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Fungal Infections in Transplant and Oncology Patients

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Introduction

Invasive fungal infections (IFIs) in oncology and transplant populations have been associated with significant morbidity and mortality. Research in this area remains in flux; as epidemiologic patterns shift, more is being learned about optimal treatment, as well as the unique risks that predispose these special populations to such potentially devastating infections. Here, we seek to highlight recent advances and important factors to consider when treating transplant and oncology patients with IFIs.

Epidemiology of Invasive Fungal Infections

Despite high associated morbidity and mortality, the epidemiology of IFIs in high risk populations has not previously been well defined. Incidence estimates have been primarily based on single-center, retrospective studies [1-3]. The Transplant Associated Infections Surveillance Program (TRANSNET), a network of 23 transplant centers in the United States (U.S.), prospectively studied the epidemiology of IFIs among solid organ and stem cell transplant populations over a five year period (March 2001 to March 2006) and provided the first true approximation of the burden of fungal disease among transplant populations in the U.S. Based on TRANSNET data, the overall incidence of IFIs in the hematopoietic stem cell transplant (HSCT) population was 3.4%, somewhat lower than previous estimates (D.P. Kontoyiannis, unpublished data, July 2009). In addition, invasive aspergillosis (IA) surpassed invasive candidiasis (IC) as the most common IFI encountered in the HSCT population: *Aspergillus* accounted for 43% of infections and *Candida* accounted for 28%, followed by

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other or unspecified moulds including *Fusarium* and *Scedosporium* (16%), and finally, Zygomycetes (8%). Pneumocystosis, endemic fungal infections, and cryptococcosis were rarely encountered in the HSCT population. Consistent with prior reports [4-7], mortality was high and one-year survival was low for HSCT patients with IFI. *Fusarium* infections and IA were associated with the lowest one year survival (6% and 25%, respectively); however, survival among patients with zygomycosis (28%) and IC (34%) was not substantially better.

Among solid organ transplant (SOT) recipients, *Candida* infections were significantly more common than *Aspergillus* infections. This held true for all solid organ groups except lung transplant recipients. In lung transplant recipients, *Aspergillus* was the most common fungal pathogen, and when coupled with other moulds, invasive mould infections were responsible for 70% of IFIs (P.G. Pappas, unpublished data, July 2009). This distribution has been shown in other studies of SOT recipients as well [8,9]. Less common overall but seen more frequently than in the HSCT population were infections due to *Cryptococcus* and endemic fungi, causing 8% and 5% of IFIs, respectively. Zygomycetes were responsible for 2% of infections (P.G. Pappas, unpublished data, July 2009). The mortality assocated with IFIs in the SOT population is high, but lower overall than in HSCT and oncology patients.

There are no recent, multicenter studies describing the incidence and clinical outcome of IFIs among the general oncology population and it is difficult to obtain an accurate estimate of the frequency of fungal infections in this population from the published literature as most reports do not provide sufficient information regarding the patients' underlying disease. In general, compared with patients with solid tumors, patients with hematologic malignancies are at increased risk for fungal disease and response to IFI treatment is lower [10]. A 1992 international autopsy survey of patients with cancer identified fungal infections in 25% of patients with leukemia, 12% with lymphoma, and 5% with solid tumors. Overall, *Candida* was the most common fungal pathogen, responsible for 58% of fungal infections, while 30% of fungal infections were caused by *Aspergillus* [11]. A more recent single center survey of autopsies performed on patients with hematologic malignancy confirmed the increased risk for IFI among patients with leukemia. Further, consistent with trends among transplant populations, the prevalence of IFI remained high and constant throughout the study period (1989-2003); although the rate of IC decreased, the prevalence of invasive mold infections increased [12].

Types of Invasive Fungal Infections

Aspergillus

Aspergillus fumigatus is the most frequent species of *Aspergillus* causing clinical disease, perhaps due to specific virulence factors unique to the organism [13]. However, other species, most commonly *A. flavus*, *A. terreus*, and *A. niger*, are also implicated in invasive infections in humans. *A. terreus* has been associated with amphotercin B resistance and a higher mortality [14] than other *Aspergillus* species although the data to support this claim was primarily gleaned from patients treated with amphotericin B as initial therapy and prior to use of triazoles as first-line treatment for IA [15].

In immunocompromised hosts, *Aspergillus* most commonly presents as invasive pulmonary aspergillosis, often with subsequent dissemination [16-18]. In lung transplant recipients, *Aspergillus* may also cause tracheobronchitis and bronchial anastomotic infection. Pulmonary infections can present with fever, hemoptysis, cough, dyspnea, drop in pulmonary function, pleuritic chest pain, respiratory failure, and altered mental status [19], however, and very importantly, the immunosuppressed patient may have few or only subtle clinical signs and symptoms present early in the course of infection. Further clouding the picture, the distinction between colonization and infection with *Aspergillus* can be difficult. For example,

Aspergillus can be recovered from the lower respiratory tract of many patients post lung transplant, but based on a review of the literature, progression from colonization to infection in lung-transplant recipients is rare [20]. In contrast, recovery of *Aspergillus* from lower respiratory tract specimens in patients with hematologic malignancy or undergoing HSCT has a high positive predictive value for invasive disease [21].

