Fungal infections in hematopoietic stem cell transplant recipients

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Fungal infections have historically been, and remain important causes of transplant-related morbidity in recipients of hematopoietic stem cell transplant (HSCT). However, there have been notable changes in the epidemiology and outcomes of invasive fungal infections, induced by changes in the transplant procedures as well as supportive care. This review discusses invasive fungal infections in hematopoietic stem cell transplant recipients, with a focus on the host and the two most common infections, candidiasis and those caused by moulds.

Keywords: Fungal infection, transplantation, hematopoietic stem cell transplantation

Introduction

Fungi are ubiquitous in the environment. Some fungi, such as Candida species, exist commensally in our bodies. Despite our daily, intimate interactions with these organisms, they do not usually cause disease; however, during the last several decades, a growing population of immunosuppressed people has led to a rise in invasive diseases caused by these opportunistic pathogens. Indeed, fungi currently are a leading cause of invasive bloodstream infection in hospitalized patients, a leading cause of infectious death in people with AIDS worldwide, and they are a leading cause of infection-related death in recipients of transplantation.

One population in which fungi have contributed to a substantial amount of morbidity and mortality has been in recipients of hematopoietic stem cell transplantation (HSCT). Transplantation of hematopoietic cells after receipt of high dose radiation and chemotherapy was first performed by Dr E. Donnell Thomas 50 years ago. This marked the beginning of an era, during which the procedure has been modified to treat numerous malignancies, inherited immunodeficiencies and other genetic and acquired illnesses (e.g., sickle cell anemia, autoimmune diseases); for the contribution, Dr Thomas shared the Nobel Prize in Medicine that was awarded for transplantation in 1990 [1].

This also marked the beginning of an era during which an increasing number of opportunistic pathogens were recognized as causes of difficult to treat human disease. Viral pathogens, most prominently Herpes viruses (cytomegalovirus, Herpes simplex virus, and Varicella Zoster Virus), and fungi (e.g., Candida species and moulds) became the most common causes of infection-related death after HSCT, triggering development of new preventative and therapeutic strategies. This review focuses on fungal infections that occur in recipients of HSCT; although it is recognized that multiple fungi cause disease in this setting, including Pneumocystis jiroveci, this review will focus on the more common infections caused by Candida species and moulds.

The host

An understanding of the host is an essential first step in clarifying the epidemiology, clinical manifestations, and management of fungal infections. As transplant modalities and preventative strategies have changed over the last several decades, the epidemiology of infections, and
outcomes have evolved. This section focuses on understanding the immune response to fungi, in the context of defects inherent to, or acquired after HSCT; this serves as a template to understand the changes in epidemiology and management of specific fungal infections, which are discussed in latter sections.

Host defenses to fungi: an overview

Fungi (yeasts or moulds) most frequently enter the body through breaches in skin (e.g., catheters) and mucosal membranes (e.g., gastrointestinal tract), and through sinopulmonary invasion. Numerous different mechanisms of innate and adaptive immunity serve to protect the healthy host from infection; antifungal defenses exist in a redundant, overlapping network, with primary protection occurring through mucosal immunity, phagocytic cells of the innate immune system, and through a well-coordinated adaptive cellular immune responses. The contributions of each, on a systematic level, are discussed briefly below.

Skin and mucosal membranes serve as a primary defense against fungi. Epithelial cells that line the both the gastrointestinal tract and airways can serve as primary defense, secreting antimicrobial effectors that have activity against both yeasts and moulds [2]. However, some fungi can invade epithelial cells, potentially as a way to obtain protection against host defenses [3]. Breaches in these physical barriers, introduced by catheters or chemical insults, such as that which occurs with cytotoxic therapies, allow these organisms to invade into the body.

