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ISHLT GUIDELINES

The 2015 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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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 anti-fungal prophylactic strategies.[1–5] In the absence of existing clinical trials, the International Society for Heart and Lung Transplantation (ISHLT) Infectious Diseases Council has committed to convening an international and multidisciplinary panel of experts in the field to address the issue. The panel members are recognized leaders in the field of heart and lung transplantation and mechanical circulatory support devices (MCSDs), 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,

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Table 1 Important Definitions Used in the Document

Term	Definition
Colonization	Presence of fungus in the respiratory secretions (sputum or bronchoalveolar lavage [BAL]) detected by the culture, polymerase chain reaction (PCR) or biomarker (galactomannan [GM]/ cryptococcal antigen) in the **absence** of symptoms, radiologic, **and** endobronchial changes.[6]
Invasive fungal disease (IFD)	Presence of fungus in the respiratory secretions (sputum or BAL) detected by the culture, PCR, or biomarker (GM/cryptococcal antigen) in the **presence** of symptoms, radiologic, **and** endobronchial changes, **or** presence of histologic changes consistent with fungal invasion of the tissue.[6]
Universal anti-fungal prophylaxis	Refers to an anti-fungal medication started in the post-operative period in all patients, before any post-transplant isolation of a fungal pathogen.
Targeted anti-fungal prophylaxis	Refers to an anti-fungal medication started in the post-operative period, before any post-transplant isolation of a fungal pathogen or serologic marker of fungus, which is prescribed only to patients deemed at higher risk for IFD (e.g., cystic fibrosis patients and those with pre-transplant fungal colonization/infection or on augmented immunosuppression).
Preemptive anti-fungal therapy	Refers to an anti-fungal medication started after post-transplant isolation of a fungal pathogen or serologic marker of fungus in the absence of any evidence for IFD.
Attack rate	Refers to the cumulative incidence of IFD over time in a colonized transplant recipient.

prophylaxis, and treatment of FIs, including therapeutic drug monitoring (TDM) of anti-fungal agents in adult and pediatric heart, lung, and MCSD patients. The panel was subsequently divided into working groups, each headed by their respective chairs, for epidemiology, diagnosis, prophylaxis, treatment, TDM, and pediatrics. A comprehensive literature search was performed by the panel chairs and was disseminated to the working groups. The working groups reviewed the existing literature to answer the identified questions based on the published evidence or, in the absence of published evidence, to provide guidance based on 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 recommendations were graded according to ISHLT Standards and Guidelines Committee documents. 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 cochairs. The articles were modified based on the feedback of the cochairs. The executive summaries for each topic were generated from the articles by the cochairs 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 jiroveci, Cryptococcus*, and endemic mycoses in CT recipients (Table 1 and Table 2).

Adult epidemiology

Incidence/prevalence of fungal colonization in lung transplant candidates

Evidence summary

All information on fungal colonization in lung transplant (LT) candidates has been obtained from observational studies, most of them from single centers. 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 is a distinct lack of data regarding colonization rates at different times pre-transplant (e.g., 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 before LT. In a study examining explanted lungs, the overall prevalence was 5% (14 of 304),[7] whereas in studies with greater proportions of CF patients, 8% to 59% of patients were colonized with fungi, of which most of the isolates were *Aspergillus* species.[8–11] The data on non-CF populations have been scarce, and studies have reported a prevalence of 0% to 52%.[8,9] Multicenter studies with diverse geographic

Table 2 International Society for Heart and Lung Transplantation Standards and Guidelines Committee Grading Criteria

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

distributions, representative pre-transplant diagnoses, and standardized sampling techniques are needed to more accurately determine the prevalence of fungal colonization in LT candidates.

Incidence/prevalence of fungal colonization in LT recipients

Evidence summary

Multiple studies have assessed the presence of fungal colonization in LT recipients (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 LT.[12–21] 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.[12–21] 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).[7–11,19,22] 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.[23] Of all the *Aspergillus* species, *A fumigatus* was the most common (59%), followed by *A flavus* (35%).

Incidence/prevalence of invasive fungal disease after LT

Evidence summary

The incidence of invasive fungal disease (IFD) is much lower than that of fungal colonization after LT,[9,10,19] with rates ranging from 3% to 14%. The rate in the largest series was closer to the lower percentage limit (e.g., 6.6% in 1 series with 335 patients and 8.6% in a large, multicenter trial).[7–18,24–27] When the rarer but potentially severe invasive infection with *Mucorales* was examined, the rate was lower again, between 0.28% and 1.4%.[26,28] In this setting, a pre-transplant diagnosis of CF was once again associated with an increased risk of post-transplant IFD.[8–10]

Incidence/prevalence of IFD after heart transplantation

Evidence summary

A paucity of studies have examined the incidence/prevalence of IFD after heart transplantation. The incidence in available studies has ranged from 0.12 per patient-year to 0.4 per 100 patient-years.[21,27] 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.[26] *Candida* species accounted for 49% of the infections, and *Aspergillus* species accounted for 23%. More than 50% of the infections occurred in the first 90 days.[26] Overall, IFD after heart transplantation is rare; when it occurs, it is usually during the first year after 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 3 months has been identified as a risk factor for early IA after heart transplantation; therefore, it is important that centers know their own epidemiology.[19] This area requires further study.

Timing of IFD after lung and heart transplantation

Evidence summary

Multiple case series have addressed this question, although no well-controlled trials have been performed to date.[8,9,13–15,25,29,30] These studies have included patients who have undergone heart-lung transplant, single LT, and bilateral LT, and all have demonstrated that invasive infections tend to occur during the first 6 months after transplant. Surveillance and interaction with the health care team is always more common during the first year after transplant, and thus, sampling bias might have played a role in the findings. However, immunosuppression is highest during the same time period, 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), most infections occurred in the first 3 months after transplant for both lung and heart transplants. Approximately 66% occurred during that interval, with total incidences in the first year of 8.6% and 4.0% for lung and heart transplant recipients, respectively.[26] This is in contrast to a previously reported literature review where a median time to onset of IA was 3.2 months.[25] The increase in the time to onset of IA in LTRs may be attributed to the widespread use of anti-fungal prophylaxis.[3]

Another study found that invasive candidiasis (IC) occurred at 52 days (range, 0–5,727 days) in LTR and at 66.5 days (range, 2–4,645 days) in heart transplant recipients, whereas IA was noted at 504 days (range, 3–4,417 days) in LTRs and at 382 days (range, 31–1,309) in heart transplant recipients.[31] A study of heart transplant recipients reported IA which occurred during the first 3 months after transplantation (early IA) accounted for 23 cases (median, 35 days [range 19–88 days] after transplantation); in the remaining 8 cases, IA occurred a median of 125.5 days (range, 91–301 days) after transplantation (late IA).[32]

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 LT.

