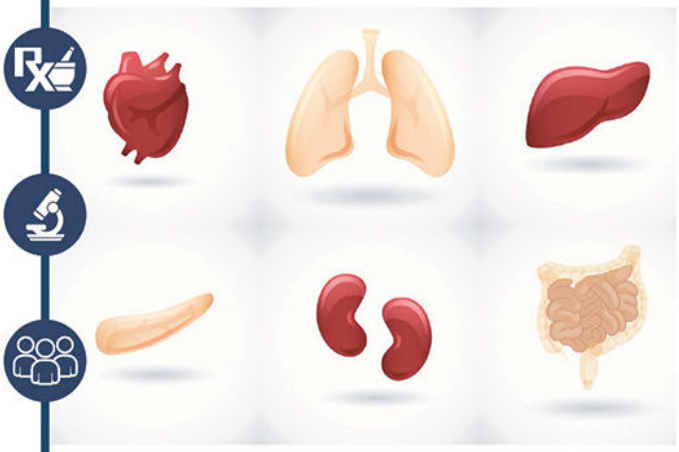
AMERICAN SOCIETY OF® TRANSPLANTATION

COMPREHENSIVE TRAINEE CURRICULUM



COMPREHENSIVE TRAINEE CURRICULUM

WATCH 52 ONLINE LESSONS INCLUDING:

- *Adult and Pediatric Liver*
- *Adult Cardiac and Pulmonary*
- *Abdominal Transplant Surgery*
- *Cardiothoracic Transplant Surgery*
- *Adult and Pediatric Kidney*
- *Transplant Pharmacy*

Solid organ transplantation is a multidisciplinary field, leading to a diverse community of professionals within the AST. As a result, it is often necessary for trainees to have extensive knowledge of all areas of transplantation—not just their specialty.

Check out this brand new resource, meant to supplement the training trainees and fellows receive at their university or hospital.

$50 members / $200 non-members

AMERICAN SOCIETY OF TRANSPLANTATION

DR. SHAHID HUSAIN (Orcid ID : 0000-0002-9216-5229)

Article type : Special Issue-Transplant Infectious Diseases

Invasive Aspergillosis in Solid Organ Transplant Recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Shahid Husain[1] and Jose F. Camargo[2] on behalf of the AST Infectious Diseases Community of Practice

[1]University Health Network, Division of Infectious Diseases, Multi-Organ Transplant Unit, University of Toronto, Toronto, ON

[2]Department of Medicine, Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, FL, 33136, USA.

Corresponding Author

Shahid Husain, MD, MS, FECMM, FRCP (Edin)

Toronto General Hospital, 585 University Avenue

11 PMB 138, Toronto, Ontario, M5G 2N2, Canada

Tel: (416) 340-4800 ext. 3144 Fax: (416) 340-5442

Email: shahid.husain@uhn.ca

Disclosures: S.H. has received research grants from Astellas, Gilead, Merck, Pfizer, Cidara and Vical. J.F.C. has no relevant disclosures.

ABSTRACT

These updated AST-IDCOP guidelines provide information on epidemiology, diagnosis, and management of Aspergillus after organ transplantation. *Aspergillus* is the most common invasive mold infection in solid organ transplant (SOT) recipients, and the most common invasive fungal infection among lung transplant recipients. Time from transplant to diagnosis of invasive aspergillosis (IA) is variable but most cases present within the first year post-transplant, with shortest time to onset among liver and heart transplant recipients. The overall 12-week mortality of IA in SOT exceeds 20%; prognosis is worse among those with central nervous system involvement or disseminated disease. Bronchoalveolar lavage galactomannan is preferred for the diagnosis of IA in lung and non-lung transplant recipients, in combination with other diagnostic modalities (e.g. chest CT-scan, culture). Voriconazole remains the drug of choice to treat IA, with isavuconazole and lipid formulations of amphotericin B regarded as alternative agents. The role of combination antifungals for primary therapy of IA remains controversial. Either universal prophylaxis or preemptive therapy are recommended in lung transplant recipients whereas targeted prophylaxis is favored in liver and heart transplant recipients. In these guidelines we also discuss newer antifungals and diagnostic tests; antifungal susceptibility testing and special patient populations.

ETIOLOGY

Aspergillus is a ubiquitous environmental fungus that causes potentially lethal infections in immunocompromised hosts[1, 2]. Inhalation is the most common route of entry of *Aspergillus* spores[1, 2].*A. fumigatus* is by far the most common species isolated (73%), and most cases (74-78%) of invasive aspergillosis (IA) are limited to the lungs[3-5].

EPIDEMIOLOGY AND RISK FACTORS

All organ transplants

In a case-controlled study of the RESITRA (Spanish Network of Infection in Transplantation) cohort, which included patients from 16 transplant centers with a follow-up of 18 months, there were 156 cases of proven or probable IA diagnosed overall. Risk factors for the development of IA within 3 months post-transplant included: use of vaso-active agents, prolonged intensive care unit (ICU) stay, post-transplantation renal failure requiring hemodialysis, cytomegalovirus (CMV) disease or one episode of bacterial infection. Older age, renal failure, CMV disease, bacterial infection, chronic graft rejection and immunosuppressive-related neoplasm were independent risk factors for IA 3 months post-transplantation[6] (**Table 1**).

Liver Transplant Recipients

Most of the epidemiological data on IA in liver transplant recipients is from 1990s, where incidence rates range from 1%-9.2%[7-10]. However, two prospective studies noted an incidence rate of less than 1%[11, 12]. Among pediatric liver transplant recipients the reported incidence of IA is 0.5%[13]. Well characterized risk factors for IA after liver transplantation include: CMV infection, requirement of dialysis and re-transplantation[14]. In the European study, CMV infection confered a 6-fold increase in the risk of IA after 100 days post-

transplant[15]. Another study noted a MELD score (model for end-stage liver disease) greater than 30 was associated with increased risk of invasive fungal infection (IFI)[16]. Liver re-transplantation has been shown to confer a 30-fold higher risk while renal failure is associated with a 25-fold greater risk and a such are the most significant risk factors for IA in liver recipients in the early period [6, 15, 17, 18]. Other factors associated with IA in living donor liver transplant recipients include transplantation for fulminant hepatic failure, CMV infection, and prolonged ICU stay[19].

Traditionally, IA had occurred earlier in liver transplant recipients, with time to presentation ranging up to 17 days[20, 21]. In more recent cohort studies, the median time to the onset of invasive mold infection or IA is now >100 days[5, 12, 14].

Liver transplant recipients have the highest rate of disseminated disease with invasive mold infection (55%), which carries a mortality rate of 64%[5]. Requirement of dialysis and CMV infection are independent predictors of mortality in solid organ-transplant (SOT) recipients (including liver transplant recipients) with IA[22]. Mortality rates remain high in patients who develop IA after liver re-transplantation (82%), particularly in those undergoing re-transplantation more than 30 days after primary transplantation (100%)[22].

Renal Transplant Recipients

IA has been reported in 0.7-4% of renal transplant recipients[7, 8, 23-28]. In a prospective study, the incidence of IA in kidney transplant recipients was reported to be 0.3%[12]. In a multinational case control study, the overall mortality among early cases of IA was 61%, and 25% of living recipients experienced graft loss. Pre-transplant diagnosis of chronic obstructive pulmonary disease (COPD) (odds-ratio [OR]: 9.96; p=0.04) and delayed graft

function (OR: 3.4; p=0.04), bacterial bloodstream infection (OR: 18.8; p=0.047) and acute graft rejection (OR: 40.7; p=0.003) within the 3 months prior to the diagnosis of invasive pulmonary aspergillosis (IPA), were identified as independent risk factors for early IA (**Table 1**). Previous occurrence of post-transplant complications attributed to over immunosuppression (e.g. pneumonia, TB, CMV, PTLD etc.) was identified as an independent risk factor for late IPA (OR: 19.3; 95%CI: 2.1-179; p=0.009)[29]. In previous studies, high doses (>3gms of methylprednisolone) or prolonged duration of corticosteroids, and graft failure requiring hemodialysis have been shown to be risk factors for IA after renal transplantation[7, 26, 30].

Lung Transplant Recipients

The overall incidence of IA in lung transplant patients ranges from 4%-23%[31]. In a US multi-center study, the incidence rate of IFI was 8.4% per year. Of these, 63% were *Aspergillus* infections[3, 32]. Other studies have noted higher prevalence of *Aspergillus* infection in lung transplant recipients[12, 33-35]. In another global retrospective study of 900 lung transplant recipients, the rate of development of the first episode was 29.6 patients per 1,000 person-years. IA occurred at a median of 7.7 months post-transplantation[36]. Among pediatric lung transplant patients the reported incidence of IA is 5%[13].

