THE 2014 INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION GUIDELINES
FOR THE MANAGEMENT OF FUNGAL INFECTIONS IN MECHANICAL CIRCULATORY SUPPORT
AND CARDIOTHORACIC ORGAN TRANSPLANT RECIPIENTS: EXECUTIVE SUMMARY

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Introduction:

The field of cardiothoracic transplantation (CT) has evolved significantly, but infections remain an important cause of morbidity and mortality, particularly fungal infections (FIs). The higher mortality associated with FIs has prompted the institution of center-specific antifungal prophylactic strategies (2-6). In the absence of existing clinical trials, the Infectious Diseases Council of the International Society for Heart and Lung Transplantation (ISHLT) has committed to convening an international and multidisciplinary panel of experts in the field. The Panel members are recognized leaders in the field of heart/lung transplantation and mechanical circulatory support (MCS) devices and were selected from established transplant centers worldwide by the Chairs. The Panel members approved the most relevant questions to be addressed in the areas of epidemiology, diagnosis, prophylaxis, and treatment of FIs, including therapeutic drug monitoring (TDM) of antifungal agents in adult and pediatric heart, lung, and MCS device patients. The Panel was subsequently divided into working groups, headed by the Chairs, for epidemiology, diagnosis, prophylaxis, treatment, TDM, and pediatrics. A comprehensive literature search was performed by the Chairs of the Panel and was disseminated to the working groups. The working groups reviewed the existing literature to answer the identified questions based upon the published evidence or, in the absence of evidence, to provide guidance based upon prevailing expert knowledge and experience. Each group reviewed, evaluated, and summarized the relevant evidence and then presented its findings at a workshop held at the annual ISHLT meeting in Montreal on April 23, 2013. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to appraise the evidence (7). Disagreements were resolved by iterative discussion and consensus. Subsequently, each group Chair prepared an article with input from the members of the group and submitted it to the co-Chairs. The articles were modified based on the feedback of the co-Chairs. The executive summaries for each topic were generated based on the articles by the co-Chairs and were submitted to the ISHLT Standards and Guidelines Committee. Each Panel member disclosed his or her potential conflicts of interest. The Panel recommendations do not include management of *Pneumocystis jirovecii*, *Cryptococcus* and endemic mycoses in CT recipients.
Box 1. Important definitions used in the document.

**Colonization**: presence of fungus in the respiratory secretions (sputum or BAL) detected by the culture, PCR or biomarker (galactomannan/cryptococcal antigen) in the **absence** of symptoms, radiological **and** endobronchial changes (1).

**Invasive fungal disease** (IFD): presence of fungus in the respiratory secretions (sputum or BAL) detected by the culture, PCR or biomarker (galactomannan/cryptococcal antigen) in the **presence** of symptoms, radiological **and** endobronchial changes OR presence of histological changes consistent with fungal invasion of the tissue(1).

**Universal antifungal prophylaxis**: refers to an antifungal medication started in the post-operative period in all patients, prior to any post-transplant isolation of a fungal pathogen.

**Targeted antifungal prophylaxis**: refers to an antifungal medication started in the post-operative period, prior to any post-transplant isolation of a fungal pathogen **or** serological marker of fungus, which is prescribed only to patients deemed higher risk for IFI (e.g. Cystic fibrosis patients, those with pre-transplant fungal colonization/infection or on augmented immunosuppression).

**Pre-emptive antifungal therapy**: refers to an antifungal medication started **after** post-transplant isolation of a fungal pathogen **or** serological marker of fungus in the absence of any evidence for invasive fungal infection.

**Attack rate**: refers to the cumulative incidence of invasive fungal infection over time in a colonized transplant recipient.
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Modified from Am J Respir Crit Care Med 2006;176:605-14
Executive Summary: Epidemiology

Q: What is the incidence/prevalence of fungal colonization in lung transplant candidates? Special consideration is given to underlying disease.

Evidence Summary:
All information on fungal colonization in lung transplant (LT) candidates has been obtained from observational studies, most of them single-center. Therefore, confidence about the exact prevalence of fungal colonization in LT candidates is limited. The data are more robust in the cystic fibrosis (CF) population due to these patients’ ability to produce sputum. Studies have included colonization at any time pre-transplant, and there are a distinct lack of data regarding colonization rates at different times pre-transplant (i.e., little or no comparison of colonization rates in the months preceding transplant vs. at the time of transplant). In addition, the frequency of sampling might influence the identification of fungal pathogens prior to lung transplantation. In a study examining explanted lungs, the overall prevalence was 5% (14/304)(8), while in studies with greater proportions of CF patients, 8% to 59% of patients were colonized with fungi, of which the majority of isolates were Aspergillus species(9-12). The data on non-CF populations have been scarce, and studies have reported a prevalence of 0% to 52%(9, 10). Multicenter studies with diverse geographic distributions and representative pre-transplant diagnoses and utilizing standardized sampling techniques are needed to more accurately determine the prevalence of fungal colonization in LT candidates.

Q: What is the incidence/prevalence of fungal colonization in lung transplant recipients (LTRs)? Special emphasis is given to underlying disease.

Evidence Summary:
Multiple studies have assessed the presence of fungal colonization in LTRs. Studies have focused primarily on colonization by molds, particularly Aspergillus species. Although these studies have differed, all have been case series of patients after lung transplantation.
The rates of fungal colonization ranged from 20% to 50%, and the numbers of patients in each of the series ranged from 32 to 455 patients(13-22). Most of the larger series had rates of colonization greater than 30% and closer to 40%, suggesting that a rate of fungal colonization of 30% is likely the most accurate.

In all series, the presence of CF greatly increased the rate of fungal colonization in LTRs. Patients with CF as their underlying diagnosis had rates from 42% to 76%. By contrast, the rates for non-CF patients ranged from 21% to 40%, and the rate was lowest among the non-CF patients in largest series (299 patients)(8-12, 20, 23). These studies demonstrate that the presence of CF results in higher rates of post-transplant fungal colonization. In another study, the Aspergillus species were most commonly responsible for colonization(24). Of all the Aspergillus species Aspergillus fumigatus was the most common (59%), followed by Aspergillus flavus (35%).

Q: What is the incidence/prevalence of invasive fungal disease (IFD) after lung transplantation?

Evidence Summary:

The incidence of IFD is much lower than that of fungal colonization after lung transplantation(10, 11, 20), with rates ranging from 3% to 14%. In the largest series, the rate was closer to the lower percentage limit (i.e., 6.6% in 1 series with 335 patients and 8.6% in a large, multicenter trial)(8-19, 25-28). When specifically examining rarer but potentially severe invasive infection with Mucorales, the rate was lower again, between 0.28% and 1.4%(27, 29).

In this setting, a pre-transplant diagnosis of CF was once again associated with an increased risk of post-transplant IFD(9-11).

Q: What is the incidence/prevalence of IFD after heart transplantation?

Evidence Summary:
There are a paucity of studies examining the incidence/prevalence of fungal disease post-heart transplantation. In available studies, the incidence has ranged from 0.12 per patient-year to 0.4 cases per 100 patient-years(22, 28). A multicenter study at 15 transplant centers in the United States suggested that the cumulative incidence of IFD after heart transplantation was 3.4% during the first year(27). Candida accounted for 49% of the infections, while Aspergillus accounted for 23%. More than half of the infections occurred in the first ninety days(27). Overall, IFD after heart transplantation is rare; when it occurs, it is usually during the first year post-transplant, likely at a time when immunosuppression levels are higher. The presence of another case of invasive aspergillosis (IA) in the same institution in the preceding three months has been identified as a risk factor for early IA after heart transplantation; therefore, it is important that centers know their own epidemiology(20). This area requires further study.

Q: When does IFD occur after lung and heart transplantation?

Evidence Summary:
Multiple case series have addressed this question, although no well-controlled trials have been performed to date(9, 10, 14-16, 26, 30, 31). These studies have included patients who have undergone heart-lung, single lung, and bilateral lung transplants and all have demonstrated that invasive infections tend to occur during the first six months post-transplant. Surveillance and interaction with the healthcare team is always more common during the first year after transplant, and thus sampling bias might have played a role in the findings. However, during the same time period, immunosuppression is highest, and patients are more frequently treated for rejection, potentially increasing their susceptibility to IFD.