Candida

The overall decrease in *Candida* infections and the shift from *C. albicans* to non-*albicans Candida* as the most common infecting *Candida* species over the past two decades are notable. Data from Brazil collected between 1997 and 2003 documented that 79% of episodes of candidemia in patients with hematological malignancies and 52% in those with solid tumors were caused by non-*albicans Candida* ($P = 0.034$) [22]. Similarly, between 2001 and 2007 at MD Anderson Cancer Center, non-*albicans Candida* species were responsible for 75% of IC cases occurring in patients with hematologic malignancy or undergoing HSCT [23]. The routine use of azole prophylaxis in high risk cancer populations has certainly contributed to the decreased incidence of IC in these populations [24,25] and likely accounts in part for the increasing frequency of non-*albicans Candida* infections [23,26,27]. While *C. albicans* remains the most frequently isolated *Candida* species among SOT recipients, a shift towards more non-*albicans Candida* infections seems to be occurring in this population as well [28].

Infections due to *Candida* can manifest as candidemia, peritonitis, empyema, endopthalmitis, esophagitis, and urinary tract or anastomotic infections. In lung transplant recipients, *Candida* can also cause tracheobronchitis [29]. Presenting clinical signs may be fever, leukocytosis, and less commonly, hypothermia [30].

Hyaline Hyphomycetes

The “other” moulds responsible for IFIs in immunosuppressed patients are a heterogeneous group of organisms. Over thirty non-*Aspergillus* hyalohyphomycetes have been implicated in human disease including, species of *Acremonium*, *Fusarium*, *Paecilomyces*, and *Scedosporium* [31]. These organisms are typically opportunistic, causing invasive disease following environmental exposures. Several of the non-*Aspergillus* hyalohyphomycetes are unique in their capability to sporulate *in vivo* which permits recovery of the organisms from the bloodstream and dissemination to other organs, particularly skin [32].

Recently, a shift towards more non-*Aspergillus* mould infections has been noticed in SOT recipients. In a prospective multicenter study, 53 invasive mould infections were reported from liver and heart transplant recipients. Pathogens included *Aspergillus* species in 70%, non-*Aspergillus* hyalohyphomycetes in 9%, phaeohyphomycetes in 9%, Zygomycetes in 6%, and other or unidentified moulds in 6% of patients. Dissemination was significantly more likely with infection due to a non-*Aspergillus* mould compared with *Aspergillus* [17].

Zygomycetes

Zygomycetes cause devastating invasive disease in a variety of different hosts. In one review of 929 reported cases of zygomycosis, 36% were seen in patients with diabetes mellitus, 7% in SOT recipients, and 5% in bone marrow transplant recipients. Among the bone marrow transplant group, just over half (52%) had pulmonary zygomycosis with 16% having infection in the sinuses. Outcome from zygomycosis varied based on the underlying condition, site of infection, and use of antifungal therapy. For patients with underlying malignancy, overall mortality was 66% [33]. Other studies cite mortality rates up to 80% among those with hematologic malignancies [34]. Unfortunately, the incidence of zygomycosis appears to be increasing in oncology centers and in HSCT populations specifically, possibly related to the use of voriconazole prophylaxis [35-39].

Pneumocystis jiroveci

The risk of *Pneumocystis jiroveci* infection (previously *P. carinii*) in HSCT and SOT recipients can be as high as 5-15% without prophylaxis [40,41]. In the era of routine *P. jiroveci* prophylaxis, transplant recipients that develop infection typically do so after stopping their prophylactic regimen [42]. Similarly, patients with cancer that develop *Pneumocystis* infection typically do so in the absence of prophylaxis [43]. *Pneumocystis* has a worldwide distribution and the organism that infects humans has been recognized as unique and distinct from that infecting animals [44]; humans appear to acquire *Pneumocystis* only from other humans but active pneumonia does not seem to be required for transmission to occur. Serologic data indicate that most humans are infected with *Pneumocystis* within the first 2 to 4 years of life [45]. Immunocompromised patients develop disease as a consequence of re-infection with a new strain or possibly, from reactivation of latent infection. However, it is thought that most cases of *P. jiroveci* pneumonia develop following acquisition of a new stain shortly before clinical symptoms manifest [46].

Particular attention was given to *P. jiroveci* infection in SOT recipients in the 1980's given to high rates of infection in heart-lung transplant recipients [47,48]. However, in the era of routine prophylaxis for at least 6 months following the transplant procedure in all solid organ groups [41], *Pneumocystis* infections in the SOT population are rare. In one retrospective review of 32,757 kidney recipients transplanted between 2000-2004, the cumulative incidence was 0.4%. Patients receiving sirolimus as part of their immunosuppressive regimen had an increased risk of developing *P. jiroveci* pneumonia which was associated with increased risk of both graft loss and death [49]. The underlying mechanism by which sirolimus predisposes to *P. jiroveci* infection is as yet undefined; however, it may ultimately be linked with sirolimus' ability to cause interstitial pneumonia, a known side effect of the drug.