A subsequent line of defense is provided by professional phagocytic cells lining the airways and gastrointestinal tract; resident macrophages both provide antifungal effector activity and serve to coordinate recruitment of other important innate immune cells such as polymorphonuclear cells (PMNs) and natural killer (NK) T cells by secretion of multiple cytokines and chemokines. A large amount of recent research has been focused on how these cells sense and kill fungal organisms. Multiple different pattern recognition receptors (PRR), both Toll like receptors and C-type lectins, recognize different components of fungal cell walls, functioning to coordinate killing and inflammatory responses. Since fungi can be both normal inhabitants of airways and GI tract, and potentially invasive pathogens, the mechanisms that coordinate inflammatory responses appear quite complex; results of most recent studies have emphasized that inflammatory responses of innate immune cells, specifically macrophages and dendritic cells, rely on differential receptor recognition of fungal components that are specific to different fungal cellular morphotypes (yeasts and hyphae). For instance, β-glucan that is exposed on the surface of Aspergillus hyphal cells (not dormant conidia) is recognized by the C-type lectin, dectin-1, initiating phagocytosis and production of inflammatory responses that serve to recruit other important effector cells such as PMNs [4–6]. Similarly, the t-helper phenotype of CD4+ T cells (Th1, Th2, Th17) appears largely influenced by the initial interaction of dendritic cells with fungal morphotype-specific cellular components [7–10]. Soluble factors, such as surfactant proteins, pentraxin 3, immunoglobulins, mannose binding lectin, and complement proteins also function to alter the interactions of fungal cells with phagocytes, shaping subsequent antifungal and inflammatory responses [11].

Other innate immune cells, namely, PMNs, monocytes and NK T cells all have important antifungal effector roles. The critical role of PMNs has been substantiated by the very high risk of invasive fungal infections (IFI) in patients who have severe and prolonged neutropenia. Upon migration through the bloodstream and tissues to the site of infection, neutrophils phagocytose and kill fungi, with production of reactive oxygen species and other molecules. However, neutrophils may also be dysfunctional despite relatively normal numbers; defective PMN killing has been well demonstrated in the setting of therapeutic modalities important in HSCT (e.g., corticosteroid therapy), and with multiple different underlying conditions that are common after HSCT, such as with diabetes and iron overload [12,13]. Monocytes circulating in the blood stream migrate into areas of infection, often as a result of chemotactic stimuli from other cells through PRR stimulation, as described above, with subsequent maturation into tissue macrophages. As is the case with PMNs (and discussed in more detail below), therapeutic modalities, such as treatment with corticosteroids, can produce a reversible monocyotosis, inhibit maturation of monocytes into macrophages, and impact macrophage function, impacting overall antifungal responses. Finally, a role for NK T cells in fungal immunity has been suggested in in vitro and animal studies, although specific cellular functions have yet to be well defined [14].

Both cellular and humoral acquired immunity is important for immunologic memory defense against yeasts and moulds. Immunoglobulins specific to fungal cellular components and secreted molecules have been described in many in vivo fungal infection models; our understanding of the role of ‘antifungal antibodies’ is being expanded, and is likely to be especially critical when considering potential therapeutic implications in
HSCT recipients. CD4+ T cells are also very important in acquired defenses against fungi. CD4+ T cells produce cytokines that stimulate phagocytes to kill fungi; direct antifungal effector activity of CD4+ T cells has also been observed, although specific mechanisms of killing remain elusive [15–17]. The CD4+ T cell inflammatory phenotype, largely driven by initial antigen presenting cell interactions with pathogen components, is currently classified as Th1, Th2, and Th17. Much of the literature focuses on the effective antifungal responses associated with Th1 phenotype and the dysregulated and ineffective responses associated with Th2 CD4+ T cells [18–22]. More recently, a role for CD4+ T cells that produce IL-17 has been suggested in defense against fungi [23].