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 LT.[8–10,19,22]

Other important risk factors for IFD after LT include the presence of fungal colonization before or early after LT. 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.[7,8,22] Early post-transplant colonization was associated with an increased risk of IFD, with a significantly increased risk in multiple studies (e.g., OR of up to 11).[13,16,28] The risk was augmented by the presence of acute rejection in the setting of early post-transplant colonization.[23] Other risk factors that have been implicated include chronic rejection, cytomegalovirus (CMV) infection, and hypogammaglobulinemia (HG).[22,23]

The type of transplant (single vs double); use of tacrolimus, cyclosporine, or sirolimus[21]; primary graft dysfunction; and airway stents have also been demonstrated to be risk factors for the development of IFD.[10,21,23,25,33] Transplant clinicians should consider these factors when they decide how to approach prophylaxis of LTRs.

In heart transplant recipients, reoperation (relative risk [RR], 5.8; 95% confidence interval [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 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.[34]

Pediatrics epidemiology

Pediatric LT is now an accepted therapy that offers carefully selected children a survival benefit.[35,36] FIs are burdensome for pediatric LT patients; however, epidemiologic data on the effect of FIs in pediatric LT have been sparse.

Most children undergo LT for end-stage CF lung disease, and many of these patients are chronically colonized with fungal pathogens. In a retrospective, single-center study from Texas Children's Hospital, 29 children (70%) were colonized before transplantation.[37] 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 of 29) and *Aspergillus* (11 of 29) species were more commonly recovered than *Scedosporium* and *Basidiomycetes*. Before LT, *Aspergillus* species are among the most important pathogens of pulmonary FIs, and the effect of pre-transplantation FI has not been assessed because anti-fungal prophylactic therapy is more frequently used today.[38] In CF patients, *Scedosporium* species have been documented more often than in non-CF patients.[39]

Incidence/prevalence of fungal colonization in LTRs

Evidence summary

Only 1 study to date has assessed colonization specifically after transplantation in the pediatric age group. In this cohort, 33 patients (60%) were colonized after transplantation.[37] In a multivariate analysis, fungal colonization after LT was associated with older patient age (hazard ratio [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).[37] CF was not associated with an increased risk of post-transplant fungal colonization.

Incidence/prevalence of IFD after LT

Evidence summary

The incidence of IFD after LT is variable, ranging from 0% to 20%.[37,40] The largest study to investigate epidemiology, risk factors, morbidity, and mortality within the first year after LT in children was conducted retrospectively and included 555 pediatric patients at 12 centers in North America and Europe.[41] In this study, 10.5% of the recipients developed proven (*Candida, Aspergillus,* or other) or probable (*Aspergillus* or other) pulmonary FIs during the first year after LT.[41] In this cohort, FI was independently correlated with lower 12-month post-transplantation survival.[41]

A recent, large epidemiologic study reporting outcomes of 960 immunocompromised patients with probable/proven IA from the Prospective Anti-fungal Therapy Alliance 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 SOT, 66.1% of whom were LTRs.[42]

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 LT in 190 children who underwent primary LT at St. Louis Children's Hospital between 1990 and 2000.[43] Another single-center study in the United States determined that post-operative FI was a significant risk factor for the development of bronchial airway anastomotic complications after pediatric LT.[44] The distribution of organisms in single-center studies are biased by factors such as the geography and use of microbiologic tools.

Incidence/prevalence of IFD after heart transplantation

Evidence summary

The epidemiology of FIs in pediatric cardiac transplantation was not substantially evaluated until recently. Groetzner et al[45] reported in 2005 that FIs were "rare" after cardiac transplantation. Data from the Prospective Anti-fungal Therapy Alliance registry reported that only 24 of 960 IA infections occurred in cardiac transplant recipients, most of whom were likely adults based on the population's demographics.[42] Importantly, 2 large studies from the Pediatric Heart Transplant Study (PHTS) recently described the epidemiology of, and associated risks for FIs.[46,47] Zaoutis et al[47] reported 1,854 pediatric patients in the PHTS database who underwent transplants between 1993 and 2004. Of these, 123 patients had 139 episodes with yeast

(66.2%), mold (15.8%), and *Pneumocystis jiroveci* (13%). *Candida* species caused 90% of the yeast infections (*C albicans*, 55%; *C parapsilosis*, 13%; *C krusei*, 4%; *C glabrata*, 2%; and *C tropicalis*, 2%), and *Aspergillus* spp (9 pulmonary, 5 cutaneous, and 1 each central nervous system, sinus, mediastinal tumor, and unspecified) caused 82% of the mold infections. The remaining 4 mold infections were caused by *Mucorales* ($n = 3$) and *Exserohilum* species ($n = 1$). Infections caused by *Trichosporon* species (bloodstream), *Trichophyton tonsurans* (bloodstream), and *Pityrosporum* species (cutaneous) were identified in 1 patient each. Of the recipients with IFD, 49% died within 6 months after transplant. Death occurred in 13 of the 22 patients (59%) with mold infections and in 43 of the 92 patients (47%) with yeast infections.

Timing of IFD after lung and heart transplantation

Evidence summary

In the study by Zaoutis et al,[47] the greatest risk for IFD in heart transplant recipients occurred during the first 2 months after transplant. In a study from Texas,[37] colonization in LTRs occurred at a mean of 58 days after transplant, and IFD occurred at a mean of 271 days after transplant (range, 9–925 days).

Risk factors for IFD after lung and heart transplantation

Evidence summary

Risk factors for FIs in pediatric cardiac transplantation were not substantially evaluated until recently. Two studies based on PHTS data suggested that IFI was associated with pretransplant invasive procedures. First, the Zaoutis et al[47] study reported an incremental risk of IFD 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. Using similar data, Gajarski et al[46] detailed an increased risk of IFI with the use of ventricular assist devices (VADs)/ extracorporeal membrane oxygenation (ECMO) pretransplant. Patients with underlying congenital heart disease also had an increased risk of IFD compared with those who received transplants for cardiomyopathy.[46]

Only a few studies have addressed risk factors for FIs after pediatric LT. Risk factors for IFI have included pretransplantation colonization, CMV mismatch, tacrolimus-based immunosuppression regimen, older age (>15 years old), acute cellular rejection (grade >A2), and HG (immunoglobulin A and M), all of which were significantly associated with IA[38,41,48] (Table 3).