Cryptococcus

Cryptococcus neoformans and *Cryptococcus gatti* [50] represent the main pathogenic species in the genus *Cryptococcus* [51]. While cryptococcosis has been most commonly encountered in the HIV infected population [52], a multicenter study reporting 306 cases of cryptococcosis in non-HIV-infected patients found 0.7% of total cases occurred in HSCT recipients, 18% in SOT recipients, 9% in patients with hematologic malignancies, and 9% in patients with other malignancies [53]. Other U.S. studies have found similarly low rates of cryptococcal infection in the HSCT population [1,5,54], most likely owing to use of routine fluconazole prophylaxis following HSCT. The overall mortality for cryptococcosis in the non-HIV population was 30%, attributable mortality 12%, and hematologic malignancy as an underlying diagnosis was associated with decreased survival [53].

Cryptococcus infection most commonly involves the lungs and central nervous system, but cutaneous infection and disseminated disease also occur. In one study, heart transplant patients were more likely than other solid organ groups to develop cryptococcosis, but kidney transplant recipients were most likely to have disseminated disease. This study also showed that serum cryptococcal antigen was not always helpful in identifying isolated pulmonary *Cryptococcus* infection; 82% of patients with cryptococcal pneumonia had a negative serum cryptococcal antigen [55].

Endemic fungi

Endemic fungi, including *Histoplasma capsulatum, Blastomyces dermatitidis*, and *Coccidioides immitus*, are present in the soil in certain geographic regions and inhalation of conidia leads to systemic infection [56]. Disease may manifest after primary exposure or through reactivation of a latent focus when there is a decrease in cell-mediated immunity.

Pulmonary involvement is common but clinical symptoms are non-specific and may be subacute in onset.

Although endemic mycoses are rarely encountered in cancer and transplant populations, immunosuppression (defined as hematologic malignancy or treatment with immunosuppressive medications) has been identified as a risk for developing histoplasmosis. Further, among immunosuppressed patients with histoplasmosis, 74% had fatal or disseminated infections compared with 7% of patients who were not immunosuppressed [57]. Histoplasmosis is the most frequent endemic mycosis reported in the SOT population [58,59] and it has been transmitted to SOT recipients via the transplanted allograft [60]. Information regarding *B. dermatitidis* in transplant populations remains limited to individual case reports and small case series [61]. The largest series included 11 cases in SOT recipients; infection occurred a median of 26 months post SOT and rejection did not precede any case [62]. *B. dermatitidis* pneumonia was frequently complicated by acute respiratory distress syndrome and accordingly, high mortality (67%) [63]. Even in endemic regions, *C. immitus* infection is rarely encountered in the HSCT population [64] and most descriptions are in SOT recipients [65]. Unfortunately, as with the other endemic mycoses in the immunosuppressed population, dissemination is common, mortality is high (up to 72%), and infection can be transmitted via donated organs [66].

Timing of Invasive Fungal Infections

IFI Timeline: HSCT

Time to development of IFI after transplantation varies according to type of fungal infection, type of transplant, and the use/duration of antifungal prophylaxis. Per Figure 1, the timeline for IFIs following HSCT is typically broken into 3 periods, early onset (≤40 days post HSCT), late onset (41-180 days post HSCT), and very late onset (>180 days post HSCT). In the TRANSNET cohort, 66% of *Candida* infections among autologous HSCT recipients occurred within the first 30 days (D.P. Kontoyiannis MD, unpublished data, July 2009). Similarly, in a single center study of 655 allogenic HSCT recipients transplanted between 1994 and 1997 and receiving routine fluconazole prophylaxis, the median time to development of candidemia was day 28 post transplant [25]. A recent, multicenter report of IFIs occurring between 2004 and 2007 reported the median timing of IC after HSCT to be 77days; IC tended to occur earlier after autologous HSCT (median 28 days) compared with allogeneic HSCT (median 108 days) [67]. In general, early onset IC following HSCT is influenced by the presence of neutropenia and mucosal injury (mucositis) while later onset is more often seen in allogeneic HSCT recipients owing to the development of graft versus host disease (GVHD) and the need for chronic central venous catheters.

