneumonia²⁹: a dense, well-circumscribed lesion or lesions (e.g., a nodule with or without a halo sign), the air-crescent sign, or a cavity. The reverse halo sign or the atoll sign should also raise suspicion for fungal pneumonia⁵⁸. However, imaging studies in this high-risk group are often non-specific and indistinguishable from other pulmonary infections. Rather than the classically described findings, HM/HSCT patients commonly present with centrilobular nodules, ill-defined consolidations, ground-glass infiltrates, and pleural effusions⁵⁹.

It has been suggested that CT angiography may be more sensitive than conventional CT in detecting fungal pneumonia in HM/HSCT patients⁶⁰, but is not standard practice. FDG-PET/CT cannot reliably differentiate malignancy from infectious pulmonary nodules. This is particularly problematic in geographic regions known to have high burdens of endemic fungi⁶¹. Serial CTs may be used to monitor the response to antifungal therapy, though it may take months for IFI-related radiologic abnormalities to resolve or stabilize. In neutropenic patients, radiographic findings may paradoxically worsen after initiating antifungal therapy or recovery from neutropenia due to increases in tissue inflammation⁵⁹.

Biopsy considerations

The definitive diagnosis of IFI requires a tissue biopsy from a sterile site demonstrating tissue invasion or culture positivity for fungal species²⁹. For fungal pneumonia, a sterile specimen of lung parenchyma can be obtained via transbronchial biopsy, CT-guided transthoracic needle aspiration or video-assisted/open surgical biopsy. Bronchoalveolar lavage (BAL) fluid is not considered sterile material in the EORTC/MSG criteria. In HM/HSCT patients in whom previous bronchoscopic procedures were non-diagnostic, CT-guided biopsy of lung lesions > 1 cm offers high diagnostic yield often detecting fungal

disease⁶². Unfortunately, lung biopsy is frequently impossible in HM/HSCT patients, due to thrombocytopenia.

The EORTC/MSG classifications of IFI as Possible, Probable or Proven addresses immunocompromised hosts when a lung biopsy is not possible^{29,63}. Possible/Probable designations allow diagnoses based on host risk factors, radiographic features, non-sterile cultures, and culture-independent assays. The definitions emphasize a multifaceted approach to diagnosing fungal pneumonia in HM/HSCT patients, acknowledging their frequently nonspecific clinical and radiographic presentations and impaired seroreactivity.

Bronchoscopy

BAL is well tolerated, safe and provides a reasonable diagnostic yield in HM/HSCT patients, even in the setting of neutropenia and thrombocytopenia^{64–67}. The yield for infectious pathogens appears comparable in HM patients and HSCT patients⁶⁸, but the clinical utility of this study appears greatest when performed within four days of developing respiratory symptoms⁶⁴. Fungal pathogens may be visualized directly on BAL samples via such techniques as Gomori methenamine silver (GMS) staining or may be grown in culture, though the sensitivity of culture may be impaired by ongoing antifungal therapy at the time of BAL. As discussed further below, BAL samples can also be submitted for fungal antigen detection.

Galactomannan

Galactomannan (GM) is an *Aspergillus* cell wall constituent released during hyphal growth in tissue. Galactomannan antigenemia is detectable via enzyme immunoassay up to a week before the onset of clinical manifestations of invasive aspergillosis, but is generally not observed in uninfected patients or those with *Aspergillus* colonization^{69,70}. The utility of serum GM assays in asymptomatic immunocompromised populations has been an area of intensive investigation, and a recent Cochrane review⁷¹ suggests that serial analysis may identify patients with IFI earlier than without screening. Some authorities suggest weekly or twice weekly screening of serum for GM during the first 100 days after allogeneic HSCT and during HM-related neutropenia. However, serum GM screening of (lower risk) autologous HSCT patients does not appear to impact clinical outcomes⁷². Further, GM surveillance is generally limited to those not receiving antifungal prophylaxis, because the low pretest risk of invasive aspergillosis renders serum GM surveillance of asymptomatic patients unreliable⁷³.