Risk factors that have traditionally conferred an increased risk of IA in lung transplant recipients are: ischemia at the bronchial anastomosis or bronchus [37], receipt of a single lung transplant[38], hypo-gammaglobulinemia[39], CMV infection[40], and pre/post-transplant colonization of the airways with *Aspergillus*[41-43] (**Table 1**).

Cystic fibrosis (CF) increases the risk of pre-transplant *Aspergillus* colonization[40, 44-48]. However, the risk of IA in lung transplant recipients with a diagnosis of CF, has not yet been clearly documented[49, 50]. Respiratory viral infections have not been associated with IA[50].

In a multicenter study, risk factors for IA included: single lung transplant (hazard ratio[HR]:1.8, p=0.02), and post-transplant colonization with *Aspergillus* spp. within 1 year of transplantation (HR: 2.11, p= 0.003). Pre-transplant *Aspergillus* spp. colonization, CMV infection and the presence of CF were not significant risk factors[36]. In a study involving 93 CF patients, intraoperative positive *Aspergillus* culture from the bronchoalveolar lavage (BAL; OR: 4.4, p=0.01) and treatment for acute cellular rejection within 90 days after transplantation (OR: 3.5, p=0.05) were independent risk factors for IA. Pre-transplant colonization with *Aspergillus* did not contribute to risk[51]. The lack of pre-transplant colonization as a significant risk factor for IA in various studies may be related to the widespread use of antifungal prophylaxis in CF patients undergoing transplantation[52, 53]. The presence of obliterative bronchiolitis after transplantation as a risk factor for IA is not well determined.

The mortality rate of IA in lung transplant recipients varies according to the clinical presentation, ranging from 23%-29% in patients with tracheobronchitis, to as high as 67-82% in patients with IPA[17]. In recent studies the survival has increased to 78%[4].

Heart Transplant Recipients

The incidence of IA in heart transplant recipients ranges from 1% - 14 %[54, 55]. A prospective multicenter study from 15 transplant centers suggested that the cumulative incidence of IFI after heart transplantation was 3.4% per year[25], with *Aspergillus* accounting for 23%. Other studies have also reported the incidence from 0.53 – 4.8%[3,48,44,12]. Among pediatric heart transplant patients the reported incidence of IA is 0.3%[13]. Risk factors for the development of IA include: isolation of *Aspergillus fumigatus* from BAL, re-operation, CMV disease, and post-transplant hemodialysis in the setting of outbreak, the existence of an episode of IA in

any patient from the heart transplant program 2 months before or after heart transplantation, and airborne *Aspergillus* spores in the ICU[56-59] (**Table 1**). In another case control study, significant risk factors for IA by multivariate analysis included: acute cellular allograft rejection (OR: 1.99, 95%CI:1.1-3.8) and increased number of pre-transplant hospitalizations (OR: 1.8, 95%CI:1.2-2.8)[60].

Overall mortality in heart transplant recipients with IA at one year was 67% in one study from 2006[54]. However, in recent years mortality has decreased to 38%[61].

CLINICAL MANIFESTATIONS

The Transplant-Associated Infection Surveillance Network (TRANSNET) reported data on 227 patients with proven/probable IA, among 1,063 SOT recipients between 2001-2006[3] with median time from transplant to IA diagnosis of 184 days[3]. Among 246 cases of proven/probable IA in SOT recipients from the Prospective Antifungal Therapy (2004-2008 PATH Alliance®) registry, the median time to diagnosis was 379 days[4]. The time to onset was shorter among liver (109 days) and heart recipients (89 days); kidney (406 days), lung (486 days), and small bowel (516 days) recipients exhibited longer time to onset of infection[5]. The Swiss Transplant Cohort Study (STCS:2008-2014) reported shorter intervals between transplantation and IA among liver (18 days) and heart (11 days) recipients[55]. Among pediatric SOT recipients, the median time from transplant to IA is 74 days (range, 19–129 days)[62]. The time to presentation in patients with donor-derived IA is variable[63, 64]. In a cluster of donor-derived *Aspergillus* infections, the kidney transplant recipients presented within 3 weeks, whereas the heart transplant recipient presented almost 6 months post-transplant[65]. Donor-derived IA frequently originate at the graft site, might involve the vascular anastomosis[64, 66] and almost invariably lead to early graft loss[65, 67]. Many reported

cases of donor-derived *Aspergillus* have occurred in recipients from donors with history of immunosuppression[65, 67, 68] so clinical suspicion should be higher in that setting. Contaminated preservation fluid is another potential mode of transmission[69].

Clinical manifestations of aspergillosis range from asymptomatic colonization to invasive presentations including sinusitis, tracheobronchitis, IPA, and empyema. In a majority of cases of IPA, the clinical symptoms are subtle with cough, pleuritic chest pain, or fever. Acute respiratory failure secondary to IPA is uncommon. Tracheobronchial aspergillosis (TBA) occurs almost exclusively in lung transplantation recipients affecting 4–6% of patients[70, 71] and it may lead to airway obstruction, bronchial ulcerations and pseudomembrane formation. Bronchial anastomotic infection can lead to dehiscence[2], necessitating aggressive combined medical and surgical therapy[72].

Sites of infection beyond the respiratory tract include: mediastinitis, the musculoskeletal system, thyroid, skin, rhinocerebral disease, ocular, organ specific, endocarditis, central nervous system (CNS) and disseminated disease forms[73], the latter ones associated with poor outcomes. Liver transplant recipients may be at particularly high risk for disseminated disease and CNS involvement[5, 6]. Disseminated disease (defined as extra-pulmonary disease, excluding sinus disease) occurred in 15% of the cases of the PATH Alliance®. The highest incidence of disseminated disease (55%) occurred in liver recipients[5]. Urinary tract aspergillosis has been reported in association with transmission through the renal graft[65, 67].

The overall 12-week post-diagnosis survival among SOT patients with IA from the PATH Alliance® registry was 78%[4]. Consistent with this, the overall 12-week mortality in the more contemporary Swiss cohort was 23%[55]. The 12-month survival after infection for the 227 patients with IA from the TRANSNET was 59%[3]. In the Swiss cohort, a diagnosis of IA was associated with lower 5-year survival compared to a control group of 210 SOT recipients

without IA (mortality was 41% vs 14%, respectively; p<0.001). Among IA cases from the TRANSNET, hepatic insufficiency (OR:3.9, 95%CI:1.3-12), malnutrition (OR:2.3, 95%CI:1.0-5.1), CNS disease (OR:6.6, 95%CI:1.4-30), and use of an amphotericin B (AmB) preparation as part of initial therapy (OR:4.4, 95%CI:2.1-9.1) were associated with increased risk of death[74]. In the Swiss cohort[55], higher risk of death was reported among older patients (OR:1.2, 95%CI:1.0-1.5), patients with disseminated IA (OR:36, 95%CI:1.6-827) and, in the univariate analysis, among liver transplant recipients (OR:32, 95%CI:3.4-293).

DIAGNOSTIC STRATEGIES

The substantial delay in establishing an early diagnosis of IA remains a major impediment to its successful treatment. Cultures of respiratory tract secretions lack sensitivity, and *Aspergilllus* isolates may only be detected in clinical samples in the later stages of the disease. Additionally, a positive culture with *Aspergillus* from respiratory tract samples is not always indicative of invasive disease. The significance of a positive culture from an airway sample also varies with the type of organ transplant. While isolation of *Aspergillus* spp. from the respiratory tract of liver transplant recipients has a high positive predictive value (PPV) for the subsequent development of IA (ranging from 41%-72%), it is an infrequent event (~1.5%)[7]. However, in airway samples of lung transplant recipients, *Aspergillus* spp. can be detected in ~25-30% of cases [14, 41, 75]. While positive airway cultures have a low PPV for the diagnosis of IA in lung transplant recipients, they portend a higher risk for subsequent invasive infection[7, 36]. Isolation of *Aspergillus* spp. from an airway sample in lung transplant recipients warrants a bronchoscopic examination, in order to exclude the presence of tracheobronchitis, bronchial anastomotic infection (BAI) or invasive disease. Radiographic studies including computed tomography (CT) scan of chest may be non-revealing at this stage. In heart transplant recipients, the estimated PPV of culturing *Aspergillus* from

respiratory tract samples for the diagnosis of IA is 60-70%[58]. In cases of *A. fumigatus*, the PPV of recovering a fungal isolate for the diagnosis of IA was 78-91% whereas it was 0% for other fungal species[58]. The isolation of *A. fumigatus* from the sputum had a PPV of 50-67% that increased to 88-100% when the sample was a respiratory specimen other than the sputum, such as BAL or bronchial aspirate[58].