Aspergillus and other mould infections tend to occur later after HSCT. In a single center study of allogeneic HSCT recipients transplanted between 1993 and 1998, 30% of IA diagnoses (N=187) were early, 53% late, and 17% very late onset following the procedure [68]. In the more recent TRANSNET cohort, 50% of IA cases among autologous HSCT recipients were early onset and 24% occurred >120 days post while 22% of cases among allogeneic HSCT recipients were early onset and 47% occurred more than 120 days after transplant (D. P. Kontoyiannis, MD, unpublished data, July 2009). In general, IA occurs more frequently and is encountered later after allogeneic HSCT compared with autologous HSCT. Late IA has been associated with a higher mortality, possibly because of increased fungal burden accompanying a delay in diagnosis as well as the cumulative burden of immunosuppression in patients with chronic/refractory GVHD [69].

The timing of non-*Aspergillus* mould infections such as Zygomycetes, *Fusarium*, and *Scedosporium*, appears to be organism-specific. One large study of over 5500 HSCT recipients

showed that the majority (56%) of Zygomycete infections occurred greater than 90 days after transplant and GVHD was associated with Zygomycete infection. On the other hand, *Scedosporium* infections were more likely to occur within the first 30 days post-transplant [5]. Similarly, nearly half (46%) of patients with fusariosis were neutropenic at the time of diagnosis and the median time from transplant to diagnosis was 64 days [6].

IFI Timeline: SOT

The timeline for infections following SOT has traditionally been divided into three phases: the first month, months 2 through 6, and more than 6 months after the transplant procedure [70]. Recent data regarding the epidemiology of IFIs following SOT suggest the timing of fungal infections may no longer fall succinctly into these risk windows.

Historically, infections due to *Candida* occurred early post SOT, typically during the transplant hospitalization [9,71]. However, TRANSNET data showed a somewhat later time to onset, with median time to diagnosis of IC of 103 days (P.G. Pappas MD, unpublished data, July 2009). In addition, a recent Australian study of candidemia in SOT recipients found that 54% of infections developed greater than 6 months after transplant, the majority of these in renal transplant recipients. Notably, nearly all these patients were hospitalized at the time of diagnosis due to complications from various bacterial infections and had been receiving broad-spectrum antibiotics [72].

Most *Aspergillus* infections historically occurred within the first year following SOT [20,73, 74]. Tracheobronchial and/or anastomotic *Aspergillus* infections typically occurred within the first 90 days post transplant compared with invasive pulmonary aspergillosis which tended to occur later [73,74]. The majority of experts agree that the risk for IA is substantially high enough immediately following lung transplant to warrant antifungal prophylaxis and American Society of Transplantation guidelines recommend continuing prophylaxis following lung transplantation at least until bronchial anastomosis remodeling is complete [75]. A 2006 international survey of lung transplant centers revealed that 69% (30/43) used universal antifungal prophylaxis during the immediate post transplant period as the anastomosis was healing, most commonly an aerosolized formulation of amphotericin B alone or in combination with itraconazole. The median duration of prophylaxis with aerosolized amphotericin B and itraconazole was 30 and 90 days, respectively [76]. In the current era of routine prophylaxis in high risk organ transplant recipients, nearly one-half of *Aspergillus* infections in SOT recipients are late-occurring (>90 days after SOT) and, as in the HSCT population, late onset IA has been associated with a higher mortality compared with early onset infection [77].

Cryptococcus and the endemic mycoses tend to occur even later in the post-transplant period [70]. In one study of SOT recipients with cryptococcosis, the median time to diagnosis in lung, heart, and kidney transplant recipients was 210, 450, and 630 days, respectively [55]. In the TRANSNET cohort, median time to diagnosis of cryptococcosis was 575 days. Similarly, the median time to diagnosis of the endemic mycoses was 343 days (P.G. Pappas MD, unpublished data, July 2009) and *P. jiroveci* infections are most often seen after routine prophylaxis is stopped, typically more than 180 days after transplant [70,78] [49].

Risk Factors Developing Invasive Fungal Infections

Unique Risks for IFIs in HSCT Recipients

Many factors impact a patient's individual risk for fungal disease, including those associated with the host, the transplanted graft, and complications of the procedure. The influence of each factor fluctuates throughout the post transplant course, creating a dynamic timeline. Host (e.g., older age) and transplant variables (e.g., human leukocyte antigen mis-match) tend to influence IFI risk early while complications of the transplant procedure (e.g., GVHD and

cytomegalovirus [CMV] disease) tend to predominate later [1,2,5,68]. Certain biological factors such as malnutrition, iron overload, diabetes mellitus, and cytopenias are influential throughout the post transplant course [79]. Risk factors specific to early onset IA have been identified as aplastic anemia, myelodysplastic syndrome, cord-blood transplantation, delayed neutrophil engraftment, and CMV disease. Risks for late onset IA were multiple myeloma, neutropenia, GVHD, and CMV disease [68]. Iron overload has been demonstrated to be a risk factor for severe bacterial infections in autologous HSCT recipients [80] and associated with IA and Zygomycete infections as well [81]. Diabetes mellitus, voriconazole prophylaxis, and malnutrition have also been identified as risks for zygomycosis [39].