Table 3 Summary of Recommendations for Epidemiology in Cardiothoracic Transplant Candidates and Recipients (International Society for Heart and Lung Transplantation Standards and Guidelines 2013)

Statement	Class of recommendation	Level of evidence	Applies to heart Tx	Applies to lung Tx	Message
Adults					
The incidence of fungal colonization in cardiothoracic candidates and recipients is not categoric.	I	B	✓	✓	Prospective multicenter studies should be performed to determine the incidence of fungal colonization in cardiothoracic candidates and recipients.
Cardiothoracic recipients should have fungal colonization diagnosed or excluded before Tx.	I	B	✓	✓	
The risk of developing IFD should be evaluated before and after cardiothoracic Tx.	I	C	✓	✓	All patients pre- and post-Tx should be evaluated for their risk of developing IFD.
Each center should have an understanding of its local IFD epidemiology in cardiothoracic Tx recipients.	I	B	✓	✓	
Pediatrics					
Evaluation of fungal colonization before Tx should be encouraged, particularly for patients with an underlying diagnosis of CF.	I	B		✓	
Risk factors for IFD should be routinely assessed in pre-Tx and post-Tx cardiothoracic patients.	I	C	✓	✓	Mainly Lung Tx: pre-TX colonization: pre-Tx invasive procedures, patients with underlying congenital heart disease.

CF, cystic fibrosis; IFD, invasive fungal disease; Tx, transplantation.

Adult diagnosis

The role of serum galactomannan in diagnosing IA in CT recipients

Evidence summary

One of the main limitations of the enzyme-linked immunosorbent assay galactomannan (GM) test is its reduced sensitivity in non-neutropenic individuals. One meta-analysis[49] showed the sensitivity of serum GM testing was 82% in a hematology population and 22% in SOT patients.

Most studies conducted in SOT recipients have shown that serum GM testing is associated with an unacceptably low sensitivity for the diagnosis of IA.[50,51] Husain et al[52] demonstrated that the test had a sensitivity of only 30% in CT recipients. In another prospective study in LTRs, the median serum GM index for LTRs with IA was 0.3, a value less than the cutoff for positivity (e.g., 0.5).[53]

The role of bronchoalveolar lavage GM in diagnosing IA in CT recipients

Evidence summary

The utility of bronchoalveolar lavage (BAL) GM was evaluated in a meta-analysis of 13 studies[54–56] that included adult and pediatric patients with hematologic malignancies, SOT, and/or solid malignancies. Overall, when a positivity cutoff threshold of 0.5 was used, the pooled sensitivity was between 82% and 86% and specificity was between 89% and 92%, respectively.

The utility of BAL GM in CT recipients was specifically evaluated in 5 studies.[53,57–60] When a positivity cutoff value of 0.5 was used, the sensitivity of BAL GM ranged from 77% to 100%, and the specificity was 40% to 100%. Raising the cutoff threshold value from 0.5 to 1.0 improved the specificity without compromising the sensitivity in 3 studies.[53,57,61] However, 1 study reported a significant sensitivity loss (93% to 67%) when the cutoff value was increased to 1.0.[59] 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 anti-fungal therapy.[62]

The role of BAL *Aspergillus* polymerase chain reaction in diagnosing IA

Evidence summary

Aspergillus polymerase chain reaction (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.[63] Detection of BAL *Aspergillus* PCR yielded similar results, with a median pooled sensitivity of 79%.[64]

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 anti-fungal resistance.[65] A positive *Aspergillus* PCR test cannot distinguish between colonization and IFD. Additional disadvantages of the *Aspergillus* PCR assay (compared with 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 anti-fungal susceptibility. Nested PCR should be avoided; real-time PCR is the preferred assay format.

Two standardized *Aspergillus* assays, Viracor (Viracor-IBT Laboratories) and MycAssay (Myconostica), have been evaluated. Compared with GM BAL, the Viracor pan-*Aspergillus* PCR BAL was more sensitive (100% vs 93%) for the detection of IFD; 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, and only 1 study has evaluated the performance of the Viracor pan-*Aspergillus* PCR assay in LTRs.

The role of the (1→3) β-D-glucan test in the diagnosis of IA in CT recipients

Evidence summary

Another component of the fungal cell wall that is released into the circulation during IFD is (1→3) β-D-glucan (BDG). Although 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 (e.g., *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%.[66–68] Subgroup analyses in these studies suggested similar diagnostic accuracy of IA and IC.

The only prospective study in post-CT recipients was designed to assess the utility of serial monitoring of LTRs with the BDG assay through Day 180. Serum BDG (cutoff threshold of 60 pg/ml; Fungitell test [Viracor-IBT]) 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, but 3 cases of probable pulmonary IA were not detected.[69] Hemodialysis was associated with falsely elevated BDG levels; however, this finding alone did not explain most of the false-positive test results. In a prospective study of 135

SOT recipients with proven, probable, or no IFI, the reported sensitivity was 79.2% and the specificity was merely 38.5%.[70]

Lateral flow device test

Evidence summary

The lateral flow device (LFD) test is a rapid single-sample point-of-care test that is based on the detection of an *Aspergillus* extracellular glycoprotein antigen by monoclonal antibody JF5. Recently, comparative data started emerging in SOT recipients in a semi-prospective study including 26 LTRs and 2 heart transplant recipients. The reported sensitivity and specificity was 91% and 83%, respectively.[71]

Radiologic criteria for invasive mold disease (IFD) in LTRs

Evidence summary

IA in SOT recipients occurs more commonly as an airway disease than as an angioinvasive infection. In a study of 62 individuals with IA,[72] the "halo sign" was observed in 56% (15 of 27) and in 8% (2 of 26) of neutropenic and SOT recipients ($p < 0.001$), respectively, and macronodules occurred in 67% (18 of 27) and in 35% (9 of 26; $p = 0.02$). By contrast, peribronchial consolidations were observed in 7% (2 of 27) of neutropenic patients and in 31% (8 of 26) of SOT recipients ($p = 0.03$), and ground-glass opacities were observed in 7% (2 of 27) and 38% (10 of 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. A recent study found an airway invasive pattern represented 37% of IPA episodes in heart transplant recipients and was associated with a more protracted clinical presentation, later diagnosis, and higher mortality rate.[73]

Limited data are available regarding the radiologic 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; Table 4).

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 IFD in pediatric CT are suggested.

Recommendation

No recommendation. See Diagnosis section in adults.