Serum galactomannan

The utility of the serum galactomannan enzyme immunoassay (GM-EIA; Platelia Assay, Bio-Rad, Marnes-la-Coquete) test for early diagnosis of IA has been assessed in a limited number of studies in SOT recipients. In kidney transplant recipients, the reported sensitivity of serum GM was 58% in 27 cases of IA[76]. Similarly, another multicenter study reported the positivity rate of 68% for serum GM[77]. In liver transplant recipients using archived sera, the sensitivity of the test was 55.6% and the specificity was 93.9%[78]. A prospective study in 154 liver transplant recipients documented a specificity of 98.5% for serum GM[79]. In another prospective study, serum GM area under the curve was 0.77, showing good sensitivity but poor specificity[80].

In lung transplant recipients, the serum GM test had a specificity of 95%, but a relatively low sensitivity (30%) for the diagnosis of IA[81]. Although the test was able to detect the only case of disseminated IA, and 29% of the cases of pulmonary IA, it detected none of the cases of *Aspergillus* tracheobronchitis[81]. A meta-analysis showed that the serum GM assay may have greater utility in hematopoietic stem cell transplant recipients than in SOT recipients, in whom the sensitivity and specificity of the test was 22% and 84%, respectively[82]. In pediatric acute lymphocytic leukemia patients, screening with serum GM resulted in higher false positivity[83]

BAL galactomannan

Sensitivity of the GM assay for the diagnosis of IA in SOT recipients may be improved by testing BAL fluid. Sensitivity of BAL GM ranged from 67%-100 % while the specificity for the diagnosis of IA has ranged from 89-93% in various studies in lung transplant recipients [84] Increasing the index cutoff value to 1.0 decreases the sensitivity and increases the specificity[85, 86, 87, 88].

False positive GM tests have been documented 13% of liver recipients and 20% of lung transplant recipients[79, 81]. Liver transplant recipients with autoimmune liver disease, and those requiring dialysis, were significantly more likely to have false-positive serum GM tests, especially during early transplant period [79, 80]. The false-reactivity with the *Aspergillus* GM-EIA has been documented in 20% (14/70) of these patients[81]. Most false-positive tests occurred in the early post-transplant period (i.e. within 14 days of transplantation in 79% of the patients)[81]. Patients undergoing lung transplantation for CF and COPD were more likely to have positive tests in the early post-transplant period[81]. Determination of pentaxin-3 levels (a biomarker of inflammation) in lung transplant recipients may aid in differentiating *Aspergillus* colonization from disease in lung transplant recipients with positive BAL GM [89]. In lung transplant recipients BAL GM was also noted to be positive with the isolation of other molds such as *Fusarium*[90], *Paecilomyces* and *Penicillium* spp[85, 91], as well as other yeast e.g. *Histoplasma*[92], *Chaetomium globosum*[93] and *Cryptococcus*[94, 95].

In pediatric patients with IA, sensitivity has ranged from 82-87% with specificity around 87-93%, with OD index value of 0.5[96, 97]

(1-3)-β-D-Glucan

Beta-D-Glucan (BDG) is a non-specific marker of fungal infection found in cell wall of pathogenic fungi including molds, yeasts (e.g., *Candida*), as well as *Pneumocystis*. However, it is notably absent in Mucorales, *Cryptococcus* and some *Blastomyces* spp. The utility of (1-3)-β-D-Glucan for the diagnosis of IA has not been fully discerned. The two studies utilizing Fungitell® (Associates of Cape Cod, East Falmouth, MA) in liver transplant at the cut-off of 80 pg/ml reported the sensitivity and specificity of 58-75% and 65-83% respectively[98,80,99]. In lung transplant, recipient's sensitivity and specificity were noted to range from of 71-80% and 59-70% respectively for diagnosis of IFI [100,101].

Aspergillus Polymerase Chain Reaction (PCR)

PCR assays have been developed in order to amplify *Aspergillus* DNA. PCR is usually performed on serum and BAL samples, however none of the test have been cleared by Food and Drug Administration (FDA). The overwhelming majority of the data have been derived from patients with hematological malignancies[102, 103]. A recent systemic review of EORTC/MSG criteria revealed that when incorporated, the sensitivities and specificities for diagnosing IA were 81.6% and 91.6% for GM-EIA , and 76.9% and 89.4% for BDG, respectively. *Aspergillus* PCR showed similar sensitivity and specificity (76.8–88.0% and 75–94.5% respectively)[104]. It is however, important to note that the detection of PCR in the respiratory sample is unable to differentiate between colonization and disease in cardiothoracic organ transplant recipients. It may also yield false positive test results, due to the cross-reactivity with certain mold species (*Penicillium*) genetically homologous to *Aspergillus*. Moreover PCR detects DNA from dead conidia or hyphae and thus might not be ideal for monitoring the efficacy of antifungal therapy[105].

It is difficult to interpret the data on sensitivity and specificity of the PCR test due to the non-

standardization of samples used, extraction techniques, and primers used in the in studies. Overall, the pooled sensitivity of blood or serum PCR is 84% among studies with ≥1 positive results and 64% among studies with ≥2 positive results, with reported specificity of 95%[103]. Similar to GM-EIA, *Aspergillus* PCR performs better in BAL than in blood. In a systematic review of nine studies sensitivity and specificity of *Aspergillus* PCR in BAL were 77% and 94%, respectively[102].

Recently, results have been reported from standardized PCR assays for *Aspergillus* spp: the MycAssay *Aspergillus,* and the Viracor pan-*Aspergillus* PCR. The sensitivity and specificity of the MycAssay *Aspergillus* PCR (Myconostica Ltd., Manchester, UK) in the serum for diagnosis of IA, varied between 60-70% and 90-100%, respectively[106]. The MycAssay *Aspergillus* PCR in BAL samples yielded a sensitivity and specificity of 86% and 87%, respectively[107]. However, there were only 3 heart transplant recipients who did not developed IA, and no lung transplant recipients were included in the study[107].

In a study of the performance of the Viracor pan-*Aspergillus* PCR (Lee's Summit, USA) and the GM in 150 BAL samples among lung transplant recipients for the diagnosis of IA[87], the test had a sensitivity and specificity of 100 and 88%, respectively. Compared to the BAL-GM (at a cutoff of 0.5), the Viracor pan-*Aspergillus* PCR was more sensitive (100 vs.93%) for detection of invasive disease; however, among lung transplant recipients with *Aspergillus* colonization, the BAL-GM was more specific than the Viracor pan-*Aspergillus* PCR (92% vs. 50%).

(1-3)-β-D-Glucan Aspergillus PCR has not been specifically studied in pediatric SOT recipients. However, in children with hematological malignancy the sensitivity of *(1-3)-β-D-*Glucan was 88% with specificity of 59.5%. Similarly, pan-fungal PCR had sensitivity of 89% and specificity of 69.2%[108]

AsperGenius (Pathonostics, Maastricht, The Netherlands) is a newer multiplex real-time PCR *Aspergillus* detection assay that can also detect azole resistance in *A. fumigatus.* It has been assessed in hematological malignancy with sensitivity and specificity of 79% and 100% respectively[109]. However, no data exists in SOT recipients.

Newer tests

The 'Lateral Flow Device' is an immuno-chromatographic assay that uses JF5, a monoclonal antibody that binds to an extracellular glycoprotein secreted during active growth of *Aspergillus*. It has been studied in SOT recipients[110], both in serum and BAL fluid. In a recent meta-analysis, it displayed a better performance in BAL, where pooled sensitivity and specificity for the diagnosis of proven/probable IA was reported as 86% and 93%, respectively [111]. Studies on the use of this device in lung transplant recipients are lacking.

Another method utilizes exhaled air for detection of volatile organic compounds (VOCs) derived from various metabolic pathways. In a study of hematological malignancies with IPA the reported detection of α-trans-bergamotene, β-trans-bergamotene, a β-vatirenene-like sesquiterpene, or a trans-geranylaceton had a sensitivity and specificity of 94% and 93% respectively [112].

Another study reported the result of lateral flow dipstick assay using galactofuranose-specific monoclonal antibody (mAb476) for the diagnosis of IA in seventeen SOT recipients. Sensitivity and specificity for diagnosis of proven/probable IA in the overall cohort was 80% and 92% respectively. In the non-cancer group, sensitivity and specificity were 64% and 93%, respectively. The antibody was not detectable in lung transplant recipients with bronchial airway diseases[113].