Clearly, only a subset of at risk patients will actually develop IFI. This has lead to a growing interest in host genetic differences that may contribute to the individual's risk of developing IFI. Recently, studies in HSCT populations have shown that polymorphisms in Toll-like receptor 4 [82] and genetic variations within the plasminogen allele may influence susceptibility to IA after transplant [83]. More research into host genetic influence on the risk of fungal disease following transplant is needed.

Unique Risks for IFIs in Oncology Patients

In patients with acute leukemia, the risk for IC in published reports varies considerably. Undoubtedly, this is related to the status of leukemia (newly diagnosed, post-remission, relapsed, or refractory to treatment), duration of neutropenia, and the types of anti-neoplastic agents used. Based on a study of cancer patients with candidemia from Brazil between 1997 and 2003, in comparison with patients with solid tumors, neutropenia and corticosteroid use were more frequent in the hematologic malignancy group. Only 22% of patients with solid tumors were neutropenic before candidemia. The presence of ileus and the use of anaerobicides were independent risk factors for candidemia in patients with solid cancers. Further, compared with candidemic patients without cancer, central venous catheters and gastrointestinal surgery were independently associated with candidemia in patients with solid tumor [22].

Unique Risks for IFIs in SOT recipients

Unquestionably, rejection and exogenous immunosuppressive agents, particularly high-dose steroids and antilymphocyte antibody treatment, lead to increased risk for IFIs in the SOT population [84]. However, within organ transplant groups, the risk for IFI is strongly influenced by medical and surgical factors including technical complexity. For example, prolonged operative time requiring multiple blood transfusions, reperfusion organ injury during transplantation, and/or multiple simultaneous organ transplants have all been associated with the development of fungal infections [85]. One study associated prolonged ischemia time with the development of IA in lung transplant recipients [86]. Liver transplant recipients have been shown to be at higher risk for IFIs if there is fulminant hepatic failure, a need to undergo re-transplantation, or renal failure. Unique risks for renal transplant recipients include diabetes mellitus or need for prolonged hemodiaylsis prior to transplant [87]. Factors predisposing to IFI, primarily IC, in pancreas transplant recipients include older donor age, enteric (versus bladder) drainage, pancreas after kidney transplant (vsersus pancreas alone), the development of post transplant pancreatitis, retransplantation, and preoperative peritoneal dialysis [88].

Infection with certain viruses following SOT has also been associated with the development of IFIs. The most frequently implicated virus is CMV. In a prospective study of liver transplant recipients, 36% of patients with CMV disease developed IFIs within the first year post transplant compared with 8% of those without CMV disease [89]. Further supporting the association is that CMV prophylaxis appears to result in fewer IFIs.

Management

Management of IFIs involves several components and is pathogen-specific. Pharmacologic treatment requires consideration of first and second line therapies, potential drug interactions, and the value of combination therapies. The role of immunomodulation, reversal of neutropenia, and surgery also needs to be considered.

Aspergillus

Treatment of IA has evolved over the past decade, but few randomized controlled trials comparing various agents exist. The therapy of choice had historically been amphotercin B deoxycholate, its administration complicated by infusion reactions and renal dysfunction [90]. A randomized controlled trial documented superiority and decreased toxicity of voriconazole over amphotericin B deoxycholate. This landmark study also noted a 12 week survival advantage for patients treated with voriconazole [91]. As a result, voriconazole is now considered the drug of choice for IA [92].

Complications of voriconazole therapy, as with other azoles, are mainly due to its drug interactions which are particularly pertinent in transplant populations. Importantly, concomitant administration of cyclosporine, tacrolimus, or sirolimus with any azole requires pre-emptive dose adjustments of the immunosuppressants and subsequent close monitoring [93]. Voriconazole is metabolized through the cytochrome p450 system and polymorphisms in the CYP2C19 gene can result in widely variable rates of drug metabolism [94]. In addition, response appears to be lower among patients with IA and low mean voriconazole plasma levels (<0.25 μg/ml). Because of these issues, voriconazole levels should be monitored during therapy [95].

The appropriate choice for therapy in the setting of voriconazole intolerance or failure is a subject of debate. Current Infectious Diseases Society of America (IDSA) guidelines for treatment of IA include echinocandins (caspofungin and micafungin) as an option for salvage therapy, along with lipid formulations of amphotericin B, itraconazole, and posaconazole [92]. Posaconazole, another triazole with activity against moulds, is available in oral formulation only and demonstrates moderate variability in absorption. In a salvage study for IA in patients previously treated with amphotericin products, favorable response was observed in 42% [96] and among SOT recipients specifically, 58% had successful outcomes on treatment. As with voriconazole, drug interactions can be frequently seen with posaconazole, absorption is variable, and therapeutic drug level monitoring is encouraged. Treatment-related adverse events included nausea, vomiting, and elevated liver function tests (the latter occurring in <3% of patients) [97]. Visual disturbances and certain rashes experienced with voriconazole are not seen with posaconazole treatment. Thus, in some patients intolerant to voriconazole, posaconazole is an acceptable alternative. However, whether failure to respond to voriconazole should prompt the switch to a different antifungal class is a different issue. Research has shown that mutations in the *Aspergillus cyp51A* gene produces clinically significant resistance to the triazoles and different mutations confer unique patterns of azole activity [98]. For example, some mutations lead to high minimal inhibitory concentrations (MICs) for both itraconazole and posaconazole, but not voriconazole and ravuconazole, while others result in high MICs for all 4 drugs [99]. Thus, in cases of voriconazole failure, susceptibility testing is recommended before switching to another triazole.