Adult prophylaxis

The effect of pre-transplant treatment of fungal colonization/infection on post-transplant outcomes and the circumstances in which treatment should 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

Table 4 Summary of Recommendations for Diagnosis of Aspergillosis in Adult Cardiothoracic Transplant Recipients

Recommendation	Class of recommendation	Level of evidence	Applies to heart Tx	Applies to lung Tx
Serum GM should not be used for the diagnosis of IA.	I	C	✓	✓
BAL-GM can be used for IA diagnosis.	I	B	✓	✓
Optimal cutoff value for positivity for BAL-GM is unknown. • Using a cutoff of 1.0 increases specificity. • Using a cutoff of 0.5 optimizes sensitivity but false positives can occur so caution should be used in interpreting the results.	I	B	✓	✓
BAL-GM can be used to distinguish between colonization and IFD.	I	C		✓
BAL-GM can be used in Tx centers to switch from universal prophylaxis to preemptive treatment.	II	C		✓
Routine use of BAL-PCR is not recommended.	II	C	✓	✓
BAL-PCR should only be used in combination with other fungal diagnostics (e.g., chest CT scan, BAL-GM, culture) for IA diagnosis.	II	C	✓	✓
The use of BAL-BDG is not recommended.	III	B	✓	✓
Only 2 radiologic features are consistent with IFD diagnosis: • Early post-Tx (usually first 3 months)—tree-in-bud nodules and bronchial wall thickening. • Late post-Tx (> 1 year)—parenchymal nodules.	II	C		✓

BAL, bronchoalveolar lavage; BDG, β-D-glucan; CT, computed tomography; GM, galactomannan; IA, invasive aspergillosis; IFD, invasive fungal disease; PCR, polymerase chain reaction; Tx, transplantation.

bronchopulmonary aspergillosis (up to 50%),[76] aspergilloma/mycetoma (3%),[77] chronic necrotizing/cavitary pulmonary aspergillosis or semi-invasive disease (2.3%),[7] and IPA (1.1%).[8] Patients in whom pre-transplant mycetomas were detected only in explanted lungs had poor post-transplant outcomes despite aggressive anti-fungal therapy.[77] Pre-transplant mold colonization is a well-described risk factor for post-transplant IFD.[7,76] No data are available on whether pre-transplant treatment improves post-transplant outcomes.

The use of preemptive treatment vs universal prophylaxis in the early period after LT

Evidence summary

Two main strategies have been used.[1,2] Universal prophylaxis is defined as the administration of anti-fungal agent(s) to all patients during the immediate post-transplant period. Preemptive treatment is defined as the administration of anti-fungal agents for mold isolated during surveillance post-transplant bronchoscopy without evidence of invasive disease (e.g., colonization).[2] No randomized trials comparing the 2 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 a 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%, 6 months post-transplant).[2]

The highest risk for IC occurs during the immediate post-transplant period (first 30 days), and there are sequential cohort data indicating the effectiveness of universal prophylaxis targeting *Candida* species during the immediate post-transplant period.[79] From 30 days forward, molds predominate in 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 (e.g., *Cladosporium* species) representing the lowest risk for progression to IFD.[30] Preemptive therapy in the setting of *Scedosporium prolificans* isolation might be warranted, given its predilection for dissemination.[80,81] However, resistance to available anti-fungal agents makes effective management of this organism very difficult. 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 anti-fungal preemptive therapy could reduce the use of anti-fungal agents (compared with universal prophylaxis) by 43%, without missing any IA cases.[62] 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.

Effective and safe anti-fungal prophylaxis after 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, 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.[27,86–88] 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 30 days after transplantation, it is essential that agents with good *Aspergillus* species activity be used. Multiple observational studies have supported the safety of inhaled AmB in the deoxycholate (AmB-d) or lipid (formulation,[24,27,86,88,90–94] with some evidence for safety and efficacy in uncontrolled studies[88,90,92] and in a recent meta-analysis.[78] No head-to-head data have been published comparing the efficacy of the various azole anti-fungal agents; however, retrospective cohort studies have supported the efficacy of voriconazole.[12,17,95] Despite these findings, voriconazole has been associated with significant toxicity, most particularly central nervous system adverse effects, drug–drug interactions, and as most recently recognized, an increased risk of squamous cell carcinoma 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]

Duration of anti-fungal prophylaxis after 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 6 months after transplant,[12,23,25,105] and an observational study indicated that at least 4 months of universal voriconazole prophylaxis effectively reduced the risk of IFD.[12] Observational studies of preemptive treatment have indicated that 85 days to 4.2 months of mold-active azole therapy was associated with a low incidence of IFD.[95,106] However, long-term voriconazole use has been associated with the development of squamous cell carcinoma and periostitis.[96–99,107–109]

Anti-fungal prophylaxis beyond the early post-transplant period

Evidence summary

Beyond the early post-transplant period (first 6 months), other times when the risk of IFD is increased include acute

Table 5 Summary of Recommendations for Prophylaxis in Adult and Pediatric Cardiothoracic Transplant Candidates and Recipients

Recommendation	Class of recommendation	Level of evidence	Applies to heart Tx	Applies to lung Tx
All patients who isolate a mold and are being considered for Tx should have additional investigations to determine the precise infection category (e.g., aspergilloma, colonization, ABPA).	I	C		✓
Mold airway colonization does not require treatment in all patients being considered for Tx.	I	C		✓
All patients with pre-Tx mold airway colonization should receive anti-fungal therapy in the early post-Tx period.	I	C		✓
The presence of an aspergilloma[a] should prompt reassessment of candidacy for Tx.	I	C		✓
Any patient with an aspergilloma[a] who is considered suitable for Tx should have anti-fungal therapy started pre-Tx and continued post-Tx. Careful planning of the Tx procedure should be implemented.	I	C		✓
The decision of any Tx center to use universal prophylaxis or PE treatment should be determined by local epidemiology, time post-Tx, and access to fungal diagnostics and TDM.	II	B		✓
Both universal prophylaxis and PE treatment may be suitable for use in any given Tx center. The choice is dependent on the time post-Tx.	II	B		✓
Depending on local epidemiology, universal prophylaxis with agents that have systemic activity against *Candida* species should be considered in the immediate post-Tx period (i.e., first 2–4 weeks).	II	B		✓
After the immediate post-Tx period (i.e., first 2–4 weeks) mold-active universal prophylaxis or PE therapy should be used.	II	B		✓
If a PE strategy is used, it should incorporate BAL-GM surveillance and TDM.	II	C		✓
nAmB ± fluconazole or an echinocandin (depending on local epidemiology) should be used in the first 2–4 weeks post-Tx to target *Candida* species.	I	B		✓
All centers should perform surveillance to determine the incidence of resistant *Candida* and *Aspergillus* species and the emergence of other fungi.	I	B	✓	✓
Photo-protective measures and enhanced surveillance for skin cancers should be implemented if voriconazole is prescribed.	I	C	✓	✓
Voriconazole should be prescribed with caution in those: • With a history of cutaneous SCC. • On other photo-sensitizing drug.[b] • From geographic areas with a high incidence of cutaneous malignancy.	I	B	✓	✓
A total of 4–6 months of universal prophylaxis is recommended.	II	C		✓
A total of 3–4 months of PE therapy is recommended.	II	C		✓
Voriconazole should be used with caution for periods longer than 6–9 months.	I	C	✓	✓
Anti-fungal prophylaxis should be considered during periods of increased risk for IFD (e.g., augmented immunosuppression).	II	C		✓
In the pediatric population, pre-Tx mold airway isolation should be treated with anti-fungal therapy in the early post-Tx period.	I	C		✓

ABPA, allergic bronchopulmonary aspergillosis; BAL, bronchoalveolar lavage; IFD, invasive fungal disease; nAmB, nebulized amphotericin B; PE, preemptive; SCC, squamous cell carcinoma; TDM, therapeutic drug monitoring; Tx, transplantation.