In a multicenter center study that assessed IFD during the first year post-transplant after solid organ transplantation (SOT), the majority of infections occurred in the first three months post-transplant for both lung and heart transplants (approximately 2/3 occurred during that timeframe, with total incidences of 8.6% and 4.0% in the first year for lung and heart transplant recipients, respectively)(27). This is in contrast to a previously reported literature review where a median time to onset of IA was 3.2 months(26). The increase in the time to...
onset of IA in LTRs may be attributed to the widespread use of antifungal prophylaxis(4). In another study, invasive candidiasis (IC) occurred at 52 days (0-5727) in lung and 66.5 days (2-4645) in heart transplant recipients, while IA in LTRs was noted at 504 days (3-4417) and 382 days (31-1309) in lung and heart transplant recipients, respectively(32). In another study involving heart transplant recipients, IA occurring during the first three months after transplantation (early IA) accounted for 23 cases (median 35 [19 to 88] days after transplantation); in the remaining 8 cases, IA occurred a median of 125.5 (91 to 301) days after transplantation (late IA)(33).

Q: What are the risk factors for IFD after lung and heart transplantation?

Evidence Summary:
Multiple studies, mostly single-center case series and cohort studies, have addressed the risk factors for IFD after lung transplantation. There has been a paucity of studies regarding the same question in heart transplantation. The main risk factor is a pre-transplant diagnosis of CF, which appears to result in increased rates of IFD after lung transplantation(9-11, 20, 23). Other important risk factors for IFD after lung transplantation include the presence of fungal colonization before or early after lung transplantation. More specifically, pre-transplant colonization was associated with post-transplant IFD in 2 studies, with odds ratios (OR) of 11 and 6.7, respectively; the latter result was derived from a multivariable analysis. However, 1 study did not show an increased risk(8, 9, 23). Early post-transplant colonization was associated with an increased risk of IFD, with a significantly increased risk in multiple studies (i.e., OR of up to 11)(14, 17, 29). The risk was augmented by the presence of acute rejection in the setting of early post-transplant colonization(24). Other risk factors that have been implicated include chronic rejection, cytomegalovirus (CMV) infection, and hypogammaglobulinemia (HG)(23, 24).

The type of transplant (single vs. double); use of tacrolimus, cyclosporine, or sirolimus;(22) primary graft dysfunction; and airway stents have also been demonstrated to be risk factors for the development of IFD(11, 22, 24, 26, 34). Transplant clinicians should consider these factors when they decide how to approach prophylaxis of LTRs.
In heart transplant recipients, re-operation (RR 5.8; 95% CI 1.8-18, p=0.002), CMV disease (RR 5.2; 95% CI 2-13.9, p<0.001), post-transplant hemodialysis (RR 4.9; 95% CI 1.2-18, p=0.02), and the existence of an episode of IA in the same heart transplant unit 3 months before or after the transplantation date (RR 4.6; 95% CI 1.5-14.4, p=0.007) were identified as risk factors for IA(35).

**Pediatrics Epidemiology:**

Pediatric lung transplantation is now an accepted therapy that offers carefully selected children a survival benefit(36, 37). Fungal infections are burdensome for pediatric LT patients. However, epidemiological data on the impact of FIs in pediatric lung transplantation have been sparse.

The majority of children undergo lung transplantation for end-stage CF lung disease; many of these patients are chronically colonized with fungal pathogens. In a retrospective, single-center study from Texas Children’s Hospital, 70% (29) were colonized prior to transplantation(38). Patients with CF were nearly 7 times more likely to be colonized than non-CF transplant patients (OR 6.7; 95% CI 1.5-30.1). *Candida* (21/29) and *Aspergillus* (11/29) species were more commonly recovered than *Scedosporium* and Basidiomycetes. Prior to lung transplantation, *Aspergillus* species are among the most important pathogens of pulmonary FIs, and the impact of pre-transplantation FI has not been assessed because antifungal prophylactic therapy is more frequently employed today(39). In CF patients, *Scedosporium* species have been documented more often than in non-CF patients(40).

**Q: What is the incidence/prevalence of fungal colonization in LTRs? Special emphasis is given to underlying disease.**

**Evidence Summary:**

Only 1 study to date has assessed colonization specifically after transplantation. In this cohort, 60% 33 (33) of patients were colonized post-transplantation(38). In a multivariate analysis, fungal colonization after lung transplantation was associated with older patient age.
(HR 2.9, 95% CI 1.1-7.6), CMV prophylaxis (HR 5.6, 95% CI 1.3-24.6), and respiratory viral infection before fungal colonization (HR 2.9, 95% CI 1.0-8.3)(38). CF was not associated with an increased risk of post-transplant fungal colonization.

Q: What is the incidence/prevalence of IFD after lung transplantation?

Evidence Summary:

The incidence of IFD after lung transplantation is variable, ranging from 0 cases to 20%(38, 41). The largest study to investigate epidemiology, risk factors, morbidity, and mortality within the first year following lung transplantation in children was conducted retrospectively and included 555 pediatric patients at 12 centers in North America and Europe(42). In this study, 10.5% of the recipients developed proven (Candida, Aspergillus, or other) or probable (Aspergillus or other) pulmonary FIs during the first post-transplantation year(42). In this cohort, FI was independently correlated with lower twelve-month post-transplantation survival(42).

A recent, large epidemiological study reporting on 960 immunocompromised patients with probable/proven IA from the Prospective Anti-fungal Therapy Alliance (PATH) registry indicated a low incidence of IA in pediatric patients, but the study population included a mixed case load: only 29.2% of patients underwent solid organ transplantation, 66.1% of whom were LTRs(43).

In another study, Candida species constituted the third most frequently isolated pathogens after coagulase-negative Staphylococcus and Pseudomonas aeruginosa in bloodstream infections within the first year after lung transplantation in 190 children who underwent primary lung transplantation at St. Louis Children’s Hospital between 1990 and 2000(44). Another study in a single center in the US determined that post-operative FI was a significant risk factor for the development of bronchial airway anastomotic complications following pediatric lung transplantation(45). The distribution of organisms in single center studies are biased by factors such as the geography and usage of microbiological tools.

Q: What is the incidence/prevalence of IFD after heart transplantation?
Evidence Summary:

Heart Transplant: The epidemiology of FIs in pediatric cardiac transplantation was not substantially evaluated until recently. In 2005, Groetzner et al. reported that FIs were ‘rare’ after cardiac transplantation(46). In addition, data from the PATH registry reported that only 24 of 960 IA infections occurred in cardiac transplant recipients, a majority of whom were likely adults based on the population’s demographics(43). Importantly, 2 large studies from the Pediatric Heart Transplant Study (PHTS) recently described the epidemiology of and associated risks for FIs(47, 48). Zaoutis et al. reported on 1854 pediatric patients in the PHTS database who underwent transplants between 1993 and 2004(48). One hundred twenty-three patients had 139 episodes with yeast (66.2%), mold (15.8%), and Pneumocystis jiroveci (13%). Ninety percent of the yeast infections were caused by Candida species (C. albicans 55%, C. parapsilosis 13%, C. krusei 4%, C. glabrata 2%, C. tropicalis 2%), and Aspergillus species (9 pulmonary, 5 cutaneous, and 1 each central nervous system, sinus, mediastinal tumor, and unspecified) were causative in 82% of the mold infections. The remaining 4 mold infections were caused by Mucorales (3) and Exserohilum species (1). Infections caused by Trichosporon species (bloodstream), Trichophyton tonsurans (bloodstream), and Pityrosporum species (cutaneous) were identified in 1 patient each. Forty-nine percent of recipients with IFD died, all within six months post-transplant. Thirteen (59%) of the 22 patients with mold infections and 43 (47%) of the 92 patients with yeast infections died.

Q: When does IFD occur after lung and heart transplantation?

Evidence Summary:

Heart Transplantation: In the study by Zaoutis, the greatest risk for IFD occurred during the first two months post-transplant(48).

Lung Transplantation: In a study from Texas(38), colonization occurred at a mean of 58 days post-transplant, while IFI occurred at a mean of 271 days post-transplant (range: 9 to 925 days).
Q: What are the risk factors for IFD after lung and heart transplantation?

Evidence Summary:

Heart Transplantation: Risk factors for FIs in pediatric cardiac transplantation were not substantially evaluated until recently. Both studies based on PHTS data suggested that IFI was associated with pre-transplant invasive procedures. First, the Zaoutis study reported an incremental risk of IFI with increasing numbers of invasive procedures (early phase 0 vs. 1, RR 1.3; 0 vs. 3, RR 2.3; p<0.001). In multivariable analysis, previous surgery (p=0.05) and mechanical support at transplantation (p=0.01) remained significant(48). Using similar data, Gajarski detailed an increased risk of IFI with the use of ventricular assist devices (VADs)/extracorporeal membrane oxygenation (ECMO) pre-transplant. In addition, patients with underlying congenital heart disease had an increased risk of IFI compared to those transplanted for cardiomyopathy(47).