In addition to serum surveillance, GM assays on BAL fluid may enhance diagnoses of invasive pulmonary aspergillosis in HM/HSCT patients with unexplained symptoms or abnormal radiographs. A recent meta-analysis suggests that BAL GM offers similar or better sensitivity and specificity than serum testing⁷⁴. Figure 1 presents the diagnostic performance in recent studies^{75–97}, revealing the strong diagnostic yield of BAL GM analysis in immunocompromised patients suspected of having pneumonia.

In the setting of established pulmonary aspergillosis, serum GM can also be used to monitor therapeutic responses⁹⁸. Decreasing GM after two weeks of antifungal therapy in patients concordant clinical responses demonstrate better survival than those without GM

declines. Failure of GM to decrease with therapy should prompt investigations to ensure adequacy of therapy.

(1,3)- β -D-glucan

(1,3)- β -D-glucan (BG) is a cell wall component of most fungal species, notably excluding Mucorales and *Cryptococcus* spp., detectable in blood during IFIs. A recent meta-analysis of studies in HM patients⁹⁹ found serum BG to have very good sensitivity but relatively low specificity for IFI. The diagnostic performance appears better among HM patients requiring ICU admissions, and is unaffected by ongoing antifungal treatment¹⁰⁰, unlike serum GM. The specificity of BG for IFI appears somewhat better in allogenic HSCT recipients¹⁰¹. Blood transfusions, renal replacement therapy, β -lactam antibiotics and bacterial infection¹⁰⁰ are may cause false positive BG result in commercially available BG assays.

MANAGEMENT OF HM/HSCT FUNGAL PNEUMONIA

As infections in severely immunocompromised HM/HSCT patients may rapidly progress to disseminated and/or fatal disease, prompt initiation of pre-emptive or empiric therapy is warranted when fungal pneumonia is suspected. In high risk patients, it is not recommended to withhold therapy while awaiting results of serologic or culture studies. Unless bronchoscopy is immediately available (< 2 h), antifungal therapy should similarly not be withheld until diagnostic procedures have been completed, even acknowledging that antifungal treatments may reduce the sensitivity of BAL.

Antifungal therapies

Concordant with the 2011 American Thoracic Society guidelines for treatment of fungal infections¹⁰², the initial treatment of HM/HSCT patients with suspected invasive pulmonary aspergillosis consists of liposomal amphotericin B or intravenous voriconazole until improvement occurs, followed by transition to oral voriconazole or itraconazole. Intravenous posaconazole, caspofungin or micafungin may be required as salvage therapy in refractory disease. Once patients demonstrate clinical improvement, these salvage therapies can be followed by oral voriconazole or itraconazole until resolution of disease.

Reversal of immune suppression, such as neutropenia or chemotherapy, is generally important for successful treatment. Surgical excision should be considered in HM/HSCT patients with focal disease or those with chronic necrotizing aspergillosis who fail antifungal treatment¹⁰³.

HM/HSCT patients with probable or proven histoplasmosis or blastomycosis are typically managed with an amphotericin preparation then transitioned to extended therapy with oral itraconazole once their symptoms begin to improve. A brief course of systemic glucocorticoid may be considered in the setting of severe pulmonary histoplasmosis or blastomycosis. In cases with persistent immune suppression, urine or serum Histoplasma antigen testing may be useful to detect breakthrough infections.

Mild, limited pulmonary coccidioidomycosis can often be managed with azole monotherapy, though treatment may be needed for as long as 18 months. Patients with diffuse pulmonary

disease often require initial treatment with an amphotericin preparation until clinical improvement is demonstrated, followed by long term treatment with oral fluconazole or itraconazole. Patients that remain immunocompromised may even require lifelong itraconazole therapy.

Limited evidence exists to recommend specific treatments for Mucorales or other less frequent fungal pneumonias in HM/HSCT patients. Early initiation of amphotericin-based therapy appears to improve outcomes in zygomycosis¹⁰⁴. In general, amphotericin preparations are accepted as the first line of therapy for these organisms, with posaconazole and isavuconazole used for salvage therapy^{105,106}. When feasible, surgical debridement should be considered, especially to avoid fatal hemoptysis in perihilar disease¹⁰⁶.