Several antibodies have been used in the diagnosis of IA. Antibody response takes an average of 11 days to develop after onset of illness, and may be detectable in 29%-100% of patients during the course of acute IA infection[114]. However, most of these studies have been done in patients with hematological malignancy and chronic pulmonary aspergillosis[115-117]. These findings are promising but need to be validated in larger scale studies before it can be widely applied.

Radiological diagnosis

There are limited studies evaluating the radiological manifestations of IA in SOT recipients. However, several studies have been performed in hematological malignancy patients[118-121]. Most common manifestations on CT scan include ground glass opacification, peri-bronchial consolidation, macro-nodules, and mass-like consolidation. The "classic" halo sign and air-crescent signs are uncommon in SOT[122, 123]. Among patients from the Swiss cohort, radiographic findings for angio-invasive IA, defined as nodular and/or cavitary or necrotic lesions were present in only half of the cases[55]. Consolidation or mass (72%) was the most common CT finding of IPA in a cohort of 46 adult SOT recipients with proven/probable IA[124]; followed by large nodules (59%) and ground-glass opacity (50%). Although clinical improvement in response to antifungal therapy is usually seen within 3-5 days, radiological improvement in IA can take up to 4-6 weeks of proper antifungal therapy[124].

Other modalities such as high-resolution CT, pulmonary angiography (CTPA) and Positron Emission Tomography CT (PET/CT) using flourodeoxyglucose (FDG) uptake have also been reported to diagnose IPA in patients with hematological malignancy with varying sensitivity and specificity[125-128]. Their role in lung transplant recipients are not defined.

Recommendations

- Serum GM is not recommended to diagnose IA in SOT recipients (S*trong; moderate*)
- BAL-GM is the preferred sampling method for the diagnosis of IPA in SOT recipients (*Strong; high quality*)
- BAL-GM index value cut off of ≥1.0 is preferred for the diagnosis of IA in lung and non-lung transplant recipients, in combination with other fungal diagnostic modalities (e.g. chest CT-scan, culture) (S*trong; moderate*)
- Standardized BAL *Aspergillus* PCR can be used in combination with other fungal diagnostic modalities (e.g. chest CT-scan, BAL-GM, culture) for the diagnosis of IA. (*Strong; low*)
- Serum or BAL β-D-Glucan are not recommended for early screening and diagnosis of IA in lung and liver transplant recipients (S*trong; low*)

TREATMENT

Prompt initiation of antifungal therapy is critical for achieving optimal outcomes in SOT recipients with IA. The three main classes of antifungal agents in clinical use for treatment of IA are the polyenes, the triazoles and the echinocandins (**Table 2**). Voriconazole is the drug of choice to treat IA[72], with isavuconazole and lipid formulations of AmB regarded as alternative agents. This recommendation is endorsed by both the Infectious Diseases Society of America (IDSA)[72], and the European Society for Clinical Microbiology and Infectious Diseases[129]. In patients with liver insufficiency, liposomal AmB (L-AmB) is usually the first therapeutic option. Posaconazole is mainly used in treatment of cases of IA that are refractory or intolerant to other first line antifungal agents[72, 130]. The echinocandins are typically used alone or in combination for salvage therapy[72].

Voriconazole remains the drug of choice for treatment of IA based on randomized controlled trial (RCT) data (only 14 SOT recipients enrolled) where it was associated with improved survival (71 vs 58%) compared with AmB deoxycholate (D-AmB) as primary treatment for IA (HR: 0.59, 95%CI: 0.40–0.88)[131]. Subsequent studies further demonstrated the efficacy of voriconazole for the treatment of IA in SOT with response rates of 50-100%[132-134]. Voriconazole has excellent CNS and eye penetration, important for cases of disseminated disease. Mean hospital length of stay in SOT recipients with IA in the current era is 30 days and initial voriconazole use was associated with decreased length of stay[135]. Intravitreal voriconazole has also been used in a lung transplant patient with *Aspergillus* endophthalmitis[136], and is now recommended by IDSA as adjuvant to systemic voriconazole in this setting[72].

A major development in antifungal therapy in recent years is the advent of isavuconazole, approved in March 2015. In the SECURE RCT conducted in hematological patients, isavuconazole was non-inferior to voriconazole for the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi, as determined using all-cause mortality through day 42 as the primary endpoint (19% vs. 20%, respectively)[137]. Isavuconazole was better tolerated than voriconazole with fewer visual, skin or subcutaneous tissue and hepatobiliary disorders[137]. Isavuconazole was safely used in a lung transplant recipient who developed QT prolongation while on voriconazole[138].

Due to poor absorption, which can effect CNI levels as well, itraconazole is considered suboptimal therapy for IA in the current era but it might be used in resource-limited settings. Although not approved by the FDA for the treatment of IA, posaconazole has been used as salvage therapy [72, 139]. In November 2013 a new formulation of posaconazole with improved

pharmacokinetic (PK) profile, the posaconazole delayed-release tablet, was approved by the FDA. More than 90% of patients on 300 mg daily of this formulation achieve therapeutic levels[140]. In a cohort of 24 lung transplant recipients, posaconazole trough levels were three times higher with the posaconazole tablets compared to the suspension[141]. Posaconazole delayed-release tablet formulation was successfully used in the treatment of *Aspergillus* brain abscess[142]. An intravenous (IV) formulation of posaconazole was subsequently approved in March 2014.

All three echinocandins have been used anecdotally for salvage therapy as single agent[143] and in combination with other drugs in SOT recipients[144, 145]. However, caspofungin is currently the only approved echinocandin by the FDA as salvage therapy for the treatment of IA. Growing evidence supports the efficacy of caspofungin not only for salvage but also for first-line therapy[146]. Anidulafungin has potent *in vitro* activity against *Aspergillus* species and a good safety profile was demonstrated in a cohort of 86 SOT (mostly liver and lung) recipients receiving anidulafungin for prevention or treatment of IFI[144]. A unique attribute of anidulafungin is that it is eliminated by non-enzymatic degradation in the blood and does not require dosage adjustments in patients with renal or hepatic dysfunction[147]. Although anidulafungin has been studied in combination therapy[148], it has not been evaluated in monotherapy as primary or salvage therapy for IA. In a study of 225 patients (including 13 SOT) favorable responses were observed in 50% and 41% of patients treated with micafungin monotherapy as primary or salvage therapy, respectively, and a third of those who received micafungin in combination with other agents[149]. All three echinocandins exhibit a high degree of binding to plasma proteins and distribute minimally to cerebrospinal fluid, urine, and the eye.

Among the polyenes, the use of conventional D-AmB is no longer recommended due to toxicity; liposomal formulations are less nephrotoxic and are preferred. Although both lipid formulations are effective in the treatment of IA, L-AmB is better tolerated than amphotericin B complex (ABLC)[150, 151]. Both D-AmB and lipid formulations can be administered as adjunctive therapy via the inhaled route achieving a high concentration in the small airways with minimal systemic side-effects. For the treatment of invasive TBA adjunctive inhaled AmB in the setting of anastomotic endobronchial ischemia or ischemic reperfusion injury due to airway ischemia associated with lung transplant is recommended[72].

Combination therapy

The combination of antifungal drugs for primary therapy of IA is not routinely recommended by IDSA, but it may be considered in salvage situations[72]. When used, the combination of echinocandins with a triazole or lipid AmB formulations are preferred, except in cases of CNS infections. Due to poor tissue penetration of echinocandins into the brain and CSF[152] a combination of voriconazole and L-AmB might be favored in these cases.

Although to date its use has not been convincingly proven to be more effective than monotherapy[153, 154], combination antifungal therapy is a commonly reported practice in the clinical setting, ranging from 28 to 71%[4, 55, 155, 156]. Combination therapy is used as first-line treatment in 47% and as salvage therapy in 80% of the liver transplant centers in North America[157]. Primary combination therapy was used in 28% of cases in the TRANSNET[74] . More than half of IA patients in the Swiss cohort[55] and 38% of patients in the PATH Alliance® registry[4] received combination antifungal therapy. In a cohort of 116 liver transplants (1985-2013) combination antifungal regimens were used in 51% of the cases[155], and combination therapy performed better than monotherapy[155]. In the International Pediatric

Fungal Network cohort, 54% pediatric IA patients received combination therapy with 2 or more concurrent agents sometime within the 12 weeks after diagnosis[158].