Lung Transplantation: Risk factors for FIs after pediatric lung transplantation have been addressed in only a few studies. Risk factors for IFI have included pre-transplantation colonization, CMV mismatch, tacrolimus-based immunosuppression regime, older age (>15 years old), acute cellular rejection (grade >A2), and HG (IgA and IgM), all of which were significantly associated with IA(39, 42, 49).

Recommendations:

Epidemiological data on the impact of FIs in pediatric lung and heart transplantation are sparse. At this time, we can recommend the following.

Given the prevalence of pre-transplant colonization, evaluation for fungal colonization prior to transplantation should be encouraged, particularly for patients with an underlying diagnosis of CF.

Strong recommendation; Low-quality evidence.

Risk factors for IFI should be routinely assessed in pre-transplant and post-transplant CT patients.

Strong recommendation; Very low-quality evidence.
Executive Summary: Diagnosis

Q: What is the role of serum galactomannan (GM) in diagnosing IA in CT recipients?

Evidence Summary:
One of the main limitations of the ELISA GM test is its reduced sensitivity in non-neutropenic individuals. In one meta-analysis(50), the sensitivity of serum GM testing was 82% and 22%, respectively, in a hematology population vs. SOT patients.

Most studies conducted in SOT recipients have shown that GM testing is associated with an unacceptably low sensitivity for the diagnosis of IA(51, 52). Husain et al. demonstrated that the test had a sensitivity of only 30% in CT recipients(53). In another prospective study in LTRs, the median serum GM index for LTRs with IA was 0.3, a value less than the cut-off for positivity (i.e., 0.5)(54).

Recommendation:
Because serum GM testing has been associated with low sensitivity in the diagnosis of IA in CT recipients, the Panel does not recommend the routine use of serum GM for the diagnosis of IA in these patients.

Strong recommendation; Low-quality evidence.

Q: What is the role of bronchoalveolar lavage (BAL) GM in diagnosing IA in CT recipients?

Evidence Summary:
The utility of BAL GM was evaluated in a meta-analysis of 13 studies(55-57). This meta-analysis included adult and pediatric patients with hematologic malignancies, SOT, and/or solid malignancies. Overall, using a positivity cut-off threshold of 0.5, the pooled sensitivity ranged between 82 to 86% and 89 to 92%, respectively.

The utility of BAL GM in CT recipients was specifically evaluated in 5 studies(54, 58-61). Using a positivity cut-off value of 0.5, the sensitivity of BAL GM ranged from 77% and 100%, and the specificity of BAL GM ranged from 40% and 100%. Raising the cut-off threshold value
from 0.5 to 1.0 improved the specificity without compromising the sensitivity in three studies (54, 58, 62). However, one study reported a significant sensitivity loss (93% to 67%) when the cut-off value was increased to 1.0 (60). In this study, BAL GM appeared to be more specific for invasive disease than for colonization because GM detects growing hyphae, whereas culture does not provide such useful information. Some preliminary data have suggested that BAL GM could be used to guide preemptive antifungal therapy (63).

Recommendations:
BAL GM is useful for the diagnosis of IA in CT recipients; however, the optimal cut-off level for positivity remains uncertain. The published data suggests using a cut-off level of 1 to increase the specificity of the test. To obtain the highest sensitivity, a cut-off level of 0.5 should be considered, although false-positive results can occur, and caution is therefore required when interpreting the results.

**Strong recommendation; Moderate-quality evidence.**

BAL GM can be useful for distinguishing colonization from invasive disease because it appears more specific for the latter.

**Strong recommendation; Moderate-quality evidence.**

BAL GM to guide antifungal prophylaxis could allow units to switch from universal prophylaxis to preemptive treatment, thus reducing costs and drug-related toxicity. A randomized, controlled trial comparing both approaches is ultimately warranted.

**Weak recommendation; Very low-quality evidence.**

Due to the small number of heart transplant recipients included in studies to date, the applicability of these recommendations is questionable.

**Strong recommendation; Moderate-quality evidence.**

**Q: What is the role of BAL Aspergillus PCR in diagnosing IA?**

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Evidence Summary:

*Aspergillus* PCR is usually performed on serum or BAL samples. The reported sensitivity for serum *Aspergillus* PCR ranged from 75% to 88% for the detection of IA (64); detection of BAL *Aspergillus* PCR yielded similar results, with a median pooled sensitivity of 79% (65). *Aspergillus* PCR testing of respiratory samples is considerably more sensitive than fungal culture. In addition, PCR testing has the potential to detect mutations associated with antifungal resistance (66). A positive *Aspergillus* PCR test cannot distinguish between colonization and invasive disease. Additional disadvantages of the *Aspergillus* PCR assay (compared to fungal culture) include its inability to distinguish between sub-species of *Aspergillus* (unless specific probes are used or DNA sequencing is performed), cross-reactivity with certain mold species that are genetically homologous to *Aspergillus* (although most of these species are environmental fungi with limited clinical relevance), a lack of standardization of DNA extraction methods with almost all assays being “in-house”, and a lack of ability to determine antifungal susceptibility. Nested PCR should be avoided; real-time PCR is the preferred assay format.

Two standardized *Aspergillus* assays, Viracor and MycAssay, have been evaluated. The Viracor pan-*Aspergillus* PCR was more sensitive (100% vs. 93%) for the detection of invasive disease; however, among LTRs with *Aspergillus* colonization, BAL GM was more specific than Viracor pan-*Aspergillus* PCR (92% vs. 50%). No studies have specifically evaluated the performance of the MycAssay *Aspergillus* PCR assay in CT recipients, while only 1 study has evaluated the performance of the Viracor pan-*Aspergillus* PCR assay in LTRs.

Recommendation:

Routine use of *Aspergillus* PCR is not recommended, but the test could be used for testing as an adjunct to imaging (chest computed tomography), conventional mycological tests (microscopy and culture), and BAL GM.

**Moderate recommendation; Low-quality evidence.**

*Q: What is the role of the (1→3) beta-D-glucan test in the diagnosis of IA in CT recipients?*
Evidence Summary:

(1→3) beta-D-glucan (BDG) is another component of the fungal cell wall that is released into the circulation during IFD. While detection of BDG in blood (serum or plasma) has been used in the diagnosis of IA, this test is not specific for IA because BDG can be detectable during invasive infection, with several other pathogenic fungi including molds and yeasts (i.e., Candida), as well as Pneumocystis.

Three meta-analyses that included 15 to 31 studies each reported moderate overall diagnostic accuracy, with a sensitivity of 76% to 80% and a specificity of 82% to 85% (67-69). Subgroup analyses in these studies suggested similar diagnostic accuracy of IA and IC.

The only prospective study in patients post-CT was designed to assess the utility of serial monitoring of LTRs with the BDG assay through day 180. Serum BDG (cut-off threshold of 60 pg/mL; Fungitell test) had a sensitivity of 71% and a specificity of 59% for the diagnosis of IFD. The test was positive in 4 of 7 IA cases, including 2 cases of tracheobronchial disease, while 3 cases of probable pulmonary IA were not detected (70). Hemodialysis was associated with falsely elevated BDG levels. However, this finding alone did not explain the majority of false-positive test results. Performance of the BDG test using samples other than blood (i.e., BAL) has not been adequately investigated.

Recommendation:

The serum BDG test has marginal accuracy for the diagnosis of IFD in LTRs. Based on one study in lung recipients, the utility of serum BDG for the diagnosis of IFD in CT recipients is questionable and thus not recommended. The utility of BDG in BAL remains unclear and is not recommended.

Strong recommendation; Moderate-quality evidence.

Q: What are the radiological criteria for IMD in LTRs?

Evidence Summary:

Invasive aspergillosis in SOT patients occurs more commonly as an airway disease than as an angio-invasive infection. In a study involving 62 individuals with IA (71), the ‘halo sign’ was
observed in 56% (15/27) and 8% (2/26) of neutropenic and SOT recipients (p<0.001), respectively, while macro-nodules occurred in 67% (18/27) and 35% (9/26) (p=0.02). By contrast, peribronchial consolidations were observed in 7% (2/27) of neutropenic patients and 31% (8/26) of SOT recipients (p=0.03), and ground-glass opacities were observed in 7% (2/27) and 38% (10/26) of neutropenic and SOT patients (p=0.007), respectively. Other studies have also demonstrated a preponderance of nodules or tree-in-bud nodules/bronchial wall thickening(72, 73).