Host-directed therapies

Successful management of fungal pneumonia in HM/HSCT patients often depends on reversal of immunocompromising conditions. This includes withdrawal of immunosuppressive or cytotoxic medications, or ideally, reversal of host defects/control of the underlying disease.

A major research focus has been correction of granulocytopenia. Preparations of G-CSF and GM-CSF are commercially available, and can reduce the duration of neutropenia^{39,107}. While evidence suggests colony-stimulating factors prevent some pneumonias in neutropenic populations⁸⁴, they are not generally recommended as a treatment of established infections. Current data support administration of G-CSF if a patient's risk of developing febrile neutropenia is greater than 20%³⁹. Infusion of donor granulocytes has also been proposed as an adjunct therapy for patients with febrile neutropenia. While this strategy holds promise, it remains investigational¹⁰⁸. Beyond increasing leukocyte counts, others have investigated manipulation of existing leukocytes through administration of recombinant cytokines. Exogenous interferon-gamma has demonstrated some success in reducing infections in patients with congenital neutropenia, and recent studies suggest efficacy against opportunistic infections following HSCT^{109,110}.

Induction of antimicrobial responses directly from lung cells offers a novel alternative strategy to prevent, and possibly treat, pneumonias in HM/HSCT patients. Lung epithelial cells are relatively chemotherapy resistant and possess the capacity to detect pathogens, to modulate local immune responses and to generate microbicidal responses through the production of antimicrobial peptides and reactive species^{111–114}. Advances in the understanding of the molecular mechanisms of these responses have allowed development of inhaled therapeutics that induce protective innate immune responses from the lung epithelium. In animal models of pneumonia, this approach provides protection against lethal pathogens, even when there is concurrent neutropenia^{112,115}. One such treatment, known as PUL-042, demonstrates inducible protection against Gram-positive, Gram-negative, fungal and viral pneumonias in animal models and is now in clinical trials. Augmentation of innate immune responses offers several hypothetical advantages in terms of rapid effect and broad specificity, but efficacy has not been established in humans.

CONCLUSIONS

Fungal pneumonias cause substantial morbidity among HM/HSCT patients. A high index of suspicion for invasive fungal infection should be maintained in immunocompromised patients with non-specific symptoms and pursued with multiple diagnostic modalities, including CT, early bronchoscopy, and complementary tests. Early initiation and on-going monitoring of antifungal therapy are essential ensuring acceptable clinical outcomes.

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Key Points

- ◆ Fungal pneumonias cause significant morbidity and mortality in patients with hematologic malignancies (HM) and recipients of hematopoietic stem cell transplants (HSCT).
- ◆ Neutropenia, cytotoxic chemotherapy, graft-versus host disease, genetic polymorphisms and other immune derangements increase the risk of developing life-threatening fungal pneumonias.
- ◆ Chest imaging is often non-specific but may aid in diagnoses. Bronchoscopy with bronchoalveolar lavage is recommended in patients at high risk fungal pneumonia with new infiltrates on chest imaging, unexplained respiratory symptoms or persistent fever.
- ◆ Immunoassays for fungal cell wall components, such as galactomannan and (1,3)- β -D-glucan, may aid the early diagnosis of invasive fungal infections in HM/HSCT patients.
- ◆ Investigations into novel preventative strategies and host directed therapies are ongoing.

Figure 1. Performance Characteristics of Bronchoalveolar Lavage Galactomannan Assay for Diagnosis of Invasive Pulmonary Aspergillosis in HM/HSCT Patients

(A) Forest plots for sensitivity and specificity of BAL galactomannan EIA for probable or possible invasive pulmonary aspergillosis. Shown are estimated sensitivity and specificity (gray squares), 95% confidence intervals (gray lines) and combined sensitivity and specificity (red dashed lines). (B) Summary receiver operating characteristic (ROC) curves for the studies in A at an optical index cutoff of >0.5 (red), >1 (blue), and >2 (green) for

probable or possible invasive aspergillosis. Dashed lines, 95% confidence intervals; AUC, area under the curve.