A prospective, multicenter study in SOT recipients compared the outcomes of 40 patients who received voriconazole plus caspofungin as primary therapy for IA, with those of 47 patients from an earlier cohort who received a lipid formulation of AmB as primary therapy[22]. Overall survival at 90 days was 68% in the cases and 51% in the control group. Combination therapy was independently associated with reduced mortality in patients with renal failure and in those with *A. fumigatus* infection, even when adjusted for other factors predictive of mortality in the study population[22]. Patients in the combination therapy arm were more likely to develop an increase in calcineurin-inhibitor (CNI) agent level or gastrointestinal intolerance[22].

In a retrospective study that assessed the efficacy of voriconazole in the treatment of 192 fungal CNS infections there was evidence for improved survival in 24/37(65%) patients who received voriconazole with other antifungal agents over those that did not 74/155 (48%, P=0.02)[159].

In a meta-analysis of studies published through May 2013 (including 8 studies in SOT) comparing the combination of triazoles or lipid AmB plus an echinocandin to non-echinocandin monotherapy for IA, dual antifungal therapy was associated with significantly improved 12-week survival at the end of treatment over monotherapy when given as salvage therapy for IA[160]. The survival benefit of combination therapy for primary treatment of IA was less pronounced.

More recently, Marr *et al* performed the first large RCT to compare combination therapy with voriconazole plus anidulafungin versus voriconazole alone in 454 hematological patients[148]. Combination therapy was administered for 2-4 weeks, followed by continuation of voriconazole. There was a trend toward decreased mortality at 6 weeks (P=0.09) in the combination therapy group. The safety profile of combination therapy was similar to that of voriconazole monotherapy; however, there was a slightly higher frequency of hepatobiliary adverse events in patients who received the combination.

Combination therapy should be considered in selected circumstances including: when *Aspergillus* species is unknown (7% of cases in TRANSNET and >50% of cases in report by International Pediatric Fungal Network)[158] until susceptibility testing results are available; when a loading voriconazole dose is not given or its metabolism is expected to be highly influenced by concomitant medications until therapeutic serum trough levels are documented; in patients with disseminated or CNS disease; and as salvage therapy in those who do not respond to monotherapy.

Duration of therapy

The optimal duration of therapy for IA depends upon the response to therapy, and the patient's underlying disease(s) or immune status. Treatment is usually continued for 12 weeks; however, the precise duration of therapy should be guided by clinical response rather than an arbitrary total dose or duration. A reasonable course would be to continue therapy until all clinical and radiographic abnormalities have resolved, and until fungal biomarkers and cultures (if they can be readily obtained) no longer yield evidence of *Aspergillus*.

Antifungal susceptibility testing and antifungal resistance

Clinical breakpoints for itraconazole, voriconazole, and posaconazole against *Aspergillus* spp. have been suggested by The Clinical & Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[161]. Epidemiologic cutoff values (ECV) by CLSI, or ECOFF by EUCAST (i.e., the upper minimum inhibitory concentration (MIC) value describing the wild type distribution) have been reported for isavuconazole[162, 163] and echinocandins[164]. Isavuconazole and voriconazole exhibit reduced efficacy against isolates with MICs ≥16 μg/mL, but there is no clearly defined relationship between *in vitro* susceptibility and clinical outcomes in cases where the MIC is <16 μg/mL[165].

Among 288 *Aspergillus* isolates prospectively collected as part of the TRANSNET, the vast majority had MIC values at or below the ECV for caspofungin, micafungin, and anidulafungin[166]. The voriconazole ECOFF for *A. fumigatus* is 1 mg/L, but 2 mg/L for *A. flavus*, *A. niger* and *A. nidulans*[161]. The EUCAST has defined voriconazole breakpoints for *A. fumigatus* in the following way: susceptibility <1 and resistance >2 mg/L. Isolates with a MIC of 2 mg/L are classified as 'intermediate"[167]. The MIC distributions of posaconazole against a variety of *Aspergillus* species have been published[161, 168]. Depending on the species, the ECOFF is 0.25–0.5 mg/L; the posaconazole ECOFF for *A. fumigatus* is 0.25 mg/L. Isavuconazole MICs have a high degree of correlation with voriconazole MICs[169]. Thus, in patients with treatment failure attributed to suspected or confirmed triazole resistance, it might be prudent to switch antifungal class. The clinical utility of *in vitro* synergy testing, if any, remains to be established[156].

A. fumigatus stricto sensu can acquire resistance to azoles by mutations in the drug target particularly after prolonged azole exposure[170-172]. IA caused by azole-resistant *A. fumigatus* is associated with high (>50%) mortality[173]. A recent surveillance study of fungal infection in SOT recipients in the US showed a low rate of triazole resistance (1/181) in *A. fumigatus* isolates[174]. A large global survey reported 3.2% of clinical *A. fumigatus* isolates to be azole resistant[175]; however, in some European countries resistance rates are even higher. Targeted antifungal prophylaxis did not lead to cyp51A resistance mutations in a small cohort of lung transplant recipients[176].

Multiple members of the *Aspergillus* family exhibit high MICs to azoles such as *A. lentulus* (voriconazole MIC typically ≥2mg/L[177]), and *A. calidoustus* (MIC to azoles typically ≥4mg/L[174, 177]). Although considered uncommon in the clinical setting (likely due to under-diagnosis), over 10% of the isolates associated with IA in transplant recipients from TRANSNET were found to be cryptic species including *A. lentulus* and *A. calidoustus*[177]. *A. calidoustus* (*A. ustus* complex) was recently reported as an emerging pathogen in lung transplant recipients receiving triazole prophylaxis[178]. Outcomes for *A. calidoustus* and *A. ustus* infections have been poor[156]. It should be noted that mixed infections due to ≥2 *Aspergillus* species occurred in 12% of cases in the TRANSNET (almost exclusively among patients with pulmonary IA)[3].

Certain *Aspergillus* species such as *A. terreus* are typically resistant to the polyenes but susceptible to voriconazole; only 5–6% of IA in SOT recipients is due to *A. terreus*[22]. Other *Aspergillus* spp. that can exhibit elevated MIC to AmB include *A. flavus, A. lentulus, A. calidoustus, A. alliaceus,* and *A. nidulans*[173].

In patients with documented infection who do not respond to initial monotherapy, especially those suspected to have an azole-resistant *Aspergillus* isolate, antifungal resistance testing should be considered to guide treatment, in addition to combination therapy.

Therapeutic drug monitoring

Consistent with other current guidelines[72, 129] AST IDCOP recommends monitoring of serum trough drug levels for azole antifungal agents and for potentially interacting drugs such as cyclosporine, tacrolimus, and sirolimus. Therapeutic drug monitoring (TDM) is highly recommended in patients receiving azole antifungals under the following clinical conditions: concerns about gastrointestinal absorption; clinical or laboratory manifestations of toxicity; uncertain compliance with oral therapy; initiation or discontinuation of interacting drugs; cystic fibrosis; critically ill patients such as those with multiorgan failure or unstable hemodynamics requiring vasopressors or ECMO; before alternation in therapy to a second line agent after the initial failure of therapy[179]. Except for such clinical scenarios, there is little role for monitoring serum drug levels in patients receiving IV formulations where expected bioavailability is 100%.

Two meta-analyses demonstrated that therapeutic voriconazole serum concentrations (>1 mg/L) are predictive of clinical success[180, 181]. In patients with disseminated or CNS aspergillosis, trough levels >2mg/L (or even >3mg/L) should be considered. Studies have suggested that a trough level/MIC ratio (when the MIC is estimated using CLSI methodology) of 2-5 is associated with a near-maximal probability of response[182]. Active dosage adjustment to keep serum concentrations <5.5mg/L prevents voriconazole-related toxicity. In patients receiving posaconazole, levels >1.0 mg/L should be targeted for treatment of IA. In a clinical study in which posaconazole was used as salvage therapy, an

average concentration of 1.25 mg/L was necessary to obtain the highest favorable outcome rates[139].

In a prospective, observational study of lung transplant recipients (n=93) receiving voriconazole prophylaxis, the median initial and subsequent serum voriconazole trough levels (n=331) were 1.91 and 1.46 mg/L, respectively. The age of the patient directly correlated with initial troughs (P=0.005). Patients that were ≥60 years old and CF patients were significantly more likely to have higher and lower initial troughs, respectively[183].