Limited data are available regarding the radiological manifestations of IA or other mold infections in LT patients. In early series(74, 75), most LTRs with IA had ill-defined pulmonary nodules, consolidations, and/or ground-glass opacities. However, the numbers of patients studied in these series by means of computed tomography were quite small (<10 per study).

Recommendation:
Based on the limited data, the Panel is unable to comment on the accuracy of the various radiological findings. Invasive aspergillosis in LTRs seems to have 2 major radiological presentations, depending on the post-transplantation period and the presence of anti-mold antifungal prophylaxis. In the first three months following lung transplantation, the principal manifestation of IA is airway disease, which is manifested mainly by tree-in-bud nodules and bronchial wall thickening. Later in the course of transplantation (usually after the first year), IA can present as a nodular disease, although airway disease remains common in these patients. The 'halo sign' is not expected to be observed in most cases. Expert opinion from an experienced radiologist is recommended.

**Moderate recommendation; Low-quality evidence.**

Pediatrics Diagnosis:

Data regarding diagnostic strategies have not been reported in the pediatric CT literature. Extrapolation with caution from adult recommendations is possible, but further investigations of accurate diagnostic biomarkers of IFI in pediatric CT are suggested.
Recommendation:

No recommendation. See Diagnosis section in adults.
Executive Summary: Prophylaxis

Q: Does pre-transplant treatment of fungal colonization/infection impact post-transplant outcomes, and in what circumstances should pre-transplant treatment be considered?

Evidence Summary:
Pre-transplant isolation of molds from the lower respiratory tract has been documented, raising questions about transplant candidacy and the need for pre-transplant treatment. The spectrum of infection has included colonization and allergic bronchopulmonary aspergillosis (up to 50%)(76), aspergilloma/mycetoma (3%)(77), chronic necrotizing/cavitatory pulmonary aspergillosis or semi-invasive disease (2.3%)(8), and invasive pulmonary aspergillosis (IPA) (1.1%)(9). Patients in whom pre-transplant mycetomas were detected only in explanted lungs had poor post-transplant outcomes despite aggressive antifungal therapy(77). Pre-transplant mold colonization is a well-described risk factor for post-transplant invasive mold disease (IMD)(8, 76). No data are available on whether pre-transplant treatment improves post-transplant outcomes.

Recommendations:
All patients being considered for transplantation who have a mold isolated from the lower respiratory tract should undergo a work-up to determine the precise infection category.

**Strong recommendation; Very low-quality evidence.**

Mold airway colonization does not need to be treated in all patients being considered for transplant, but all patients with pre-transplant mold airway colonization should receive antifungal therapy in the immediate post-transplant period.

**Strong recommendation; Very low-quality evidence.**

The presence of an aspergilloma, semi-invasively or as an IFI, should prompt reassessment of candidacy. If lung/heart-lung transplantation remains indicated, antifungal treatment should
be initiated pre-transplant and continued post-transplant, along with careful planning of the transplant procedure.

**Strong recommendation; Very low-quality evidence.**

Q: Is the use of preemptive treatment non-inferior to universal prophylaxis during the early period after lung transplantation?

**Evidence Summary:**

Two main strategies have been employed(2, 3). Universal prophylaxis is defined as the administration of antifungal agent(s) to all patients during the immediate post-transplant period. Preemptive treatment is defined as the administration of antifungal agents for mold isolation during surveillance post-transplant bronchoscopy without evidence of invasive disease (i.e., colonization)(3). No randomized trials comparing the two strategies have been performed to date. A recent meta-analysis concluded that universal anti-*Aspergillus* prophylaxis did not result in a significant reduction in IA or *Aspergillus* colonization(78), and one recent non-comparative, retrospective analysis of preemptive voriconazole prophylaxis indicated that the agent appeared as effective as universal prophylaxis in minimizing the incidence of IA (1.6%, six months post-transplant)(3).

The highest risk for IC occurs during the immediate post-transplant period (first thirty days), and there are sequential cohort data indicating the effectiveness of universal prophylaxis targeting *Candida* species during the immediate post-transplant period(79). From day thirty forward, molds predominate in terms of IFD risk, but there have been no comparative data regarding whether universal or preemptive treatment is optimal. In terms of mold type, *Aspergillus* colonization places patients at the greatest risk for IFD, followed by Mucorales, with dematiaceous molds (i.e., *Cladosporium* species) representing the lowest risk for progression to IFD(31). Preemptive therapy in the setting of *Scedosporium prolificans* isolation might be warranted, given its predilection for dissemination(80, 81). However, resistance to available antifungal agents precludes effective management of this organism. A combination of voriconazole and terbinafine has been used in some instances(82-84).
As reported in the Diagnostic section of this executive summary, GM is released from growing hyphae. Detection in BAL fluid appears to have utility for IA diagnosis. One prospective cohort study demonstrated that the use of BAL GM to guide antifungal pre-emptive therapy could reduce the use of antifungal agents (compared with universal prophylaxis) by 43%, without missing any IA cases (63). However, for such a strategy to be useful, the turnaround time from sampling to results must be <48 hours. Similarly, in the TDM section, TDM is recommended with commonly used azoles to maximize efficacy and minimize toxicity, but again, timely access to TDM is required.

Recommendations:
Institutional decisions to use universal or preemptive treatment are dependent on predominant organisms, the time post-transplant, and access to sensitive diagnostic tests and to TDM. In some institutions, both approaches could be used for patients at different time points post-transplantation.

**Weak recommendation; Low-quality evidence.**

Depending on local epidemiology, a systemic agent with activity against *Candida* species should be included in the prophylactic regime in the very early post-transplant period. This should be followed by either a universal or preemptive strategy of surveillance and treatment for pathogenic molds.

**Weak recommendation; Low-quality evidence**

If a preemptive strategy is selected we recommend incorporating BAL GM surveillance and TDM.

**Weak recommendation; Very low-quality evidence.**

Q: **What is the optimal agent to achieve effective and safe antifungal prophylaxis following CT?**

Evidence Summary:
A number of factors influence the choice of prophylactic agent, including the local epidemiology, time post-transplant, susceptibility profile, drug efficacy, toxicity profile, drug-drug interactions, need for intravenous or nebulized formulations, degree of need, and access to TDM and cost. As noted in the previous evidence summary/recommendation, candidemia has been observed almost exclusively during the very early post-transplant period (85). There is some evidence that inhaled amphotericin B (AmB) is safe and efficacious during the early post-transplant period (28, 86-88). A recent resurgence in candidemia rates in SOT recipients has been documented, which might be related to the emergence of resistant Candida strains (89).

Because molds (particularly Aspergillus) predominate beyond the first thirty days post-transplantation, it is essential that agents with good Aspergillus species activity be used. Multiple observational studies have supported the safety of inhaled amphotericin in either the deoxycholate or lipid formulation (25, 28, 86, 88, 90-94), with some evidence for safety and efficacy in uncontrolled studies (88, 90, 92) and in a recent metanalysis (78). No head-to-head data have been published comparing the efficacy of the variousazole antifungal agents; however, retrospective cohort studies have supported the efficacy of voriconazole (13, 18, 95). Despite these findings, voriconazole has been associated with significant toxicity, most particularly central nervous system side-effects, drug-drug interactions and as most recently recognized an increased risk of squamous cell carcinoma (SCC) of the skin (96-99), particularly with long-term use. As noted in the TDM section, some centers have reported an increase in the incidence of infections caused by triazole-resistant Aspergillus species (100-104).

Recommendations:
In the first thirty days post-transplantation we recommend nebulized amphotericin B (nAmB) with or without fluconazole or an echinocandin (depending on local epidemiology) to target Candida species.

**Strong recommendation; Low-quality evidence.**
We recommend implementing surveillance programs at an institutional level to determine the rates of resistant Candida and Aspergillus species and the emergence of other fungi. This will ensure that the prophylactic antifungal agents used locally are effective against the predominant fungi.

**Strong recommendation; Low-quality evidence.**

We recommend appropriate photo-protection advice if voriconazole is prescribed.

**Strong recommendation; Very-low-quality evidence.**

Voriconazole should be prescribed with caution in those: with a history of cutaneous SCC; who are on other photo-sensitizing drugs (i.e., trimethoprim-sulfamethoxazole, ciprofloxacin, tetracyclines, diuretics, amiodarone and angiotensin converting enzyme inhibitors) and from geographic areas with a high incidence of cutaneous malignancy.