**HSCT-induced immunosuppression and invasive fungal infections**

Underlying diseases leading to HSCT, and therapeutic modalities employed during HSCT- both early, during conditioning regimens, and later, during modulation of graft vs. host disease (GVHD), all impact the immunologic defenses to fungi described above. Obvious variables, such as receipt of high doses of cytotoxic agents and total body irradiation, cause prolonged neutropenia and breakdown of gastrointestinal (GI) tract mucosa to increase risks for IFI. GVHD, and its therapies, such as corticosteroids and immunosuppressive antibodies (e.g., alemtuzimab, infliximab) variably impact PMN, monocyte, and cellular antifungal defenses [24,25]. Also, specific cellular engraftment is dictated by the numbers, and types of stem cells infused; relative T cell depletion is a common practice that decreases symptomatic GVHD, but prolongs cellular engraftment, increasing risks for infection. Of particular interest are the results of recent studies suggesting that polymorphisms in ‘innate immunity’ genes such as in IL-10, TNF-α receptor, and Toll like receptors 1, 4, and 6 play a role in modulating risks for fungal infection after HSCT or receipt of chemotherapy [26–30]. Specific risks, and how these have evolved with changes in transplant modalities, are discussed in more depth below.

Table 1 lists host and therapeutic variables, and common post-HSCT complications that have been described to impact risks for the most common IFI. As many of the risks associated with candidiasis are clustered during the earlier post-HSCT period (e.g., GI tract mucositis), and other risks associated with aspergillosis tend to occur later after HSCT (e.g., GVHD), overall risks for IFI are frequently described as having a bimodal distribution (Fig. 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Candidiasis</th>
<th>Aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Iron overload</td>
<td>+</td>
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<tr>
<td>Receipt of high doses total body irradiation</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Peripheral blood or cord blood rather than bone marrow as stem cells</td>
<td>+</td>
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<tr>
<td>Donor HLA mismatch</td>
<td>+</td>
<td>+</td>
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<tr>
<td>GI tract mucositis</td>
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<tr>
<td>Receipt of antibacterial drugs</td>
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<tr>
<td>Colonization</td>
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<tr>
<td>Indwelling central venous catheter</td>
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<tr>
<td>Neutropenia and delayed engraftment</td>
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<tr>
<td>Lymphopenia and delayed engraftment</td>
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<tr>
<td>Graft vs. host disease</td>
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<tr>
<td>Corticosteroid therapy</td>
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<tr>
<td>Other immunosuppressant therapies (e.g., infliximab, campath)</td>
<td>+</td>
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<tr>
<td>CMV seropositivity and/or disease</td>
<td>+</td>
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<tr>
<td>Respiratory virus infection</td>
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<tr>
<td>Transplant environmental conditions (e.g., building construction, summer, lack of LAF)</td>
<td>+</td>
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Many studies have documented that the epidemiology of IFI has evolved, with the incidence of invasive candidiasis decreased, and the incidence of mould infections increased during the 1990s [31–36]. The most obvious explanation for this change is the widespread use of azole drugs as prophylaxis during the neutropenic period, which effectively decreased the incidence of *C. albicans* infections [37,38]. However, other changes in transplant modalities also impact the epidemiology of IFI. For instance, use of different sources of stem cells, specifically peripheral blood rather than bone marrow, increased use of human leukocyte antigen (HLA)-mismatched donors, and use of non-myeloablative rather than myeloablative conditioning regimens have increased the importance of the late risk period associated with severe and prolonged GVHD [31–36]. How alternative stem cell products and conditioning regimens influence the primary risk periods for IFI is shown in Fig. 1.

**Candida infections: clinical manifestations, management and outcomes**

*Candida* infections, especially those caused by *C. albicans*, were recognized as especially common during the early post-HSCT in the 1980s. During this period of time, before widespread introduction of...
fluconazole prophylaxis, the incidence of invasive candidiasis estimated 11%, with associated 39% mortality [39]. Azole prophylaxis has decreased the overall attack rate of invasive candidiasis, and changed the prominent organisms, such that infections caused by fluconazole-resistant \(C.\) glabrata, and less so, \(C.\) krusei, have become more common [40]. Most recently, the incidence of candidiasis has been reported to be especially low in recipients of allogeneic HSCT after non-ablative conditioning, likely associated with low degrees of neutropenia and GI tract toxicities [36].