For isavuconazole, in the IA trial patients (n=66) achieved mean ±SD (range) day-14 trough plasma concentration of 3.35±1.81mg/L (0.81-9.95mg/L), with assumed steady state concentrations (≥ day21) trough of 3.91mg/L[137]. A post-hoc analysis of the SECURE trial found no relationship between isavuconazole exposure and either efficacy (including overall mortality and clinical response at the end of therapy) or safety endpoints. Consequently, there is no current clinical evidence for recommending routine TDM for isavuconazole[184]. Although concentrations of isavuconazole will begin to change immediately after the dose or dosing interval is amended, the time to a new steady state is approximately 4-weeks[185], which makes TDM for this agent impractical from a clinical standpoint.

Special populations

Pediatric patients

Data are limited on the safety and efficacy of triazoles and echinocandins in children[186]

Due to the higher weight-adjusted clearance of voriconazole that is observed in pediatric patients, children require higher doses of voriconazole than adults **(Table 3)** [179, 187, 188]. A

dose of 8 mg/kg of voriconazole IV in children approaches that for 4 mg/kg in adults[189]. TDM is highly recommended[129].

Intestinal transplant recipients

Among SOT recipients, intestinal/multi-visceral transplantation (IMVT) carries the highest risk for IFI[3]. Fungal infections are major causes of morbidity and mortality in IMVT recipients[190, 191]. In addition to inhalation, conidial ingestion[192] is a potential port of entry for mold infections in IMVT recipients. It is conceivable that the same risk factors from liver transplant recipients confer risk of IA in this population[190] as many IMVT procedures include livers[193]. All the small bowel transplant recipients with IA from the PATH Alliance® registry (n=4) died within 12-weeks of diagnosis[5]. Dissemination to CNS in IMVT is common[194, 195]. Successful outcomes in IMVT recipient patients with disseminated IA, have been reported with the use of combination antifungal therapy[194, 195].

Cystic fibrosis

Colonization of the airway by *A. fumigatus* is common in CF patients (41-58% in some series) with the highest prevalence among those aged 16-years and older[196-198]; and high rates of azole-resistance[199]. CF patients 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; 4) changes in the volume of distribution and 5) increased creatinine clearance. In patients with CF having undergone transplantation, increased doses are necessary to maintain therapeutic concentrations compared to healthy subjects[200, 201]. Lower than expected serum isavuconazole levels were reported in a CF double lung transplant recipient treated with the recommended dose[202].

Critically ill patients

Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients have been recently published[203]. The PK-profile of

antifungals in the setting of extracorporeal membrane oxygenation (ECMO) is difficult to predict due to multi-organ dysfunction, the large volume of exogenous blood required to prime the circuit, and drug extraction by the circuit[204]. Micafungin is extracted by the ECMO circuit especially when a hemofilter for patients with renal failure is present[204] whereas case reports indicate this might not be true for adinulafungin[205]. Sub-therapeutic drug exposure has also been reported in some[206, 207], but not all [208] ECMO patients treated with caspofungin. Voriconazole pharmacokinetics are highly variable in critically ill patients requiring ECMO support [208, 209]. Thus, it is highly recommended to monitor azole plasma levels in critically ill and ECMO patients to ensure efficacy and avoid toxicity. When unable to document adequate blood azole or echinocandin concentrations in ECMO patients, L-AmB might be indicated.

Renal failure

Although significant accumulation of cyclodextrin can occur in hemodialysis patients treated with IV voriconazole, clinical significant adverse reactions associated with the accumulation of cyclodextrin in this setting have not been reported[210-212]. The use of IV voriconazole in critically ill patients with pretreatment impaired renal function was not associated with renal or liver damage nor with an increase in ICU mortality[213]. In another study, IV voriconazole was associated with less acute renal toxicity than D-AmB-containing regimens for treatment of IFI[211] in patients with baseline renal insufficiency. Thus, several clinical reports indicate that IV voriconazole can be safely administered to patients with renal dysfunction. The PK-profile of echinocandins does not seem to be affected by renal replacement therapy in critically ill patients[214, 215].

Influenza co-infection

Influenza-associated aspergillosis is now increased reported in critically ill patients[216-221]. The majority of cases are due to the A (H1N1) strain[217, 221, 222]. At least 8 cases of influenza-associated aspergillosis have been reported in transplant patients[221] including 2 kidney[218] and

2 liver recipients[222]. The median time between influenza and IA diagnoses is 6 days (range, 0-32)[219, 221]; in addition to H1N1 infection, risk factors may include steroids and viral-induced lymphopenia[218, 221]. In a report of 57 cases, two thirds of the patients required mechanical ventilation and 21% required ECMO[221]. High mortality rates were noted (46-61%)[217-219, 221], primarily from respiratory and/or multi-organ failure. Prompt diagnosis and early antifungal therapy are recommended [218, 221].

Complications during therapy

Decreasing immunosuppression should be done with caution in SOT patients with IFI including IA[223]. In a cohort of 68 lung transplant recipients with proven/ probable IA followed for 12 months, 5 (7%) patients developed an immune reconstitution syndrome-like entity, and three of these patients with immune reconstitution syndrome (IRS) died (2 deaths due to chronic rejection). The risk of IRS correlated significantly with change in CNI therapy. The odds for developing IRS were 29.5 (P=0.002) with discontinuation and 9.9 (p=0.046) with ≥50% reduction in calcineurin-inhibitor agent[224]. Other risk factors for IRS included heart–lung transplantation, T-cell depletion, and disseminated IA.

A well-known side effect of itraconazole, voriconazole and posaconazole is QT interval prolongation, especially when given in combination with other QT-prolonging agents. Unlike other triazole antifungals, isavuconazole can shorten the QT interval in a concentration-dependent manner, and it is contraindicated in patients with familial short QT syndrome[138]. In a case series of adult patients treated for IFI, 24/26 (92%) patients, experienced shortening of QT interval while on isavuconazole therapy[225].

Patients on long-term triazole therapy should be monitored for neurological symptoms. A 10% incidence of peripheral neuropathy after an average of 4 months (range, 1-18 months) of antifungal therapy was reported in a cohort of 222 patients receiving triazole therapy for chronic aspergillosis. Risk was highest for itraconazole (17%) compared to voriconazole (9%) and posaconazole (3%) [226]. If peripheral neuropathy is suspected, diagnosis should include nerve conduction studies, exclusion of other causes and consideration of dose reduction or cessation of therapy.

Skin cancer is another well-established complication of voriconazole therapy[227, 228]. In a cohort that included 900 lung transplant recipients, exposure to voriconazole alone (adjusted hazard ratio [aHR]: 2.4, 95%CI:1.3-4.4) and exposure to voriconazole and other azole(s) (aHR:3.5, 95%CI:1.1-11) were associated with squamous cell carcinoma (SCC)[228]. However, the association of voriconazole with an increased risk in SCC in vulnerable lung transplant recipients should be weighed carefully with its benefits in preventing or treating IFI. There is no established association between posaconazole or isavuconazole and risk of malignancy, and these are potential alternatives for patients who require prolonged antifungal therapy.

Another adverse consequence of long-term voriconazole therapy is periostitis, which is characterized by bony pain and diffuse periosteal ossification resulting from accumulation of fluoride levels. This condition typically resolves after discontinuation of voriconazole. Since this phenomenon does not appear to be a class-effect, substitution to posaconazole or isavuconazole can be considered[229].

Drug interactions of antifungal agents with immunosuppressants

Drug interactions must be carefully considered when treating transplant recipients with IA. Drug-drug interactions between triazole antifungal agents and immunosuppressants have been reviewed elsewhere[230, 231]. The triazole agents are potent inhibitors of the CYP34A isoenzymes and have the potential to increase the levels of CNI agents and mTOR inhibitors such as sirolimus[209]. A 50–60% reduction in the dose of CNIs may be necessary with the concurrent use of voriconazole[209]. The use of sirolimus is contraindicated in patients receiving voriconazole. In some reports, however, the two agents have been safely co-administered with sirolimus dose reduction by 75–90%[232, 233]. When concurrently used with voriconazole, liquid formulation of sirolimus can be used for more accurate dosing..

Co-administration with isavuconazole increased the area under the concentration-time curves of tacrolimus, sirolimus, and cyclosporine by 125%, 84%, and 29%, respectively[234]. In a study that evaluated the interaction between isavuconazole and tacrolimus among 55 SOT recipients, a 1.3-fold decrease in tacrolimus daily dose was required to maintain desired tacrolimus levels[235]. After initial dose reduction, adjustments in CNI dosing in patients receiving triazoles should be guided by TDM.

Adjunctive therapies

Surgical excision or debridement remains an integral part of the management of IA for both diagnostic and therapeutic purposes[236-241]. Specifically, surgery is indicated for a persistent or life-threatening hemoptysis, for lesions in the proximity of great vessels or pericardium, for sino-nasal infections, for single cavitary lung lesions which progress despite adequate treatment, and for lesions invading the pericardium, endocardium, bone, subcutaneous, or thoracic tissue[72, 242]. Surgical resection is also indicated for intracranial abscesses depending upon the location, accessibility of the lesion and neurologic sequelae.