[a]Semi-invasive or invasive.

[b]For example, trimethoprim-sulfamethoxazole, ciprofloxacin, tetracyclines, diuretics, amiodarone, and angiotensin-converting enzyme inhibitors.

and chronic rejection,[105,110] augmented immunosuppression, and CMV infection,[23] but no studies have been performed specifically to determine the magnitude of these risks or the efficacy of anti-fungal prophylaxis during these periods of increased risk (Table 5).

Pediatric prophylaxis

Very limited data exist to respond to any of the questions related to anti-fungal prophylaxis for pediatric LTRs, and a recent multicenter survey showed the wide range of anti-fungal prophylaxis strategies as current international practice in pediatric LTRs.[111]

The effect of pre-transplant treatment of fungal colonization/infection on post-transplant outcomes and the circumstances in which treatment should be considered

Evidence summary

Two studies have addressed this first question. First, a large, retrospective, multicenter assessment in North America and Europe noted that pre-transplant colonization was associated with an increased risk of post-transplant pulmonary FI.[42] 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.[37]

The use of preemptive treatment vs. universal prophylaxis during the early period after LT

Evidence summary

No published data.

Effective and safe anti-fungal prophylaxis after LT

Evidence summary

No published data.

Anti-fungal prophylaxis duration after LT

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 of 33 with pre-transplantation fungal colonization), and prophylaxis was administered for a median of 51 days (range, 14–272 days).[37] In the large International Pediatric Lung Transplant Collaborative study conducted at 12 pediatric LT centers, anti-fungal prophylaxis was not unified or well described.[41] The optimal duration of prophylaxis is uncertain.

Anti-fungal prophylaxis beyond the early post-transplant period

Evidence summary

No published data.

Adult therapy

The role of combination anti-fungal 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 anti-fungal 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 sub-sets. Singh et al[112] performed a retrospective, multicenter comparison of 40 SOT recipients with IA treated with combination voriconazole and caspofungin, and 47 treated with lipid formulations of AmB (L-AmB). No statistically significant difference in 90-day survival was found overall; however, the sub-groups with renal failure and with *A fumigatus* infections did show significantly improved 90-day survival. More recently, Marr et al[113] performed a randomized, multicenter, multinational trial to compare combination therapy with voriconazole plus anidulafungin vs voriconazole alone in 454 patients with hematologic malignancies or who underwent hematopoietic stem cell transplantation. Combination azole/echinocandin therapy was administered for 2 to 4 weeks, followed by continuation of voriconazole. There was a trend toward decreased mortality at 6 weeks ($p = 0.09$) in the combination therapy group, and this trend was statistically significant in patients who were diagnosed based on serum or BAL GM (6-week mortality of 15.7% 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 sub-groups of patients might benefit from combination therapy.

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 anti-fungals (nAmB -d or nL-AmB) as an adjunctive or primary therapy has been proposed.

The idea of delivering anti-fungal agents directly to the airway is intuitively appealing and has the goal of delivering a high concentration to the infected area while avoiding systemic toxicity.[116] However, evidence is lacking at this time 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 before 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 combined with systemic voriconazole and nAmB.[117] Although intriguing, more evidence is needed before this approach could become standard.

Aerosolized AmB in the treatment of IPA

Evidence summary

Studies have been published on the use of nAmB for prophylaxis against IFD in LT (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.

Evidence for an additive benefit of nAmB in the treatment of IA is limited because studies of this agent have primarily focused on prophylaxis rather than treatment. However, nAmB could be used in combination with voriconazole/other systemic anti-fungal 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.

Treatment 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 (previously known as bronchiolitis obliterans syndrome [BOS]). Such research has raised the question of whether any intervention with anti-fungal 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[15] studied 201 LTRs and determined that colonization with *Aspergillus* species was independently associated with BOS and BOS-related mortality. *Aspergillus* colonization preceded BOS by a median of 261 days.[15] More recent results from the University of California Los Angeles 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 et al[118] reported that isolation of *Aspergillus* species from the respiratory tract of LTRs was associated with increased mortality (HR, 2.2). In addition, Sole et al[23] determined that *Aspergillus* infection was significantly associated with increased 5-year mortality, particularly for invasive infections, bronchial anastomotic infections, late-onset disease, and chronic allograft dysfunction. In this study, the isolation of *Aspergillus* from the airways preceded acute rejection.[23]

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. However, whether systemic anti-fungal therapy will prevent these allograft outcomes is less clear. Well-designed observational studies in this area are urgently needed.

Maintenance anti-fungal therapy after successful therapy for an IFD

Evidence summary

Given the severity of aspergillosis and other IFDs in transplant recipients, clinicians are sometimes tempted 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)[108,119,120] have called such practices into question. At the present time, there is no firm evidence for prolonging anti-fungal 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 LT, and/or chronic allograft dysfunction, augmentation of immunosuppression, or other factors (e.g., CMV infection; Table 6).

Pediatrics therapy

Combination anti-fungal therapy has been addressed in only 1 single-center study that evaluated results in 11 patients[37] (azole and AmB or an echinocandin; some subjects received aerosolized amphotericin as part of the therapy).

Aerosolized AmB in the treatment of IPA

Evidence summary

No published data.

Treatment for colonization with filamentous fungi in protocol BAL cultures

Evidence summary

No published data.

Maintenance anti-fungal therapy after successful therapy for an IFD

Evidence summary

No published data.

Recommendation. Data regarding the treatment of IFD have not been substantially reported in the pediatric CT literature. Further investigation is warranted into combination anti-fungal therapy, aerosolized therapeutics, and maintenance anti-fungal therapy after treatment for IFD in patients with pediatric CT.

No specific recommendation. See Treatment section.