Echinocandins, which act by inhibiting the synthesis of beta-D-glucan in the cell wall, are generally very well tolerated and offer an appealing option for treatment if intolerance to or failure of voriconazole develops. Caspofungin was studied alone or in combination in 90 patients with IA refractory to or intolerant of other licensed therapy. Favorable response was achieved in 45% and only two patients discontinued drug owing to adverse events [100].

Micafungin, in contrast to caspofungin, does not have a formal indication as salvage treatment for IA, but it has been studied for this use. In an open-label, multi-center study of micafungin in the treatment of IA, an overall favorable response rate of 36% was reported [101]. The main drawback to echinocandin therapy is the relatively narrow spectrum of activity and lack of an oral preparation.

Clearly, there is a need for better outcomes in IA. While it appears that combination antifungal therapy as primary therapy for IA may confer some benefit, this has not yet been rigorously tested in a controlled trial and the decision regarding what combination to use is based primarily on *in vitro* data, retrospective cohort outcomes, and animal data [102]. Only one, small, prospective randomized trial of combination anti-*Aspergillus* therapy has been published to date. This study included only 30 patients with hematologic malignancy and IA. Patients were randomized to caspofungin plus liposomal amphotericin B (3 mg/kg/day) versus monotherapy with high dose liposomal amphotericin B (10 mg/kg/day). The combination therapy group had a 66% (10/15) favorable response which was statistically superior to the 27% (4/15) clinical response in the monotherapy group. However 12 week survival was not statistically different and there was significantly more nephrotoxicity in patients treated with the high dose monotherapy. Thus, it is unclear whether the superiority of combination therapy was due to the lower dose of liposomal amphotericin B or the addition of caspofungin [103]. Another study compared 40 SOT recipients with IA who received caspofungin plus voriconazole as primary therapy to a historical cohort of 47 SOTs treated with a lipid formulation of amphotericin B. Survival at 90 days, the primary endpoint, was not significantly different between the two groups [104].

A phase III prospective, randomized, double blind trial comparing voriconazole monotherapy with combination voriconazole plus anidulafungin as primary therapy for IA is currently enrolling and should help definitively conclude the efficacy of azole-echinocandin combination therapy for this disease. Until such data is available, combination therapy should be reserved for patients in whom voriconazole monotherapy has failed or is contraindicated and for high-risk patients with unusual or resistant isolates.

Candida

Several randomized control trials comparing various antifungals have been performed over the years and are summarized in Table 1. In 2009, the IDSA revised it's guidelines on the treatment of *Candida* infections, reflecting new data on the use of echinocandins and the increasing prevalence of non-albicans *Candida* species. For non-neutropenic adults with candidemia, fluconazole or an echinocandin is recommended as initial therapy. For candidemia in neutropenic patients, initial therapy with a lipid formulation of amphotericin B or an echinocandin is recommended, unless the patient has had limited prior azole exposure, in which case initial therapy with fluconazole is appropriate. Once the infecting pathogen has been identified, treatment can be further tailored. For *C. glabrata*, treatment with an echinocandin is recommended unless the isolate has been confirmed susceptible to fluconazole or voriconazole, in which case, transition to either drug is appropriate. For *C. krusei*, which is intrinsically resistant to fluconazole, therapy with a lipid formulation of amphotericin B, voriconazole, or an echinocandin is recommended [105].

Zygomycetes

Treatment of invasive zygomycosis has evolved to some extent; perhaps most importantly, lipid formulations of amphotericin B have replaced amphotericin B deoxycholate as the cornerstone of primary therapy [106]. Further, prompt initiation of amphotericin B-based therapy (i.e., initiating treatment within 6 days of diagnosis) has been shown to significantly improve outcome [107]. Although it cannot be recommended as primary therapy for

zygomycosis on the basis of available data, posaconazole has been increasingly studied as a therapeutic alternative. In one retrospective review of patients who had intolerance to or progression of infection on an amphotericin B-based regimen, 66% had a complete or partial response to posaconazole [108]. Importantly, the Zygomycetes include many pathogenic moulds and the minimal inhibitory concentration of posaconazole varies considerably between these organisms [109].