Enhancement of the host's immune status with immunomodulatory agents is an attractive therapeutic adjunct in the management of IA. Neutropenia (<500 cells/μl) has been associated with increased 12-week attributable mortality in patients with IA[243]. Colony stimulating factors (G-CSF or GM-CSF) stimulates proliferation and maturation of myeloid precursor cells and also augments neutrophil (and macrophage) function[244, 245]. G-CSF use in SOT recipients appears to be safe; however, there are no studies that have evaluated its efficacy as adjunctive to antifungal therapy specifically in these patients. *In vitro* studies and case reports have also demonstrated a potential role of interferon-γ (IFNγ) against *Aspergillus*[246-253]. However, the use of interferon-γ (IFNγ) in SOT recipients is of concern given the risk of potential graft rejection.

Key recommendations (Treatment of IA)

- Early initiation of antifungal therapy in patients with strongly suspected IA is warranted while a diagnostic evaluation is conducted (*Strong; high*).
- Voriconazole is the drug of choice to treat all forms of IA (*Strong; high*).
- Isavuconazole and lipid formulations of AmB, preferably L-AmB, can be considered as alternative agents (*Strong; moderate*).
- Posaconazole can be considered for salvage therapy in patients who fail or do not tolerate first line antifungals (*Strong; low*).
- Primary therapy with an echinocandin is not recommended (*Strong; low*). However, echinocandins can be considered when other antifungals are contraindicated (*Weak; low*).
- Combination therapy can be considered in select cases such as in patients with disseminated or CNS disease (*Weak; low*).

- Inhaled AmB (in conjunction with systemic antifungal therapy) may be used in the setting of tracheobronchial aspergillosis associated with anastomotic endo-bronchial ischemia, or ischemic reperfusion injury due to airway ischemia associated with lung transplant (*Weak; low*).
- Duration of treatment should be guided by clinical and radiological response; most cases will require a minimum of 12 weeks, if tolerated (*Strong; moderate*).
- Secondary prophylaxis should be considered in patients with history of IA who undergo augmentation of immunosuppression (e.g., T-cell depletion, high dose steroids) and during episodes of prolonged neutropenia (e.g., <500 cells/µl longer than 7 days) (*Weak; low*).
- Routine antifungal susceptibility is not recommended but it can be considered for patients suspected to have an azole-resistant isolate and those who are unresponsive to antifungal agents (*Weak; low*).
- Antifungal TDM is recommended for all patients receiving voriconazole-based therapy for IA (*Strong; moderate*).
- Dosing of antifungals should be adjusted in coordination with a transplant pharmacist in special populations including pediatrics, CF and ECMO/critically ill patients (*Strong; low*).
- Dose of CNI/mTOR inhibitor should be reduced (and increased) in coordination with the respective organ transplant subspecialist and a transplant pharmacist in patients starting (and completing), triazole therapy respectively; and CNI/mTOR inhibitor levels monitored closely (*Strong; moderate*).
- Baseline and follow-up electrocardiogram to assess QT interval (for patients receiving triazoles other than isavuconazole) and regular skin examination (for patients

receiving voriconazole) are indicated in patients receiving chronic azole therapy (*Strong; high*).

- Surgery and reduction of immunosuppression are important adjunctive components of management in selected patients (*Strong; low*).
- Colony-stimulating factors may be considered in neutropenic patients with IA (*Strong; low).*

PREVENTION

General Measures

All transplant recipients should avoid activities that increase the exposure to *Aspergillus* conidia such as gardening, mulching, and raking leaves in the fall[254, 255]. If this cannot be avoided, personal protective equipment including shoes/boots, long pants, long-sleeved shirts, and more importantly mask and gloves should be used when handling materials such as soil, moss, or manure. Transplant recipients should also avoid construction areas or excavation sites, and wear an N95 respirator at all times in such areas to prevent inhalation of dust. Hand wash is also highly recommended after exposure to soil or dust. It's important to note that although these actions are recommended, they haven't been proven to prevent aspergillosis.

Liver transplant

At present, universal prophylaxis against IA is not routinely recommended in liver transplant recipients. A more rational approach is to target prophylaxis specifically for high risk liver transplant recipients. It is to be noted, however, that the clinical risk factors are derived from small, single center, retrospective cohort studies in the earlier era. An optimal approach to the prevention of IA in these patients therefore has not yet been defined.

It is difficult to assess the efficacy of the antifungal prophylaxis strategies against IA in liver transplant recipients, as most of the prophylaxis were directed specifically against the prevention of *Candida* infections. Several meta-analysis of antifungal prophylactic trials in liver transplant recipients have documented a beneficial effect in decreasing the overall rate of fungal infection/colonization. However, this has come at the cost of increasing the emergence of non-*albicans Candida* spp. infections, without an overall benefit in mortality rate[256, 257].

In a meta-analysis, the mortality attributable to fungal infection was significantly reduced with the use of prophylaxis, without any reduction in the rate of IFI due to IA[258].

The strategy of targeted vs. universal prophylaxis with voriconazole was studied in 382 high risk liver transplant recipients. Targeted prophylaxis was safe and effective at preventing IFIs, and reduced the number of patients exposed to antifungals. No difference in the rate of IFI was noted between universal vs. targeted prophylaxis groups. It is to be noted that only one case of IA was noted among 145 liver transplant recipients who receive targeted prophylaxis. The median duration of therapy was 11 days[259]. In another study of 174 high risk liver transplant recipients who received voriconazole prophylaxis, no cases of IA were noted after 90 days of follow-up[260].

Two randomized trials have assessed the effect of echinocandin prophylaxis. The first was a double blind RCT of anidulafungin versus fluconazole for antifungal prophylaxis, in 200 high risk liver transplant patients. The overall incidence of IFI was similar for the anidulafungin (5.1%) and the fluconazole groups (8.0%; OR: 0.61, 95%CI: 0.19–1.94, p=0.40). However, anidulafungin prophylaxis was associated with a trend to less *Aspergillus* colonization or

infection (3% vs. 9%, p=0.08). Both drugs were well-tolerated. Graft rejection, fungal-free survival, and mortality were similar for both groups. Median duration of therapy was 21 days[261].

Since anidulafungin does not undergo hepatic metabolism, it has theoretical advantage above other echinocandins. However, in a study of treatment of IFI among patients with severe abnormal liver function, 62% of patients experienced greater than two times elevation of liver enzymes[262].

The second study to assess the effect of echinocandin prophylaxis was an open label, RCT of 344 high risk liver transplant recipients. Administration of 100 mg of micafungin was compared to standard of care (caspofungin, amphotericin B, or fluconazole). Clinical success rate at the end of prophylaxis was 98.6% in the micafungin group, in comparison to 99.3% in the standard of care group. However, there were three breakthrough infections with *Aspergillus* noted in the micafungin group. The median duration of therapy was 21 days[263].

In another propensity score analysis of 195 high risk liver transplant recipients, caspofungin use resulted in significant reduction of IA (absolute risk reduction: 0.06; 95%CI: 0.001-0.11; p=0.04)[264]. Targeted antifungal prophylaxis using the lipid formulations of amphotericin B, in doses ranging from 1-5mg/kg/day has been shown to be effective in observational studies[265-268].

Data for risk factors and prophylaxis for aspergillosis in pediatric liver transplant recipients are lacking, and the following recommendations in adult liver transplant recipients should be extrapolated to pediatrics with caution.