**Strong recommendation; Low-quality evidence.**

**Q: What is the optimal duration of antifungal prophylaxis following CT?**

Evidence Summary:

No studies have directly addressed this issue. Several observational studies have indicated that greater risk for Aspergillus infection occurs during the first six months post-transplant(13, 24, 26, 105), and 1 observational study indicated that at least four months of universal voriconazole prophylaxis effectively reduced the risk of IFD(13). Observational studies of preemptive treatment have indicated that 85 days to 4.2 months of mold-activeazole therapy was associated with a low incidence of IFD(95, 106). However, long-term voriconazole use has been associated with the development of SCC and periostitis(96-99, 107-109).

Recommendations:

We recommend universal prophylaxis for a total of four to six months.

**Weak recommendation; Low-quality evidence.**
We recommend preemptive treatment for three to four months.

**Weak recommendation; Very low-quality evidence.**

We recommend that voriconazole should be used with caution for periods longer than six to nine months.

**Strong recommendation; Very low-quality evidence.**

We recommend that if voriconazole is prescribed, appropriate photo-protection advice should be given *along with enhanced surveillance for skin cancers.*

**Strong recommendation; Very low-quality evidence.**

Voriconazole should be prescribed with caution in patients with histories of cutaneous SCC; who are on other photo-sensitizing drugs; and who are from geographic areas with a high incidence of cutaneous malignancy.

**Strong recommendation; Low-quality evidence.**

**Q: Should antifungal prophylaxis be considered beyond the early post-transplant period?**

**Evidence Summary:**

Beyond the early post-transplant period (first six months), other times when the risk of IFD is increased include acute and chronic rejection(105, 110), augmented immunosuppression and CMV infection(24), but no studies have been performed specifically to determine the magnitude of these risks or the efficacy of antifungal prophylaxis during these periods of increased risk.

**Recommendation:**

We recommend that, beyond the early post-transplant period, antifungal prophylaxis be considered during periods of increased risk for IFD.

**Weak recommendation; Very low-quality evidence.**
Pediatrics Prophylaxis:

Very limited data exist to respond to any of the questions related to antifungal prophylaxis for pediatric LTRs, and a recent multi-center survey showed the wide range of antifungal prophylaxis strategies as current international practice in pediatric LTRs(111).

Q: Does pre-transplant treatment of fungal colonization/infection impact post-transplant outcomes, and in what circumstances should pre-transplant treatment be considered?

Evidence Summary:
Two studies have addressed this first question. First, a large, retrospective, multi-center assessment in North America and Europe noted that pre-transplant colonization was associated with an increased risk of post-transplant pulmonary FI(43). Post-transplant outcomes related directly to pre-transplant fungal colonization were not assessed. In a smaller single-center study, fungal colonization was not associated with the development of chronic graft rejection or death(38).

Q: Is the use of preemptive treatment non-inferior to universal prophylaxis during the early period after lung transplantation?

Evidence Summary:
No published data.

Q: What is the optimal agent to achieve effective and safe antifungal prophylaxis following lung transplantation?

Evidence Summary:
No published data.

Q: What is the optimal duration of antifungal prophylaxis following lung transplantation?
Evidence Summary:

Only 1 study in pediatric patients has reported on the duration of prophylaxis. In Texas, only 14 of 55 patients received fungal prophylaxis (11/33 with pre-transplantation fungal colonization), and prophylaxis was administered for a median of 51 days (range 14-272)(38). In the large IPLTC study conducted at 12 pediatric LT centers, antifungal prophylaxis was not unified or well described(42). The optimal duration of prophylaxis is uncertain.

Q: Should antifungal prophylaxis be considered beyond the early post-transplant period?

Evidence Summary:

No published data.

Recommendation:

The optimal agents and durations and the utility of preemptive therapy and its use beyond the early post-transplant period in pediatric patients require additional investigations. Because pre-transplant colonization could be associated with an increased risk of post-transplant invasive pulmonary fungal infection, targeted antifungal prophylaxis in patients with pre-transplant colonization should be strongly considered.

**Weak recommendation; Low-quality evidence. See Prophylaxis section.**
Executive Summary: Therapy

Q: What is the role of combination antifungal therapy?

Evidence Summary:
Given the poor prognosis of IFD in many previous studies, some investigators have sought to improve outcomes with the administration of combination antifungal therapy. To date, no randomized trials of combination therapy for IA in CT recipients have been performed. However, in addition to case reports, 2 studies have suggested a possible benefit of such therapy in certain patient subsets. Singh et al. performed a retrospective, multicenter comparison of SOT recipients with IA treated with combination voriconazole and caspofungin (n=40) and those treated with lipid formulations of AmB (n=47)(112). No statistically significant difference in ninety-day survival was found overall; however, the subgroups with renal failure and with A. fumigatus infections did show significantly improved ninety-day survival. More recently, a randomized, multicenter, multinational trial was performed by Marr et al. to compare combination therapy with voriconazole plus anidulafungin vs. voriconazole alone in 454 patients with hematologic malignancies or who underwent hematopoietic stem cell transplantation (HSCT)(113). Combination azole/echinocandin therapy was administered for two to four weeks, followed by continuation of voriconazole. There was a trend toward decreased mortality at six weeks (p=0.09) in the combination therapy group, and this trend was statistically significant in the group of patients who were diagnosed based on serum or BAL GM (15.7% six-week mortality in the combination group vs. 27.3% in the voriconazole-alone group, p<0.05). Although the interpretation of these results is a topic of debate, there is at least a suggestion that certain subgroups of patients might benefit from combination therapy.

Recommendations:
Given the lack of randomized trials in SOT recipients, combination therapy cannot currently be recommended as a routine treatment for CT recipients with IA.

Weak recommendation; Moderate-quality evidence.
Evidence for the duration of combination therapy is lacking, and thus it is suggested that this therapy be limited to no more than two weeks, with azole monotherapy continuing beyond that time until clinical and radiographic resolution has occurred.

**Weak recommendation; Low-quality evidence.**

*Q: What role is there for aerosolized AmB in the treatment of Aspergillus tracheobronchitis?*

**Evidence Summary:**

Tracheobronchial forms of aspergillosis, including ulcerative tracheobronchitis and anastomotic infections, occur principally in LTRs(114). The current guidelines(115) recommend voriconazole as the first-line therapy. The possibility of delivering nebulized antifungals (amphotericin B deoxycholate [AmB-d] or lipid formulations of AmB [L-AmB]) as an adjunctive or primary therapy has been proposed.

The idea of delivering antifungal agents directly to the airway is intuitively appealing, and it has the goal of delivering a high concentration to the infected area while avoiding systemic toxicity(116). However, at this time, evidence is lacking to support the use of nAmB for the primary treatment of *Aspergillus* tracheobronchitis or anastomotic infection. In addition, there are many potential issues with nAmB (dose, devices, pulmonary deposition) that require consideration prior to its implementation as the sole therapeutic option. Until further evidence becomes available, treatment of *Aspergillus* tracheobronchitis should follow the established guidelines for the treatment of aspergillosis in other sites.

There is a single case report of a complex airway infection involving an endobronchial prosthesis that was treated with topical instillation of L-AmB in combination with systemic voriconazole and nAmB(117). Although intriguing, more evidence is needed before this approach could become standard.

**Recommendations:**

We suggest that nAmB as a primary treatment for tracheobronchitis/anastomotic infection should not be used as a sole antifungal therapy.
Weak recommendation; Very low-quality evidence.

Nebulized amphotericin could be used in combination with voriconazole or other systemic antifungal drugs, depending on the extent and burden of bronchial infiltration. Nebulized amphotericin has demonstrated some additional effects when added to standard therapy.

Weak recommendation; Very low-quality evidence.

Q: What is the potential role of aerosolized AmB in the treatment of IPA?

Evidence Summary:

Studies have been published on the use of nAmB for prophylaxis against IFD in lung transplantation (see Prophylaxis section). The current question relates to whether the addition of aerosolized AmB adds any efficacy to a standard regimen for IPA as a part of combination therapy.

There is limited evidence for an additive benefit of nAmB in the treatment of IA, as studies of this agent have primarily focused on prophylaxis rather than treatment. However, nAmB could be used in combination with voriconazole/other systemic antifungal drugs, depending on the severity of IFD, or possibly in situations in which large cavitary lesions might render the penetration of systemic agents difficult. However, additional evidence would be helpful.