Invasive candidiasis is described as either ‘acute’, with bloodstream infection, or ‘chronic’, which is used to describe hepatosplenic disease [41]. Pathophysiology of the two complications, management, and outcomes differ. Bloodstream infection, or candidemia typically originates from either the GI tract or through intravenous catheters. Patients are frequently febrile and may exhibit signs of sepsis; peripheral manifestations, such as chorioretinitis, skin lesions, or organ abscesses (e.g., liver, kidneys) can occur. Most recent surveillance studies have reported a low (<5%) incidence of candidemia in HSCT recipients, with a high representation of azole-resistant species, as mentioned above.

Drugs approved for therapy of candidemia include fluconazole, amphotericin B, voriconazole, and three new echinocandins (caspofungin, micafungin, and anidulafungin). Given the use of prophylactic azoles and species distribution, and concomitant administration of other nephrotoxic drugs, echinocandins are rapidly becoming a drug of choice for primary therapy. Given the incidence of unrecognized peripheral manifestations, therapy should be administered for at least two weeks after the last positive blood culture. Guidelines indicate that intravenous catheters should be removed in patients with candidemia [42]; while this is advised, in practice, removal of an indwelling catheter, especially those that are tunneled, becomes a difficult therapeutic maneuver in HSCT recipients, who are frequently thrombocytopenic and requiring of multiple intravascular medications.

Hepatosplenic candidiasis typically develops during periods of neutropenia and mucositis, when organisms colonizing the GI tract invade into the portal vasculature and disseminate to the liver and spleen. The infection usually becomes apparent only after neutrophil engraftment, with increased inflammation causing the classic presentation of fever, elevated liver enzymes,
and flank pain. Inflammation in hepatic lesions can be necrotic or granulomatous; organisms may, or may not be seen on gram stain. *Candida albicans* is considered to be the most common cause of disease, likely associated with its ability to undergo the yeast to hyphal transition for GI tract invasion; however, few large epidemiologic studies have been performed to evaluate hepatosplenic candidiasis, although one autopsy study documented a low incidence of infection after use of fluconazole prophylaxis, with a low number of cases caused byazole-resistant organisms [43].

Few studies have been performed to specifically evaluate treatment of hepatosplenic candidiasis; guidelines suggest that primary therapy involves amphotericin B, followed by azole antifungals [42]. In most recent years, echinocandins are being used, with success. Therapy should be prolonged, lasting months, and dependent on the clinical course and subsequent plans for immunosuppression. As inflammation is a prominent driver of symptoms and signs, patients frequently exhibit prolonged courses of fever, with increasing lesion size, before eventual slow improvement. During this period of time, perplexed clinicians often attempt courses of different antifungals and perform multiple ‘diagnostic’ biopsies; care should be taken to avoid unnecessary changes in therapies and procedures.

**Mould Infections: clinical manifestations, management and outcomes**

Mould infections, especially those caused by *Aspergillus fumigatus*, were recognized as occurring at greater incidence in allogeneic HSCT during the 1990s [31]. Incidence estimates range from approximately 5–12% in recipients of allogeneic HSCT after myeloablative therapies [31–37,44–47]. During this period of time, associated mortality of infection was reported to be as high as 80–90% [32,48–51]. More recent studies have shown that the incidence of invasive aspergillosis (IA) has likely stabilized; large surveillance studies have found that the incidence continues to range between 5 and 10%, however, center reported rates are highly variable, likely due to differences in diagnostic aggressiveness and different methods of patient long-term follow-up after HSCT [47].

Although *A. fumigatus* is the most common species to cause invasive disease, other species, including *A. terreus* and *A. flavus* cause disease; the former, with its relatively high resistance to amphotericin B, is often associated with particularly poor outcomes [52]. More recent studies have noted infection caused by other species that also exhibit high or variable anti-fungal susceptibilities *in vitro*; this includes *A. ustus* and *A. lentulus*, a newly discovered species that is morphologically similar to *A. fumigatus* and not routinely identified in clinical microbiology laboratories [53–56]. *Aspergillus fumigatus* has also been reported to acquire resistance toazole drugs *in vitro*, and possibly, *in vivo* [57,58]. Despite these reports, the true toll of antifungal resistance in *Aspergillus* species, with respect to microbial epidemiology and outcomes, is not clear.