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Table 1

Proven or Probable Invasive Fungal Infections in HM/HSCT Surveillance Studies

Study	Patients, Centers	IFI Incidence	IFI - Attributed Mortality
USA ³⁴ (1989–2008) Lewis 2013	1,213 HM autopsies (371 IFIs), single center	N/A	49%
Austria ¹² (1995–2005) Auburger 2008	1,095 HM/HSCT, single center	11.3%	35%
SEIFEM, Italy ¹¹⁶ (1999–2003) Pagano 2006	11,802 HM, 18 centers	4.6%	39%
SEIFEM B, Italy ¹¹⁷ (1999–2003) Pagano 2007	3228 HSCT, 11 centers	1.2% Auto, 7.8% Allo	65%
TRANSNET, USA ¹⁷ (2001–2005) Kontoyiannis 2010	16,200 HSCT, 23 centers	1.2% Auto, 5.8–8.1% Allo	35%
PATH Alliance, North America ¹¹⁸ (2004–2007) Neofytos 2009	250 HSCT with IFI, 16 centers	N/A	47%
Japan ⁵⁵ (2006–2008) Kurosawa 2012	2,821 HM (597 HSCT), 22 centers	0.8% Auto, 5.4% Allo	37%
SIMIFF, Italy ⁵⁷ (2009–2011) Montagna 2014	113 HM/HSCT, 119 non-HM with IFI, 23 centers	N/A	44%
CAESAR, China ¹¹⁹ (2011) Sun 2015	4,192 HM, 35 centers	2.5%	12%
Assessment of Antifungal Therapy in Hematological Disease, China ⁴¹ (2011) Sun 2015	1401 HSCT, 31 centers	4.0% Auto, 8.9% Allo	13%

HM, hematologic malignancy; HSCT, hematopoietic stem cell transplantation; N/A, not applicable; IFI, invasive fungal infections; Auto, autologous stem cell transplantation; Allo, allogeneic stem cell transplantation

Table 2

Incidence of Invasive Fungal Infections by Hematologic Diagnosis

	SEIFEM¹¹⁶ Pagano 2006	Japan⁵² Kurosawa 2012	CAESAR¹¹⁹ Sun 2015
Acute myeloid leukemia	12%	3%	4.4%
Acute lymphoblastic leukemia	6.5%	4%	2.4%
Acute hyperleukocytic leukemia	NR	NR	6.3%
Acute promyelocytic leukemia	NR	NR	0%
Myelodysplastic Syndrome	NR	2.5%	5.3%
Chronic myeloid leukemia	2.5%	NR	2.4%
Chronic lymphocytic leukemia	0.5%	NR	3.5%
Hodgkin lymphoma	0.7%	1.1%	0%
Non-Hodgkin lymphoma	1.6%	0.3%	1.5%
Multiple myeloma	0.5%	0.8%	0.1%
Other	NR	NR	4.8%
Cumulative	4.6% 538/11802	1.3% 38/2821	2.5% 103/4192

NR, not reported

Table 3

Selected Genetic Polymorphisms Associated with Altered Susceptibility to Invasive Aspergillosis in HM/ HSCT Patients

Allele of Interest	Association with <i>Aspergillus</i> infections
IL-10 promoter ⁵³	IL-10 1082(AA) genotype is associated with reduced IPA in HM
TNF receptor type 2 promoter ⁵⁴	Variable number tandem repeats associated with increased IPA in HM
TLR4 ⁵⁵	Donor TLR4 S4 haplotypes increased risk for IA in HSCT recipients
Dectin-1 ⁵⁶	Dectin-1 Y238X polymorphism associated with increased IA in HSCT
Plasminogen ¹²⁰	Homozygosity for D472N polymorphism associated with increased IA in HSCT

IL-10, Interleukin-10; IPA, invasive pulmonary aspergillosis; TNF, tumor necrosis factor; HM, hematologic malignancy; TLR4, Toll-like receptor 4; IA, invasive aspergillosis; HSCT, hematologic stem cell transplantation