Adult therapeutic drug monitoring

TDM for azole anti-fungal agents

Evidence summary

Much of the data on the use of TDM for azoles have come from other patient groups (e.g., the hematopoietic stem cell transplantation population). One retrospective audit of heart and lung transplant recipients demonstrated considerable

Table 6 Summary of Recommendations for Treatment in Adult Cardiothoracic Transplant Candidates and Recipients

Recommendation (treatment or procedure)	Class of recommendation	Level of evidence	Applies to heart Tx	Applies to lung Tx	Message
Combination anti-fungal therapy.	IIb	B	✓	✓	This therapy cannot be recommended routinely as primary treatment for IA.
Combination therapy should not be used for more than 2 weeks.[a]	IIb	C	✓	✓	Azole monotherapy should be used beyond the 2-week time point until clinical and radiographic resolution has occurred.
NAmB as primary treatment for tracheobronchitis and/or anastomotic infection.	III	C	✓	✓	nAmB should not be used alone as primary treatment.
The addition of nAmB to standard regimens for treatment of pulmonary IA.	III	C	✓	✓	Not recommended.
Fungal colonization despite voriconazole treatment, check plasma concentration of azole.	I	C	✓	✓	If asymptomatic fungal colonization develops on azole therapy, ensure that the plasma concentrations of voriconazole are adequate before any change of anti-fungal drug.
Voriconazole, posaconazole or itraconazole can be used as PE therapy.	I	B	✓	✓	Check plasma concentrations.
After cured IA, close monitoring of patients for relapses is recommended.	I	C	✓	✓	Once IA has been successfully treated, anti-fungal therapy can be discontinued and the patients should be closely monitored.
High-risk patients may be considered for longer courses of therapy or for secondary prophylaxis.	I	C	✓	✓	In such cases, careful monitoring with concentrations and for toxicity is recommended.

IA, invasive aspergillosis; nAmB, nebulized amphotericin B; PE, preemptive; Tx, Transplantation.
[a]Situations where combination therapy may be appropriate: high burden of infection (multilobar nodularity), hypoxia.

inter- and intrapatient variability in itraconazole concentrations and sub-therapeutic concentrations (see Table 7 for the therapeutic range).[121] IFD developed in 6 of 57 patients (10.5%), but itraconazole concentrations were sub-therapeutic in 3 (50%) of those with IFD (Table 7).[121] One prospective, observational study has specifically examined voriconazole TDM in the CT setting,[14] and only 32% of the patients had concentrations in the therapeutic range (Table 7).[14] Overall, IFD developed in 10%, and fungal colonization developed in 27%.[14] There was a trend toward significantly lower voriconazole concentrations in those patients with IFD or colonization compared with those who did not develop infections (1.72 mg/liter vs 0.92 mg/liter; $p = 0.07$).[14] Posaconazole (suspension) levels have only been examined in 1 cohort of CT patients, which revealed that the initial concentrations were sub-therapeutic (Table 7) in 47%, and patients with concentrations consistently > 0.5 mg/liter 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 MCSD. Posaconazole delayed-release tablets have recently been approved by the Federal Drug Administration for use as prophylaxis and second-line treatment of IA in clinical practice. This new formulation has more consistent bioavailability and minimal dietary requirements compared with the oral suspension.[123] Higher serum concentrations have been reported with the tablet formulation than with the oral suspension.[124] However, more data are required to determine the precise role that TDM plays with the use of new delayed-release tablet formulation of posaconazole in clinical practice (Table 7 and Table 8).

Table 7 Target Trough and Peak Concentrations for the Various Azole Agents in Adults[a]

Anti-fungal drug	Target trough (mg/liter)		Upper limit of non-toxic range or peak (mg/liter)
	Prophylaxis	Treatment	
Itraconazole	0.5	0.5–1	2
Voriconazole	1-2	1–2[a]	4–5
Posaconazole	0.7	1.25	Not available

[b]Higher concentrations may be required for specific infections (e.g., central nervous system infections)[126]
[a]Adapted by permission from Macmillan Publishers Ltd: Bone Marrow Transplant[125]

Table 8 Measures to Maximize the Absorption of Posaconazole Suspension in Adults[a]

Coadminister posaconazole with 1 or more of the following (with each dose of posaconazole suspension)
• 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 400 mg of posaconazole per dose
• Regimens of 200 mg TID/QID (preferred) or 400 mg BID
Avoid proton pump inhibitors
• Use of H_2 antagonists allowed if needed but can result in reduced posaconazole concentrations
• Use of aluminum- or magnesium-containing antacids allowed if needed, but good data to ascertain effect on posaconazole concentrations are not available
Coadministration of drugs that increase posaconazole clearance or impair absorption is to be avoided (i.e., cimetidine, phenytoin, rifamycin derivatives)

QID, 4 times/day; TDS, 3 times/day.
[a]Adapted by permission from Macmillan Publishers Ltd: Mycoses[127] and from Ananda-Rajah et al.[128]

TDM in clarifying toxicity/drug–drug interaction

Evidence summary

Voriconazole, itraconazole, and fluconazole are metabolized by the cytochrome P450 system, as are many other agents administered to CT patients and to those with MCSD (Tables 9A and 9B), which may result in under-exposure or over-exposure to the azole being used and/or the interacting drug being coadministered. 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.

Table 9 Drugs Commonly Used in Cardiothoracic Transplant Settings that Interact with Azole Anti-fungal Agents 9A: Increase in Exposure of a Given Drug Due to Azole Use

Drug A[a]	Flu	Itra	Posa	Vori
Amitriptyline[a]	(↑)	(↑)		
Calcium channel blockers	(↑)	(↑)		(↑)
Lovastatin/simvastatin		↑		(↑)
Methadone				(↑)
Midazolam	(↑)	(↑)	(↑)	(↑)
Oral anti-coagulants	(↑)	(↑)		(↑)
Oral hypoglycemics	(↑)	↑		(↑)
Tacrolimus	(↑)	(↑)	(↑)	(↑)
Cyclosporin	(↑)	(↑)	(↑)	(↑)
Sirolimus	(↑)	(↑)	X	X
Everolimus	(↑)	X	X	X

Flu, fluconazole; Itra, itraconazole; Posa, posaconazole; Vori, voriconazole; X, contraindicated.
[a]Drug A refers to the drug in question in each row. For example in row 1 it is what happens to amitriptyline in the setting of azole administration. Arrows in parenthesis show clinically significant interaction.

TDM in determining optimal dose regimens for CF patients

Evidence summary

CF patients are a special group of CT patients who have a number of characteristics that can influence the pharmacokinetics of azole anti-fungal agents, including (1) younger age, (2) relatively lower body mass index, (3) altered gastrointestinal function (e.g., delayed absorption), (4) bile-dependent malabsorption, (5) changes in the volume of distribution, (6) increased creatinine clearance, and (7) high rates of gastroesophageal reflux disease. An evolving body of evidence indicates that higher doses of azoles should be administered to achieve therapeutic concentrations in CF patients.[129,130]

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 higher or lower minimum inhibitory concentrations (MICs) than others.[29,131] 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 anti-fungal resistance patterns is critically important. To be effective, serum concentrations of azoles should exceed the MIC of the organism in question.