Members of this genus usually cause disease after inhalation into the sinuses or lungs. Sinus invasion, and/or invasive pulmonary infection, with possible hematogenous dissemination to other organs (brain, skin) can occur (Fig. 2). The classical radiographic lesion is described as a nodular infiltrate, with, or without a ‘halo’ sign and progression to cavitation; however, the radiographic presentation of invasive aspergillosis can also include lobar infiltrates in a focal unilateral or bilateral distribution (Fig. 2). Small, but recent studies suggest that bronchopneumonia may occur more commonly in patients during the post-engraftment period in allogeneic HSCT recipients [59]. Tracheobronchitis, a manifestation that has been reported most frequently in lung transplant recipients, also occurs in HSCT recipients [60,61]. Finally, there are early reports that at least some component of disease, and radiographic abnormalities, may result from immune-reconstitution, and resultant inflammation, rather than actual fungal invasion, especially in patients who have or are recovering from neutropenia [62]. This is consistent with results of animal studies performed in the 1990s [63]. Our clinical experience also supports this observation, with presentation, and progression of *Aspergillus*-associated infiltrates that are more consistent with an inflammatory pneumonitis rather than florid fungal invasion [64].

Recognizing that radiographic abnormalities are neither sensitive nor specific, in a time when antifungal drugs have differential activity to different filamentous fungi, attention has been focused on improving diagnostic methods for pulmonary aspergillosis. This is particularly important given the difficulty in culturing *Aspergillus* species from either tissue biopsy or bronchoalveolar lavage (BAL) fluid. Studies have shown variable sensitivity of BAL culture, approximating 40–50% [65]. Results of studies support increased use of non-culture-based screening using blood and application of these assays to BAL fluid; specifically, the *Aspergillus* galactomannan enzyme immunoassay increases sensitivity of BAL beyond culture alone, and positive blood assays provide indication of infection prior to presentation of clinical signs and symptoms of disease [66,67]. Multiple other assays, reliant on
identification of other antigens (e.g., glucan) and nucleic acids, are also in development.

*Aspergillus* species, and other moulds, can also invade through a breach in the skin, and even through the gastrointestinal tract, particularly during periods of GI tract mucositis caused by drugs or GVHD. In this setting, organisms that are common inhabitants in food and other ingested products (e.g., medicines) have been documented to cause GI tract disease, either with focal invasion, or in association with dissemination to the liver.

Amphotericin B formulations were the ‘gold standard’ therapy for invasive aspergillosis in the 1990s. A randomized trial that compared voriconazole to amphotericin B suggested superiority with the azole [68]; since publication, voriconazole has been considered the ‘gold standard’ therapy of documented and suspected diseases. More recently, successful outcomes of treating invasive aspergillosis with liposomal amphotericin B suggest its applicability, although comparative outcomes are not available [69]. There are considerations that are particularly important in HSCT recipients. Organ function, specifically, the presence of liver disease that complicates azole therapy, and renal disease that complicates polyene therapy, should always be considered when choosing appropriate first line

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**Fig. 2** Radiographic and clinical manifestations of documented invasive aspergillosis in lungs (A and B), with nodular density and surrounding halo (B) and cavitating lesion (A). Multiple views of radiographic lesions in brain are shown in C and D.
agents. Also, administration of complicating drugs such as sirolimus is important in this setting, when management of GVHD is as important as treatment of infection.

The echinocandin, caspofungin, is also approved for ‘salvage’ therapy of invasive aspergillosis. Although this is an option in patients who cannot tolerate other medicines, few clinicians believe that echinocandin therapy should be considered first-line; reasons include lack of ‘cidal’ activity, increasing reports of breakthrough infections, and lack of large datasets to assess outcomes. More commonly, echinocandins are being explored as agents administered in combination with either voriconazole or polyenes; in this setting, in vitro data and small uncontrolled studies suggest potential utility [70,71]. Definitive conclusions regarding the efficacy (and safety) of such combinations await results of randomized trials.