Recommendation:

No recommendations in favor of adding nebulized amphotericin preparations to standard regimens for IPA can be made at this time.

Weak recommendation; Very low-quality evidence.

Q: What treatment is indicated for colonization with filamentous fungi in protocol BAL cultures?

Evidence Summary:
The interactions between colonizing organisms and hosts have recently become the focus of new research suggesting a relationship between fungal colonization and the development of chronic lung allograft dysfunction (BOS). Such research has raised the question of whether any intervention with antifungal therapy might improve outcomes in fungal colonized LTRs. Recent results regarding the potential effects of fungal colonization on long-term allograft function have stimulated new attention in such colonization. Weigt et al. studied 201 LTRs and determined that colonization with Aspergillus species was independently associated with BOS and BOS-related mortality(16). Aspergillus colonization preceded BOS by a median of two hundred sixty-one days(16). More recent results from the UCLA group, with a validation cohort from Duke, support these results, indicating that Aspergillus species with small conidia (A. fumigatus, A. terreus, and A. nidulans) were more highly associated with BOS risk, which was attributed to a greater likelihood of deposition in the smaller airways(105). Felton and colleagues reported that isolation of Aspergillus species from the respiratory tract of LTRs was associated with increased mortality, with a hazard ratio of 2.2(118). In addition, Sole et al. determined that Aspergillus infection was significantly associated with increased five-year mortality, particularly for invasive infections, bronchial anastomotic infections, late-onset disease, and chronic allograft dysfunction(24). In this study, the isolation of Aspergillus from the airways preceded acute rejection(24).

Treatment of Aspergillus species has primarily focused on preventing the development of invasive infection, but these new results suggest that the goal should be eradication of the organism itself. It is less clear, however, whether systemic antifungal therapy will prevent these allograft outcomes. Well-designed observational studies in this area are urgently needed.

Recommendations:
Asymptomatic fungal colonization within the first post-transplant year on protocol BAL cultures should be treated preemptively with antifungal therapy.

Strong recommendation; Very low-quality evidence.
For patients who are already on therapy with voriconazole, there are no data to suggest that changing to posaconazole, intravenous lipid amphotericin, or an echinocandin will be of any clinical benefit. Ensuring that adequate azole levels are obtained might be beneficial.

**Strong recommendation; Very low-quality evidence.**

We recommend voriconazole, posaconazole or itraconazole for preemptive treatment with the demonstration of adequate antifungal levels (Table 1, 2).

**Strong recommendation; Very low-quality evidence.**

Q: Should maintenance antifungal therapy be continued after successful therapy for an IFD and for how long?

Evidence Summary:
Given the severity of aspergillosis and other IMDs in transplant recipients, it is sometimes tempting to clinicians to administer a lengthy course of secondary prophylaxis after successful treatment for invasive infections, with the goal of prevention of recurrences. No randomized trials have addressed this issue. Increasingly, reports of adverse consequences of long-term voriconazole therapy (skin cancers, periostitis, peripheral neuropathy)\(^\text{(108, 119, 120)}\) have called such practices into question. At the present time, there is no firm evidence for prolonging antifungal therapy beyond clinical and radiographic resolution. Exceptions can be made for patients who are at continued risk due to excessive environmental exposure, persistent colonization with single lung transplant and/or chronic allograft dysfunction, augmentation of immunosuppression, or other factors (i.e., CMV infection).

Recommendation:
Once successful treatment of the IA has been completed, therapy can be discontinued. Patients should be monitored very closely for relapses and the necessity for preemptive treatment.

**Strong recommendation; Very low-quality evidence.**
High-risk patients might be considered for longer courses of treatment or for secondary prophylaxis. If such a course is administered, careful attention to the monitoring of antifungal drug levels is important, as is monitoring for toxicity, particularly for voriconazole.

**Strong recommendation; Very low-quality evidence.**

**Pediatrics Therapy:**

Combination antifungal therapy has been addressed in only 1 single-center study that evaluated results in 11 patients (38) (azole and AmB or an echinocandin; some subjects received aerosolized amphotericin as part of the therapy).

**Q: What role is there for aerosolized AmB in the treatment of IPA?**

Evidence Summary:

No published data.

**Q: What treatment is indicated for colonization with filamentous fungi in protocol BAL cultures?**

Evidence Summary:

No published data.

**Q: Should maintenance antifungal therapy be continued after successful therapy for an IMD and for how long?**

Evidence Summary:

No published data.
Data regarding the treatment of IFD have not been substantially reported in the pediatric CT literature. Further investigation is warranted into combination antifungal therapy, aerosolized therapeutics and maintenance antifungal therapy after treatment for IFD in patients with pediatric CT.

**No specific recommendation.** *See Treatment section.*
Executive Summary TDM

Q: Should TDM be performed for azole antifungal agents? What are the levels of evidence for TDM use in prophylaxis and treatment?

Evidence Summary:

Much of the data on the use of TDM for azoles have come from other patient groups (i.e., the HSCT population). One retrospective audit of heart and LTRs demonstrated considerable inter- and intra-patient variability in itraconazole levels and sub-therapeutic levels (see Table 1 for the therapeutic range)(121). Six of 57 (10.5%) patients developed IFD, but 50% (3 of 6) of those with IFD had sub-therapeutic itraconazole levels (Table 1)(121). Only 1 prospective, observational study has specifically examined voriconazole TDM in the CT setting(15). Only 32% of the patients had levels in the therapeutic range (Table 1)(15). Overall, 10% developed IFD, and 27% developed fungal colonization(15). There was a trend toward significantly lower voriconazole levels in those patients with IFD or colonization compared with those who did not develop infections (1.72 mg/L vs. 0.92 mg/L; p=0.07)(15). Posaconazole (suspension) levels have only been examined in one cohort of CT patients, which revealed that the initial levels were sub-therapeutic (Table 1) in 47% of patients, and patients with levels consistently >0.5 mg/L were more likely to have successful outcomes (p=0.055)(122). No data regarding the utility of TDM for fluconazole are available for CT patients or for those with an MCS device.

Recommendations:

All patients on itraconazole should have a trough level performed one to two weeks after (i) initiation; (ii) any change in itraconazole dose; or (iii) the initiation of/cessation of/change in the dose of an interacting agent.

Strong recommendation; Low-quality evidence.

All patients on voriconazole should have a trough level performed five to seven days after (i) initiation; (ii) any change in voriconazole dose; or (iii) initiation of/cessation of/change in the
dose of an interacting agent. Levels should be obtained weekly thereafter until stable levels in the therapeutic range are attained. Once stable levels are achieved, monthly TDM is recommended.

**Strong recommendation; Low-quality evidence.**

All patients on posaconazole (suspension) should have a trough level performed seven days after (i) initiation; (ii) any change in posaconazole (suspension) dose; or (iii) initiation of/cessation of/change in the dose of an interacting agent. We also recommend the implementation of a number of measures to ensure adequate absorption (Table 2).

**Strong recommendation; Low-quality evidence.**

Fluconazole TDM is only recommended in unstable or critically ill patients in intensive care units or in patients undergoing renal replacement therapy.

**Strong recommendation; Very low-quality evidence.**

Q: What is the role of TDM in clarifying toxicity/drug-drug interaction?

Evidence Summary:

Voriconazole, itraconazole and fluconazole are metabolized differently by the cytochrome P450 system, as are many other drugs administered to CT patients and to those with MCS device (Tables 3A and 3B), which may result in under-exposure or over-exposure to the azole being used and/or the interacting drug being co-administered. These include many of the immunosuppressant agents used in lung and heart transplantation. Many of these interactions can be difficult to predict in the clinical setting.

**Recommendation:**

We recommend that, when co-administering an azole and an interacting drug, TDM be performed for both drugs.

**Strong recommendation; Low-quality evidence.**
Q: How does TDM assist in determining the optimal dose regimens for patients with CF, and how often should it be performed?

Evidence Summary:

CF patients are a special group of CT patients who have a number of characteristics that can influence the pharmacokinetics of azole antifungal agents, including (i) younger age; (ii) relatively lower body mass index; (iii) altered gastro-intestinal function (i.e., delayed absorption); (iv) bile-dependent malabsorption; (v) changes in the volume of distribution; (vi) increased creatinine clearance; and (vii) high rates of gastro-esophageal reflux disease. An evolving body of evidence indicates that higher doses of azoles must be administered to achieve therapeutic levels in CF patients(123, 124).