Drug assays within and between laboratories

Evidence summary

The technologies required are similar to those used for immunosuppressant drugs. The other requirements for the implementation of TDM at any given institution include (1) validation of a published assay, (2) a critical mass of patients requiring TDM, (3) a turn-around time (from sampling to results) of < 72 hours, (4) laboratory resources, and (5) 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.

Although participation in a recognized quality assurance TDM program is mandatory in many countries, further interlaboratory collaborations in this area are very important to identify gaps and areas for future investigation[132,133] (Table 10).

Pediatrics TDM

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

Table 9B Effect of Other Drugs on Azole Exposure and/or the Reciprocal Interacting Drug

Drug A[a]	Flu	Itra	Vori	Posa
H_2 antagonists and antacids		(↓azole)		(↓azole)
Proton pump inhibitors (PPI)		(↑PPI) (↓azole)	(↑PPI) (↓azole)	(↑PPI) (↓azole)
Carbamazepine (voriconazole contraindicated)		(↓ azole)	X	(↓azole)
Hydantoins (e.g., phenytoin)	↑hydantoin (↓azole)	↑hydantoin (↓azole)	↑hydantoin (↓azole)	↑hydantoin (↓azole)
Rifamycins (RF) (e.g., rifampicin\rifabutin)	(↑RF) (↓azole)	(↑RF) (↓azole)	(↑RF) (↓azole)	(↑RF) (↓azole)
Isoniazid		(↓azole)		

Flu, fluconazole; Itra, itraconazole; Posa, posaconazole; Vori, voriconazole; X = contraindicated
[a]Drug A refers to the drug in question in each row; for example, in row 5, Drug A refers to rifamycins and the effect these have on azole concentrations and the reciprocal effect azoles have on rifamycins. Arrows in parenthesis indicate clinically significant interaction.

Adult MCSD

Background

The field of MCSD has made tremendous progress in recent decades, with more than 30,000 patients receiving durable MCSDs worldwide.[134] The initial device design consisted of a pulsatile-flow pump, which could be intracorporeal or extracorporeal. During 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, smaller-width drivelines, and are intracorporeal.[135]

Infection is one of the major challenges in and limits to the successful use of MCSD. Device-specific and device-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.[136]

Table 10 Summary of Recommendations for Therapeutic Drug Monitoring in Adult and Pediatric Cardiothoracic Transplant Candidates and Recipients

Recommendation	Class of recommendation	Level of evidence	Applies to heart Tx	Applies to lung Tx
All patients on itraconazole should have trough concentrations measured 1–2 weeks after • Initiation. • Change in itraconazole dose. • Initiation, cessation, or change in the dose of an interaction drug.	I	C	✓	✓
All patients on voriconazole should have trough concentrations measured 5–7 days after • Initiation. • Change in voriconazole dose. • Initiation, cessation, or change in the dose of an interaction drug.	I	C	✓	✓
Voriconazole concentrations should be measured weekly until in therapeutic range (Table 5), and once in therapeutic range, every 2 weeks thereafter.	I	C	✓	✓
All patients receiving posaconazole suspension should have trough concentrations measured 7 days after • Initiation. • Change in posaconazole dose. • Initiation, cessation, or change in the dose of an interaction drug.	I	C	✓	✓
For patients receiving posaconazole suspension, it is recommended that a number of measures be taken to ensure adequate absorption (Table 6).	I	C	✓	✓
Fluconazole TDM is only recommended in unstable or critically ill patients in intensive care or in patients undergoing renal replacement therapy.	I	C	ü	ü
If an azole and an interacting drug are coadministered, then it is recommended that TDM be performed for both drugs.	I	C	✓	✓
Azole TDM should be performed in all post-Tx CF patients.	I	C		✓
TDM should be performed for all infections where the causative fungus has a high MIC or in centers with high rates of *Aspergillus* or *Candida* triazole resistance.	I	C	✓	✓
All centers preforming TDM should participate in external quality assurance programs.	I	C	✓	✓
The adult TDM recommendations can be extrapolated to the pediatric Tx populations with caution.	I	C	✓	✓

CF, cystic fibrosis; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring; Tx, transplantation.

Prevalence and spectrum of FIs in MCSD recipients

Evidence summary

The prevalence of FIs in MCSD 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 midyear data collection) was 11.79%, and the mean prevalence since 2000 has been 4.41% ($p = 0.01$).[136–156] Most FIs are caused by *Candida* species, with a few case reports of *Aspergillus* species and other mold infections.

Risk factors for developing a FI in MCSD recipients

Evidence summary

Use of total parenteral nutrition was significantly associated with the development of a fungal VAD infection in multivariate analysis in a study that compared bacterial and fungal VAD infections.[136] 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 total parenteral nutrition and 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 anti-biotics, the presence of central venous catheters, mechanical ventilation, the severity of illness, immunosuppression, and neutropenia.[157]

Effectiveness of anti-fungal prophylaxis in MCSD recipients

Evidence summary

Given the relatively high rates of FI seen in earlier studies, the use of anti-fungal agents for prophylaxis against MCSD infections has been of great interest. However, an analysis of the various studies demonstrated a similar mean rate of FIs in studies that did and did not use anti-fungal prophylaxis (11.78% vs 10.4%, respectively; $p = 0.9$).[136,158]

In summary, a low rate of FIs has been noted in recent studies, and no evidence has demonstrated that the routine use of anti-fungal prophylaxis decreases FIs in MCSD recipients.

FI management in a MCSD recipient

Evidence summary

Device-based infections in MCSD 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 central venous catheter infection have shown that L-AmB complex, caspofungin, micafungin, and anidulafungin lead to a significant decrease in biofilm fungal burden.[159–164]

Owing to the lack of publications regarding the treatment of FIs in MCSD recipients, we have based our recommendations on the published guidelines for the management of candidiasis and of infections of cardiac devices[157,164,165] (Table 11).