Treatment duration is perhaps one of the most complicated decisions to make, as there is virtually no data to indicate appropriate courses, and few quantitative markers of active disease available for measurement. Most clinicians treat for at least 6 months time, with the course dependent on progression of resolution of radiographic lesions and amount of immunosuppression that the patient is receiving. It is important to note that radiographic abnormalities might not resolve completely, with some scarring not indicative of active disease.

Use of other therapeutic modalities accompanying antifungal therapy, such as surgical removal of pulmonary lesions, and immunomodulatory therapy, has attracted attention in case series, but definitive utility remains unknown. Immunosuppressive therapy should be decreased, whenever possible; however, this often represents a difficult situation managing GVHD. Administration of granulocyte infusions, interferon gamma, and even cellular immunotherapy are being explored as potential methods to enhance antifungal immunity [15,72].

Other moulds, such as Fusarium species, Scedosporium species, and Zygomycetes, have been increasing in frequency as a cause of invasive disease in HSCT recipients since the late 1990s [44,71,73,74]. Clinical manifestations can be very similar to infections caused by Aspergillus species, although organisms such as Fusarium species can propagate in vivo, resulting in frequent positive blood cultures and disseminated disease. Outcomes of these infections, as well as those caused by Scedosporium species, are particularly poor, although there may be improved experiences subsequent to the introduction of new antifungal drugs.

Infections caused by Zygomycetes have attracted particular attention during the last several years, with reports of increased infections occurring in patients who received voriconazole, either prophylactically or therapeutically [74–76]. This presents a particularly important emphasis on diagnostic aggressiveness, given differential susceptibilities to voriconazole and polycene antifungals. It is likely that there are multiple different reasons that Zygomycetes are recognized more frequently, including diagnostic bias and changes in underlying hosts. Specifically, patients with Zygomycetes infections typically have subtle differences in underlying diseases, with concomitant diabetes and/or iron overload [73,74]. In allogeneic HSCT recipients, these infections typically occur later, during GVHD, rather than during the pre-engraftment period.

Both voriconazole and posaconazole have been studied as prophylactic agents in allogeneic HSCT recipients, with large studies showing potential utility in preventing aspergillosis [77,78]. Only the future can tell how these agents will be employed, and how they will change microbial epidemiology and outcomes. Already, there are signs that advances in transplant modalities, advances in diagnostics, and new antifungal therapies are resulting in sequential improvement in outcomes of invasive aspergillosis [79]; a large retrospective study from one transplant center reported that the survival after a diagnosis of aspergillosis improved substantially since the early 1990s, with two sequential changes that occurred in the mid-1990s and early 2000s [33]. Multivariable analyses suggest that multiple therapeutic, host, and transplant variables were associated with these improved outcomes. One very important recent observation is that the outcomes of IA appear to be better in patients who have received non-myeloablative conditioning regimens rather than myeloablative regimens [36]. With this in mind, non-myeloablative therapies should also be considered, when feasible, in patients who have documented invasive aspergillosis prior to transplant conditioning [80].

Conclusions: the past, and the future

With availability of new antifungal drugs and diagnostic tests, we have already witnessed several changes in the epidemiology and outcomes of fungal infection in HSCT recipients. However, there are many preventative and therapeutic questions that remain unanswered.

Some of the more important questions surrounding IFI in this setting remain focused on how to improve outcomes. Trials evaluating the utility of combination antifungal therapies, and studies employing...
immunomodulatory strategies should yield a great deal of information. Recent observations of immune reconstitution syndromes emphasize that the pathogenesis of these diseases, especially those caused by moulds, remain ill-defined.

Although two large prophylaxis studies indicate that we may be able to successfully employ broad-spectrum antifungal therapies to decrease both yeast and mould infections, efforts to optimize preventative strategies should not stop here. Costs of these drugs, toxicities, and drug interactions continue to present problems with administration long-term after allogeneic HSCT, suggesting that more efforts are necessary to ‘target’ preventative therapies, and/or to develop novel methods to diagnose infection early or employ other options, such as vaccines. Sequential successes in preventing, and treating IFI-related mortality after HSCT will hopefully allow for survival during the prolonged periods of immunosuppression that are necessary to treat underling diseases, improving overall outcomes of HSCT.

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