Most recently, echinocandins have been shown *in vitro* to exhibit immunomodulatory activity as well as synergistic activity in combination with amphotericin B against the Zygomycetes [110,111]. Clinical data supporting the addition of an echinocandin to an amphotericin B based regimen is limited to a retrospective review of 34 diabetic patients with rhino-orbital-cerebral zygomycosis [112]. Treatment was successful for all evaluable patients (n=6) who received amphotericin B-caspofungin combination therapy compared with 41% (14/34) in patients treated with amphotericin B monotherapy (p=0.19). Whether the addition of an echinocandin offers a significant advantage to the patient awaits further clinical study.

Other Moulds

Although correlation between *in vitro* antifungal susceptibility testing of moulds and clinical outcomes is limited, information regarding intrinsic patterns of resistance for the various non-*Asperigllus* hyalohyphomycetes has emerged [31]. Unfortunately, many of these moulds are intrinsically resistant to available antifungal agents. Susceptibility to amphotericin B and triazoles is variable for *Fusarium* and the echinocandins offer no activity against this pathogen. Currently, most experts consider voriconazole as first line therapy for *Fusarium* [93]. Species of *Scedosporium* are considered intrinsically resistant to polyene antifungals and as with *Fusarium*, third generation triazoles are considered first line therapy for *S. apiospermum* [113], however, *S. prolificans* is intrinsically resistant to all antifungal agents. Data to support the use of combination antifungal therapy for the management of the hyalohyphomycoses are currently limited to those obtained *in vitro* and case reports.

Pneumocystis jiroveci

Trimethoprim-sulfamethoxazole (TMP/SMX) remains the treatment of choice for *P. jiroveci* pneumonia. Oral administration is appropriate for those able to take medication by mouth, given good bioavailability of the TMP/SMX. One of the most problematic side effects of TMP/SMX in the transplant population is cytopenia; all cell lines can be affected and patients must be monitored for this side effect. Duration of therapy for PCP is generally accepted to be 14-21 days. Although data have shown that adding prednisone to the treatment regimen accelerates clinical improvement and improves survival in HIV-infected patients with moderate or severe *P. jiroveci* infection, no randomized data are available in cancer or transplant patients to support this practice. With that said, assuming the patient was not already on corticosteroids at the time symptomatic infection developed, most clinicians presume efficacy based on data from the HIV literature and would consider adding corticosteroids in transplant and other non-HIV patients with severe disease. If allergic to or intolerant of TMP/SMX, atovaquone, dapsone, or pentamidine have been used as alternative agents [114].

Cryptococcosis

Treatment recommendations for cryptococcal disease in the transplant population are based, in large part, on data extrapolated from clinical trials in other hosts and expert opinion. Current IDSA guidelines recommend amphotericin B plus flucytosine for 2 weeks, followed by fluconazole orally at 400-800 mg for up to 10 weeks, followed by a decreased dose of fluconazole (200 mg) for 6-12 months [115] for CNS or other severe disease. There is some data to suggest that in SOT recipients with isolated pulmonary cryptococcosis, prolonged

treatment with oral fluconazole is sufficient and induction therapy with amphotericin B may not be necessary [116].

Several management issues unique to the transplant population need to be considered. Owing to concomitant use of calcineurin inhibitors, lipid formulations of amphotericin B are preferred. In addition, flucytosine levels need to be monitored closely to avoid toxicity and side effects [117]. A gradual decrease in corticosteroids is another common management strategy; however, development of immune reconstitution syndrome (IRIS) in this setting has been seen and may be difficult to distinguish from manifestations of the cryptococcal infection itself.

Other management strategies

Reducing immunosuppression requires a delicate balance between improving outcome from infection versus inducing rejection of the graft or an accelerated inflammatory reaction. As noted, rapid reduction of immunosuppressive therapy in conjunction with initiation of antifungal therapy in SOT recipients may lead to the development of IRIS, the clinical manifestations of which mimic worsening disease [118]. Reversal of neutropenia is another oft-used strategy in managing IFIs. The updated 2008 IDSA guidelines for treatment of IA include considering the use of a granulocyte-macrophage colony stimulating factor in those with prolonged neutropenia [92]. Granulocyte infusions may also be used as a bridge to recovery from neutropenia but data to support this practice is scant. In one study of neutropenic patients with hematologic malignancies and IFI refractory to treatment with amphotericin B, 15 patients received granulocyte transfusions from related donors and 8 of the 15 had favorable outcomes [119].

Surgery

The role of surgery in the treatment of IFIs can be paramount, but its utility depends on the type of IFI present. The IDSA recommends that surgery be considered in patients with IA who have a solitary lung lesion prior to chemotherapy or HSCT, those with hemoptysis from a lung lesion, disease that invades the chest wall, or situations in which the infection involves the pericardium or great vessels [92]. For zygomycosis in particular, treatment often requires surgical intervention in addition to pharmacologic therapy [120]. In one review of 86 cases of pulmonary zygomycosis reported in the literature, mortality was higher (55%) in those not receiving adjuvant sugery compared with those who did (27%) [121]. Finally, for infections with highly resistant fungi, particularly for localized infection, surgical debridement and debulking should be considered.