Pediatrics MCSD

MCSD have been increasing in use as the preferred intermediate and long-term means for MCSD in pediatric heart failure patients, predominantly as a bridge to transplant but also as bridge to recovery or destination therapy. Most of the pediatric literature focused on VADs has reported substantial complications related to infections after implantation. Single-center and multicenter case series have both consistently reported infectious episodes, including sepsis and non–device-related infections, in approximately 30% to 60% of patients.[166–171] Interestingly, Blume et al[166] reported infections in only 12% of 26 pediatric patients supported with devices designed for short-term use, and Miera et al[172] described no infectious events in their series of 7 patients supported with the HeartWare (HeartWare International) VAD. Device-related infections, predominantly infections involving the driveline, have been reported in 7% to 17% of patients.[170,173–175]

Few studies have reported the pathogens recovered in these device-associated infections, including the 2 largest series of pediatric device recipients by Blume et al[166] and Fraser et al,[173] but case series have reported *S aureus, S epidermidis, Pseudomonas aeruginosa,* and *C albicans.*[167,168,171,175,176] Specifically, *C albicans* was reported in 1 driveline infection and 1 urine culture among the combined 39 cases in which pathogens were reported.[167,168,171,175] In the most recent literature, Cabrera et al[177] reported 51 patients at a single institution, including 3 *Candida* species with mortality in 2 patients. The infections included an MCSD-specific *C albicans* infection and 2 MCSD-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.[170,173]

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

Future directions

The landscape of IFD in CT organ transplant recipients continues to evolve. Although more resistant fungal infections are on the horizon, the availability of novel preparations of azoles (e.g., posaconazole tablets or isavuconazole) provide better opportunities in prophylaxis and treatments of IFD. The development of novel point-of-care fungal diagnostic tests coupled with refinements in TDM may shape the future of fungal infection management.

Table 11 Summary of Recommendations for Mechanical Circulatory Support in Adults and Pediatrics

Recommendation	Class of recommendation	Level of evidence
Routine peri-operative anti-fungal prophylaxis for MCSD implantation is not recommended.	III	C
Pre-operative anti-fungal prophylaxis for MCSD implantation should be considered for certain high-risk populations. • On TPN. • Recent colonization with *Candida* species (≥3 sites). • Patients hospitalized and on broad-spectrum anti-biotics for >48–72 hours before MCSD implantation.	I	C
If peri-operative anti-fungal prophylaxis is administered (e.g., in high-risk patients) then 400–800 mg of fluconazole at the time of induction of anesthesia and then daily for up to 48 hours post-implantation is preferred.	IIb	C
Candida spp MCSD pump/cannula infections:		
• Recommend treatment with an echinocandin or L-AmB	I	C
• Therapy should be given for 8–12 weeks from the first negative blood culture, followed by long-term suppression with an oral agent.	I	C
• Flucytosine can be added to L-AmB in select patients.	IIa	C
• Routine device replacement in the setting of an FI is not recommended.	IIb	C
Candida spp pump/cannula infections:		
• Device exchange or placement on the cardiac transplant list is recommended if the patient has a relapse despite appropriate treatment (anti-fungal agent, dose, and duration).	IIa	C
• If replaced surgically, then anti-fungal agents should be continued for a minimum of 6 weeks and possibly longer if surgical cultures are positive.	IIa	C
Candida spp MCSD driveline/pocket infections:		
• Routine blood cultures should be performed to diagnose/rule out concomitant fungemia.	I	C
• Superficial infection in a clinically stable patient with negative blood cultures should be treated with an azole for a minimum of 2 weeks.	I	C
• If the depth of the infection cannot be determined (by physical examination, ultrasound, or CT) then the recommended treatment is the same as for a deep driveline/pocket infection.	I	C
• Deep drive-line/pocket infection should be treated with an echinocandin or L-AmB for 6–8 weeks, followed by long-term oral suppressive therapy thereafter.	I	C
• Surgical drainage may be required for control of extensive infection.	IIa	C
• Routine device replacement in the setting of an FI is not recommended.	IIa	C
• If the device requires replacement then the new driveline needs to be placed in a different site.	IIa	C
• If replaced surgically or after cardiac transplantation, then anti-fungal agents should be continued for a minimum of 6 weeks and possibly longer if surgical cultures are positive.	I	C
Candidemia		
• Investigations are recommended to determine the precise source, including microbiologic cultures (driveline, pocket, and CVC) and imaging.	I	C
• Empiric therapy (before ID and S) with an echinocandin or L-AmB is recommended.	I	C
• Once ID and S have been established, patient is clinically stable, and blood cultures are negative, anti-fungal agents should be de-escalated to the narrowest spectrum agent possible.	IIa	C
• If the source of the candidemia is a CVC, it has been removed, blood cultures become negative within 24–48 hours, and there is no obvious metastatic infection, then 2–4 weeks of anti-fungal	I	C

Continued on page 277

Table 11 (*Continued*)

Recommendation	Class of recommendation	Level of evidence
therapy is adequate from the date of first negative blood culture.		
• A complete ophthalmologic examination for endophthalmitis before discontinuation of therapy is recommended.	I	B
Candida spp mediastinitis/ infective endocarditis:		
• Thorough surgical débridement of mediastinitis with an open chest ± a VAC wound closure is recommended.	I	C
• Type and duration of anti-fungal therapy for mediastinitis and infective endocarditis is the same as for a MCSD pump/ cannula infection.	I	C
Non-MCSD related *Candida* spp infections		
• *Candida* in respiratory cultures —isolation from sputum or BAL fluid with no evidence of a lung abscess or disseminated infection is consistent with colonization and does not need treatment.	I	C
• *Candida* in urinary cultures—isolation from urine in the absence of symptoms does not require treatment. If an IDC is in situ, then replacement is recommended.	I	B
• *Candida* in urinary cultures and the patient has symptoms consistent with cystitis and the *Candida* isolate is fluconazole-sensitive, then treat with 200 mg of fluconazole once daily for 2 weeks.	I	B
• *Candida* in urinary cultures and the patient has symptoms consistent with cystitis and the *Candida* isolate is fluconazole-resistant, then treat with AmB-d (0.3 to 0.6 mg/kg daily) and flucytosine (25 mg/kg 4 times daily) for up to 7 days. Bladder irrigation with AmB-d can be considered. Flucytosine should not be continued after cessation of AmB-d. Echinocandins are not recommended due to limited penetration into the urinary tract.	I	B
• If cystitis is due to a fluconazole-resistant *Candida* spp, the treatment options include AmB-d at a dose of 0.3 mg/kg to 0.6 mg/kg daily for 1 to 7 days, flucytosine at a dose of 25 mg/kg 4 times daily for up to 7 days, and may consider AmB-d bladder irrigation. Flucytosine should not be continued after the cessation of AmB-d. Echinocandins are not recommended due to limited penetration into the urinary tract.	I	C

AmB-d, amphotericin B deoxycholate; BAL, bronchoalveolar lavage; CT, computed tomography; CVC, central venous catheter; FI, fungal infection; ID and S, identification and sensitivity; IDC, indwelling catheter; L-AmB, liposomal amphotericin B; MCSD, mechanical circulatory support device; TPN, total parenteral nutrition; VAC, vacuum-assisted closure.

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