Recommendation:

Azole TDM monitoring should be performed in all post-transplant CF patients.

Strong recommendation; Low-quality evidence.

Q: What is the role of TDM according to pathogen type?

Evidence Summary:

Aspergillus species is the most common mold isolated from CT patients. However, even within this genus, some species have lower minimum inhibitory concentrations (MICs) than others(30, 125). In addition, other molds, such as Scedosporium prolificans, have increased MICs compared with Aspergillus species. Acquired resistance related to the increased use of azoles in hospitals and agricultural settings has been increasingly documented(100-104). Knowledge of local antifungal resistance patterns is critically important. To be effective, serum levels of azoles should exceed the MIC of the organism in question.

Recommendation:

TDM should be performed for all patients with an infection caused by a fungus with a high MIC and at all centers with known high rates of Aspergillus and/or Candida triazole
resistance. Dose adjustments and levels must be assessed weekly until the trough levels are greater than the MIC of the target organism.

**Strong recommendation; Low-quality evidence.**

**Q: What do the results mean? How reproducible are drug assays within and between laboratories, and what quality assurance programs are in place?**

**Evidence Summary:**

The technologies required are the same as that used for immunosuppressant drugs. The other requirements for the implementation of TDM at any given institution include (i) validation of a published assay; (ii) a critical mass of patients requiring TDM; (iii) a turn-around time (from sampling to results) of <72 hours; (iv) laboratory resources; and (v) clinicians who understand the value of TDM and how to interpret TDM results. The different azoles can be measured simultaneously using conventional high-performance liquid chromatography or mass spectrometry. While it is mandatory in many countries to participate in a recognized quality assurance TDM program, further inter-laboratory collaborations in this area are very important to identify gaps and areas for future investigation(126, 127).

**Recommendation:**

All institutions performing TDM should participate in external quality assurance programs.

**Strong recommendation; Very low-quality evidence.**

**Pediatrics TDM:**

Data regarding TDM strategies have not been reported in the pediatric CT literature.

**Recommendation:**

Extrapolation with caution from adult recommendations is possible, but further investigation into the utility of TDM for the prevention and treatment of IFIs in pediatric CT is suggested.
Strong recommendation; Very low-quality evidence. See TDM section.
Table 1: Target Trough and Peak Levels for the Various Azoles

<table>
<thead>
<tr>
<th>Antifungal drug</th>
<th>Target trough-prophylaxis (mg/L)</th>
<th>Target trough-treatment (mg/L)</th>
<th>Upper limit of non-toxic range or peak (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>0.5</td>
<td>0.5-1</td>
<td>2</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>1-2</td>
<td>1-2*</td>
<td>4-5</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.7</td>
<td>1.25</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adapted from Ashbee and Gilleece(128)

*Higher levels may be required for specific infections (e.g. central nervous system infections) (129)
### Table 2: Measures to Maximize the Absorption of Posaconazole

Co-administer posaconazole with 1 or more of the following (with each dose of posaconazole):

- High-fat meal (containing >20 g of dietary fat)
- 180-240 mL of a commercially available nutritional supplement
- Ascorbic acid (500 mg)
- 120-180 mL of an acidic drink (i.e., cola, ginger ale, orange juice)

Administer a maximum of 200 mg of posaconazole per dose:

- Regimens of 200 mg TDS or 200 mg QID preferred

Avoid proton pump inhibitors:

- Use of H₂ antagonists allowed if needed but can result in reduced posaconazole levels
- Use of aluminum- or magnesium-containing antacids allowed if needed, but no good data available to ascertain impact on posaconazole levels

Co-administration of drugs that increase posaconazole clearance or impair absorption is to be avoided, i.e., cimetidine, phenytoin, rifamycin derivatives

Adapted from Greene and Woolery(130) and from Ananda-Rajah et al.(131)

TDS = three times a day; QID = four times a day
Table 3: Drugs Commonly Used in Cardiothoracic Transplant Settings that Interact with Azole Antifungal Agents

3A: Increase in Exposure Due to Azole

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Flu</th>
<th>Itra</th>
<th>Posa</th>
<th>Vori</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↑A</td>
<td>↑A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>↑A</td>
<td>↑A</td>
<td>↑A</td>
<td>↑A</td>
</tr>
<tr>
<td>Lovastatin/simvastatin</td>
<td></td>
<td>↑A</td>
<td>↑A</td>
<td>↑A</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
<td>↑A</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>↑A</td>
<td>↑A</td>
<td>↑A</td>
<td>↑A</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>↑A</td>
<td>↑A</td>
<td></td>
<td>↑A</td>
</tr>
<tr>
<td>Oral hypoglycemia</td>
<td>↑A</td>
<td>↑A</td>
<td></td>
<td>↑A</td>
</tr>
</tbody>
</table>

3B: Effect of Drugs on Azole Exposure and/or Reciprocal Interacting Drug

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Flu</th>
<th>Itra</th>
<th>Vori</th>
<th>Posa</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂ antagonists and antacids</td>
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<td>↓ azole</td>
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<tr>
<td>Proton pump inhibitors</td>
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</tr>
<tr>
<td></td>
<td>↓ azole</td>
<td>↓ azole</td>
<td>↓ azole</td>
<td>↓ azole</td>
</tr>
<tr>
<td>Carbamazepine (vori C/I)</td>
<td>↓ azole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydantoins (phenytoin)</td>
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Executive Summary: MCS

Background:

The field of MCS has made tremendous progress over the past several decades, with more than 30,000 patients receiving durable MCSs worldwide(132). The initial device design consisted of pulsatile flow pump, which could be either intra- or extra-corporeal. Over the past decade, continuous flow devices have superseded the pulsatile flow design; these devices have superior outcomes with better adverse event profiles, significantly lower rates of infection, smaller pump sizes, and smaller-width drivelines and are intracorporeal(133). One of the major challenges in and limits to the successful use of MCS devices is infection. Device-specific and -related infections are difficult to treat and have been associated with poor quality of life and increased mortality. Mortality could be as high as 90% in the case of VAD-specific FIs(134).

Q: What is the prevalence and spectrum of FIs in MCS device recipients?

Evidence Summary:
The prevalence of FIs in MCS device recipients (defined as (number of FIs/number of devices)*100) has decreased since these devices were originally introduced. The mean prevalence of FIs from 1990 to 1999 (based on mid-year data collection) was 11.79%, and the mean prevalence since 2000 has been 4.41% (p=0.01)(134-154). The majority of FIs are due to Candida species, with a few case reports of Aspergillus species and other mold infections.

Q: What are the risk factors for developing a FI in MCS device recipients?

Evidence Summary:
Use of total parenteral nutrition (TPN) was significantly associated with the development of a fungal VAD infection in multivariate analysis in a study that compared bacterial and fungal VAD infections(134). Other factors that were significant on univariate analysis included a greater number of invasive devices, longer operative time, a greater number of transfusions, post-operative need for hemodialysis, and the occurrence of abdominal surgery. Use of TPN and receipt of renal replacement therapy are also notable as risk factors for IC based on the general medical and surgical literature, as summarized in the recent management guidelines for IC. Other risk factors include prolonged use of antibiotics, the presence of central venous catheters (CVCs), mechanical ventilation, the severity of illness, immunosuppression, and neutropenia(155).

Q: Is antifungal prophylaxis in MCS device recipients effective?

Evidence Summary:
Given the relatively high rates of FI seen in earlier studies, there has been great interest in utilizing antifungal agents for prophylaxis against MCS device infections. However, an analysis of the various studies demonstrated a similar mean rate of FIs in studies that used antifungal prophylaxis vs. those that did not (11.78% vs. 10.4%, p=0.9), respectively(134, 156).

In summary, a low rate of FIs has been noted in recent studies, and no evidence has demonstrated that the routine use of antifungal prophylaxis decreases FIs in MCS device recipients.

Recommendations:
Routine peri-operative antifungal prophylaxis for MCS device implantation is not recommended.

Strong recommendation; Low-quality evidence.

The use of antifungal prophylaxis can be considered in certain high-risk populations:

- Patient has used TPN;
- Patient has experienced recent colonization with *Candida* species (≥3 sites); and
- Patient is hospitalized and has been treated with broad-spectrum antibiotics for >48 to 72 hours at the time of MCS device implantation

**Weak recommendation; Low-quality evidence.**

In high-risk populations, as defined above, 400 mg to 800 mg fluconazole at the time of the induction of anesthesia and then daily for up to 24 hours to 48 hours post-implantation is the preferred agent for fungal prophylaxis.