Conclusion

Clearly, recent shifts in the epidemiology of IFIs among transplant and oncology populations has brought with it new recommendations on treatment; however, it has brought with it new controversies as well. New pharmacologic therapies are being studied, both alone and in combination, and guidelines for management of several IFIs have been changed accordingly. More information is being discovered about unique genetic factors that put some transplant recipients at greater risk for fungal infection than others. The role of immunomodulation continues to be investigated; as always, the delicate balance of maintaining some immune integrity while assuring protection of the graft remains critical. Despite advances in the field, further studies are needed. For transplant and oncology patients, the diagnosis and management of IFIs remains a challenge and improving outcomes depends on continued progress in all of these arenas.

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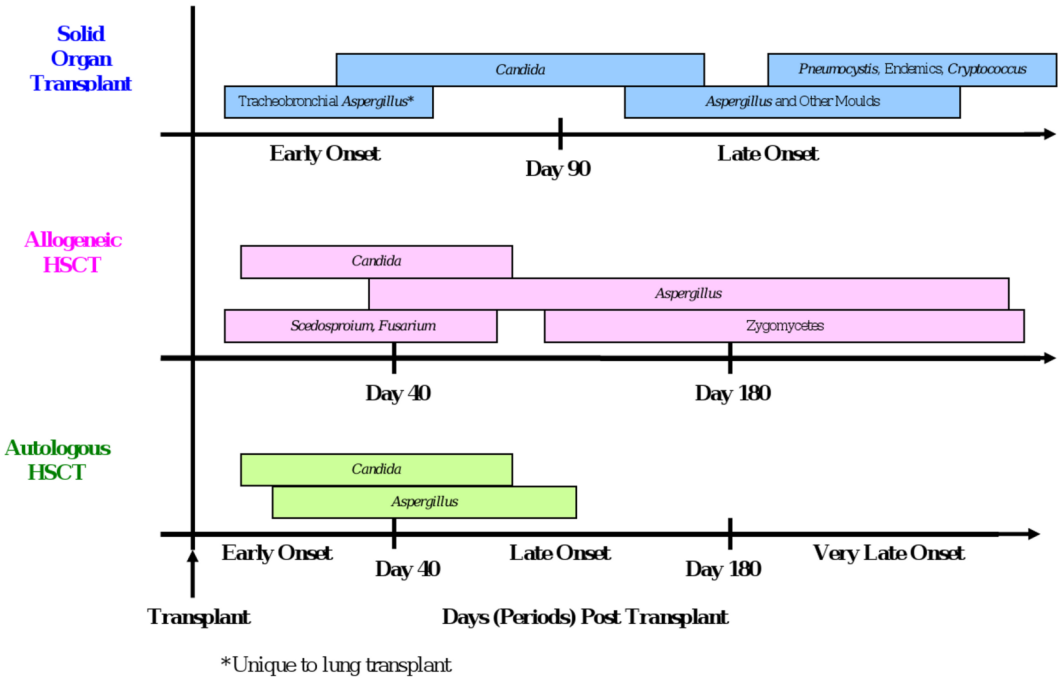

Figure 1. Timing of invasive fungal infections based on transplant type

Table 1

Major prospective randomized controlled trials of invasive candidiasis

Author, Year	Comparators	Number Enrolled*	Proportion Candidemic (%)	*C. albicans* Infections (%)	End of Therapy Success (%)	Significance (P value)	Comments
Rex 1994 [122]	Fluconazole	113	100	70	72	0.17	Non-neutropenic population; Less toxicity with fluconazole.
	Amphotericin B	111	100	63	80		
Rex 2003[123]	Fluconazole plus Placebo	107	100	68	56	0.043	Higher APACHE II scores in fluconazole arm; Mortality not improved with combination; Higher nephrotoxicity with combination.
	Fluconazole plus Amphotericin B	112	100	68	69		
Kullberg 2005[124]	Voriconazole	248	100	43	70	0.42	Non-blinded, non-neutropenic population; More renal toxicity & SAEs with AmB.
	Amphotericin B followed by Fluconazole	122	100	51	74		
Mora-Duarte 2002[125]	Caspofungin	109	83	36	73	0.09	No difference in mortality; More drug related adverse events with AmB.
	Amphotericin B	115	79	54	62		
Kuse 2007[126]	Micafungin	264	83	39	74	NS	12% of study population neutropenic
	LAMB	267	84	43	70		
Reboli 2007[127]	Anidulafungin	127	91	64	76	NS	3% of study population neutropenic; Microbiologic response higher with anidulafungin.
	Fluconazole	118	87	59	60		
Pappas 2007[128]	Caspofungin	188	86	44	72	NS	9% of study population neutropenic
	Micafungin 100mg	191	85	48	76		
	Micafungin 150 mg	199	84	51	71		

NS, not significant; LAMB, liposomal amphotericin B; AmB, amphotericin B; SAEs, serious adverse events

*Modified intent to treat population