**Weak recommendation; Low-quality evidence.**

**Q: What is the optimal management for a FI in an MCS device recipient?**

Evidence Summary:

Device-based infections in MCS device recipients originate from a biofilm, which consists of organisms that are adherent to the underlying prosthetic surface and to each other and that are encased within a polysaccharide matrix. *In vitro* studies have demonstrated that *Candida* species biofilms have very high MICs for azoles and AmB-d, although planktonic forms are susceptible to these drugs. By contrast, *in vitro* and animal models of CVC infection have shown that L-AmB complex, caspofungin, micafungin and anidulafungin lead to a significant decrease in biofilm fungal burden(157-162).

Due to the lack of publications regarding the treatment of FIs in MCS device recipients, we have based our recommendations on the published guidelines for the management of candidiasis and of infections of cardiac devices(155, 162, 163).

Recommendations:

**Medical treatment of fungal MCS pump/cannula infection:**

*Candida* species infection of the pump or cannula should be treated with an echinocandin or L-AmB.

**Strong recommendation; Low-quality evidence.**
The duration of treatment should be eight to twelve weeks from negative blood culture, followed by step-down treatment with an oral agent for long-term suppression.

**Strong recommendation; Low-quality evidence.**

The optional addition of flucytosine to L-AmB can be considered in select patients.

**Weak recommendation; Low-quality evidence.**

*Surgical therapy for MCS device-pump/cannula infection:*

Device exchange or placement on the cardiac transplantation list (if appropriate) should be considered if the patient has a relapse of infection despite treatment with appropriate antifungal agents, at the appropriate dose and for the appropriate duration.

**Weak recommendation; Very low-quality evidence.**

After surgical replacement of the infected device or cardiac transplantation, antifungal agents should be continued for at least six weeks or possibly longer if surgical cultures are positive.

**Strong recommendation; Low-quality evidence.**

Routine device replacement in the setting of a FI is not recommended.

**Weak recommendation; Very low-quality evidence.**

*Medical treatment of fungal MCS device drive-line/pocket infection:*

Blood cultures should be drawn routinely to exclude concomitant fungemia.

**Strong recommendation; Low-quality evidence.**

Superficial driveline infection in a clinically stable patient with negative blood cultures should be treated with an azole for at least two weeks. If the depth of infection (assessed by physical examination, ultrasound, or computed tomography) is unclear, the recommended treatment is the same as that for deep driveline or pocket infection.

**Strong recommendation; Low-quality evidence.**
Deep driveline or pocket infection should be treated with empiric echinocandin or L-AmB for six to eight weeks, with consideration of long-term oral suppression thereafter.

**Strong recommendation; Low-quality evidence.**

*Surgical treatment of fungal MCS device drive-line/pocket infection:*

Surgical drainage could be required for the control of extensive FIs.

**Weak recommendation; Low-quality evidence.**

If the device is replaced, the new driveline should be placed in another area that is separate from the originally infected area.

**Weak recommendation; Low-quality evidence.**

After surgical replacement of the infected device or cardiac transplantation, antifungal agents should be continued for at least six weeks or possibly longer if surgical cultures are positive.

**Strong recommendation; Low-quality evidence.**

Routine device replacement in the setting of a fungal driveline/pocket infection is not recommended.

**Weak recommendation; Low-quality evidence.**

*MCS-Related Infections: Candidemia:*

In patients who develop *candidemia*, additional testing is recommended to determine the source of *candidemia*. This testing could include cultures of the driveline, pocket, and CVCs and imaging, as indicated by the individual clinical scenario.

**Strong recommendation; Low-quality evidence.**

Empirical treatment of *candidemia* (before organism identification and/or susceptibility is available) with an echinocandin or L-AmB is recommended.

**Strong recommendation; Low-quality evidence.**
If the source of the *candidemia* is a CVC and it has been removed and blood cultures clear promptly with no obvious metastatic infection, two to four weeks of treatment from the date of the first negative blood culture are recommended.

**Strong recommendation; Low-quality evidence.**

All patients should undergo a complete ophthalmologic exam to assess endophthalmitis prior to discontinuation of antifungal treatment.

**Strong recommendation; Low-quality evidence.**

Once the identity and sensitivity of an organism are established, blood cultures are negative, and the patient is clinically stable, antifungal therapy can be de-escalated to an organism-specific continuation/step-down phase of treatment.

**Weak recommendation; Low-quality evidence.**

**MCS Device-Related Infections: Mediastinitis, Infective Endocarditis:**

Thorough surgical debridement of mediastinitis with an open chest and consideration of vacuum-assisted wound closure are recommended. The antifungal agents and durations are similar to that those listed for MCS device pump/cannula infection.

**Strong recommendation; Low-quality evidence.**

We recommend treatment of *Candida*-species infective endocarditis similar to that described for MCS device pump/cannula infection.

**Strong recommendation; Low-quality evidence.**

**Non-MCS Device Infections: Candida in Respiratory Cultures:**

Isolation of *Candida* species from sputum or BAL fluid in the absence of a lung abscess or evidence of disseminated candidiasis is generally indicative of colonization and does not require treatment.

**Strong recommendation; Low-quality evidence.**
**Non-MCS Device Infections: Candida Species in Urinary Cultures:**

Isolation of *Candida* species from urine, particularly when associated with an indwelling urinary catheter and in the absence of symptoms, does not require antifungal treatment, but change/removal of the catheter is recommended.

**Strong recommendation; Moderate-quality evidence.**

In a patient with symptoms of cystitis and a positive urine culture with fluconazole-susceptible *Candida* species, two weeks of treatment with fluconazole 200 mg daily are recommended.

**Strong recommendation; Moderate-quality evidence.**

If cystitis is due to a fluconazole-resistant *Candida* species, the treatment options include AmB-d at a dose of 0.3 mg/kg to 0.6 mg/kg daily for one to seven days, fluycytosine at a dose of 25 mg/kg 4 times daily for up to seven days, and may consider AmB-d bladder irrigation. Fluycytosine should not be continued after the cessation of AmB-d. Caspofungin is not recommended because of its limited penetration into the urinary tract.

**Strong recommendation; Low-quality evidence.**

**Pediatrics MCS:**

MCS devices have been increasing in use as the preferred intermediate and long-term means for MCS in pediatric heart failure patients, predominantly as a bridge to transplant but also as bridge to recovery or destination therapy. The majority of the pediatric literature focused on VADs has reported substantial complications related to infections after implantation. Both single-center and multi-center case series have consistently reported infectious episodes, including sepsis and non-device-related infections, in approximately 30% to 60% of patients(164-169). Interestingly, Blume et al. reported infections in only 12% of 26 pediatric patients supported with devices designed for short-term use(164), and Miera et al. described no infectious events in their series of 7 patients supported with the HeartWare® VAD(170). Device-related infections, predominantly infections involving the driveline, have been reported in 7% to 17% of patients(168, 171-173).
Few studies have reported the pathogens recovered in these device-associated infections, including the 2 largest series of pediatric device recipients by Blume and Fraser (164, 171), but case series have reported *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Candida albicans* (165, 166, 169, 173, 174). Specifically, *Candida albicans* was reported in 1 driveline infection and 1 urine culture among the combined 39 cases in which pathogens were reported (165, 166, 169, 173). In the most recent literature, Cabrera reported on 51 patients at a single institution, including three *Candida* species with mortality in 2 patients (175). The infections included an MCS device-specific *C. albicans* infection and 2 MSC device-related infections (*C. parapsilosis* and *C. tropicalis*). Infections of the internal device were not reported in 2 major case series, including a series with the Berlin Heart EXCOR® Pediatric VAD (168, 171).

With only scant reporting of the epidemiology of FI in recipients of MCS devices, information is lacking regarding risk factors, prophylaxis efficacy, and optimal management in the developing area of pediatric MCS device.

**Recommendation:**

Studies in pediatric MCS device, including the PEDIMACS registry, should optimally collect and report data to fill gaps related to the incidence, risk, prevention, and treatment of FIs.

*Strong recommendation; Low-quality evidence. See MCS section.*
Reference List


63. Husain SS, L.; Akinlolu, Y.; Chaparro, C.; Rotstein, C.;. Utility of BAL galactomannan (GM) and culture based preemptive antifungal therapy (PET) strategy in lung transplant recipients (LTRs). 52nd Interscience Conference on Antimicrobial Agents Chemotherapy (ICAAC); San Francisco, California, United States2012.