Recommendations:

- Targeted prophylaxis in patients with any of the following high-risk factors is recommended (*Strong; moderate).*
    - Re-transplantation (second or third liver transplant).
    - Renal replacement therapy (hemodialysis or continuous venovenous dialysis) at the time of or within 7 days of transplantation.
    - Reoperation involving thoracic or intra-abdominal cavity e.g., exploratory laparotomy or any intrathoracic surgery.
- Anidulafungin, micafungin or caspofungin in standard dose, or voriconazole is recommended for the use of targeted prophylaxis against IA in liver transplant recipients (*Strong; high)*
- Targeted prophylaxis with a lipid formulation of amphotericin B in dosages ranging 3-5mg/kg may be considered (*Weak; moderate)*
- Targeted prophylaxis should be continued for 14-21 days (*Strong; high)*
- Screening with serum GM and β-D-Glucan is not recommended for pre-emptive therapy (*Weak; low*)

Lung Transplant Recipients

Like it is the case for other organs, the optimal *Aspergillus* prevention strategy in lung transplant recipients remains to be defined. Current practices of antifungal prophylaxis in lung transplant recipients are derived from non-randomized clinical trials of small sample size, single center non comparative case series, or case control studies[31, 269-276]. In a meta-analysis of universal vs. no antifungal prophylaxis in lung transplant recipients, 19 of 235 (8.1%) and 28 of 196 (14.3 %) developed IA in the universal prophylaxis and no prophylaxis arms respectively (RR: 0.36, 95%CI: 0.05-2.62). No significant reduction in IA or

Aspergillus colonization with universal anti-*Aspergillus* prophylaxis was noted[277]. Another meta-analysis involving universal and targeted antifungal prophylaxis strategies, showed reduction in the rate IA in lung transplant recipients[278]. Several studies have used a risk stratification strategy for anti-fungal prophylaxis using itraconazole, voriconazole and posaconazole, with varying reported efficacy rates[279-281].

Two studies have specifically evaluated preemptive therapy in this setting. In one study involving more than 300 lung transplant recipients, culture directed therapy was effective in preventing subsequent development of IA. However, half of the cases of IA occurred in patients without pre-transplantation or post-transplantation airway colonization with *Aspergillus* spp[282]. In the second study, both BAL culture and BAL-GM (index value cutoff used in this study was 1.0) directed pre-emptive therapy were utilized in 519 lung transplant recipients; preemptive therapy was associated with significantly lower rates of IA at 1 year post-transplantation compared with no pre-emptive therapy (HR: 0.23, 95%CI: 0.09-0.58). Mortality rates among patients receiving pre-emptive therapy were similar to those who did not have any positive *Aspergillus* culture or BAL GM at one year[283]. In a cohort of 62 lung transplant recipients, preemptive treatment with voriconazole was effective at preventing progression to invasive disease, with reported low incidence of IFIs (1.6% and 3.2% at 6 and 12 months after initiation of prophylaxis, respectively)[281]. The median (range) duration of prophylaxis was 85 (4–455) days.

Among the antifungal drugs, aerosolized amphotericin B allows the direct administration of the drug into the transplanted lung, avoiding systemic side effects and drug-drug interactions. Its use however, is limited by tolerability. Common side effects include cough, bronchospasm and nausea. D-AmB and the lipid formulations have been shown to be safe and well tolerated[270, 284]. Aerosolized ABLC was associated with fewer side effects in one study[270] but

in the meta-analysis, the side effect profile was not significantly different between inhaled ABLC/L-AmB and D-AmB[277]. A major disadvantage of aerosolized amphotericin B is the fact that distribution in single lung transplant recipients occurs preferentially in the allograft, with unreliable distribution in the native lung, which could remain as a source of infection[285]. It is also important to note that use of aerosolized amphotericin B may fail to prevent systemic fungal infections such as candidemia and pleural candidiasis in lung transplant recipients[286]. Triazoles including itraconazole and voriconazole have been shown to decrease the rate of IA in lung transplant recipients.

In one study using voriconazole prophylaxis, liver enzyme abnormalities developed in more than 40% of the patients[31]. Itraconazole appears to be less hepatotoxic than voriconazole in lung transplant recipients receiving antifungal prophylaxis[287]. Recently, posaconazole has also been evaluated in lung transplant recipients showing lower rates of hepatotoxicity than voriconazole[280, 281]. The data on the newer azole, isavuconazole is minimal in lung transplant recipients.

Data for risk factors of *Aspergillus* infection in lung transplant and prophylactic strategies in pediatric patient population are lacking. Recommendations regarding prophylaxis in adult lung transplant recipients should be extrapolated to pediatrics with caution.

Recommendations:

These recommendations are intended for the first year following the lung transplant. No definite recommendation can be made for the later years following lung transplantation due to the lack of published data.

- Either universal prophylaxis or preemptive therapy can be employed as a strategy to prevent IA in lung transplant recipients, depending on the availability of the diagnostic tests (*Strong; moderate*).
- In cases where a preemptive therapy strategy is employed, both BAL culture and BAL-GM should be incorporated into the protocol (*Strong; low*).
- A BAL-GM index value of 1.0 is preferred as a threshold for the initiation of preemptive therapy (*Strong; low*).
- It is recommended to initiate targeted antifungal prophylaxis if any one of the following risk factors are present in lung transplant recipients (*Strong; moderate)*
  - Pre-transplant *Aspergillus* colonization
  - Post-transplant *Aspergillus* colonization within a year of transplant
  - Single lung transplant
  - Positive intraoperative *Aspergillus* culture in CF patient
- Targeted antifungal prophylaxis against IA may be considered if more than one of these risk factors are present in lung transplant recipients (*Weak; low*)
  - Early airway ischemia
  - Induction with alemtuzumab or anti-thymocyte globulin
  - Cytomegalovirus infection
  - Rejection and augmented immunosuppression (particularly the use of T-cell depleting monoclonal antibodies post-transplant)
  - Acquired hypogammaglobulinemia (IgG level <400mg/dl)
- The use of serum-GM for the screening of IA is not recommended in lung transplant recipients (*Strong; moderate*).

- In cases of universal and targeted antifungal prophylaxis, the recommended duration is 4-6 months. However, when using a preemptive strategy, the duration of antifungal therapy should be 3-4 months (*Strong; moderate*).

With regards to the choice of the drugs against *Aspergillus* in lung transplant recipients, the following recommendations are made:

- No data exist regarding the use of inhaled amphotericin (lipid or deoxycholate) in pre-emptive therapy (i.e., positive *Aspergillus* culture or positive BAL-GM) and they should be used with caution in this setting (*Strong; low*).
- Inhaled amphotericin B or lipid preparation of amphotericin B can be used for targeted prophylaxis post operatively in patients with a risk of developing IA. Caution should be exercised in single lung transplant recipients. The dosage of D-AmB may vary from 20 mg three times a day to 25 mg/day. The duration of prophylaxis should be guided by interval airway inspection, respiratory surveillance fungal cultures, and clinical risk factors (*Weak; low*).
- Nebulized ABLC can be used at a dose of 50 mg once every two days for two weeks, and then once per week for at least 13 weeks (*Weak; low*).
- Nebulized L-AmB can be administered as 25 mg three times/week for two months, followed by weekly administration for 6 months, and twice per month thereafter (*Weak; low*).
- Systemic antifungal agents active against *Aspergillus* such voriconazole (6 mg/kg for two doses followed by 4 mg every 12h, or itraconazole 200mg every 12h, or posaconazole 300 mg/day (delayed-release tablets) can be used for prophylaxis or preemptive therapy. The role of isovuconazole for antifungal prophylaxis or pre-emptive treatment remains to be determined (*Strong; moderate*).

- Liver enzymes should be monitored to assess the hepatic toxicity in patients receiving systemic antifungal prophylaxis with azoles (*Strong; moderate*).
- Voriconazole should be used with caution in patients with previous history of squamous cell carcinoma, or who are residing in geographical areas with higher incidence of cutaneous malignancy. Voriconazole use warrants photo-protective measures to be put in place, and enhanced skin surveillance (*Strong; high*).
- Alternatives to voriconazole may include posaconazole or isavuconazole (*Weak; low*).

Heart Transplant Recipients

Data on the prophylactic strategies in heart transplant recipients have been primarily reported in single center studies[57, 59, 288-290]. Most of these studies have used targeted prophylaxis with the exception of one study, which used universal prophylaxis and screening along with a CT scan of the chest and serum GM[290].

No recommendations can be made for prophylaxis in heart transplant recipients in pediatric heart transplant recipients, owing to the lack of data.

Recommendations:

- Targeted prophylaxis with itraconazole or voriconazole at a dosage of 4mg/kg every twice daily for 50-150 days, or echinocandins up to 120 days, is recommended in recipients with one or more of the following risk factors *(Strong; low*)
  - Isolation of *Aspergillus* species in respiratory tract cultures without radiological abnormality
  - Presence of airborne *Aspergillus* spores in the ICU
  - Re-operation (thoracic)
  - Presence of CMV disease

- Post-transplant hemodialysis
- Existence of an episode of IA in any patient within the heart transplant program, 2 months before or after heart transplant.

Other solid organ transplant recipients:

There are insufficient data to routinely recommend anti-*Aspergillus* prophylaxis in other solid organ transplant recipients.

RESEARCH AND FUTURE AREAS OF INVESTIGATION

Although the field of IA in SOT has advanced significantly over the last few years, there are areas that require further investigation.

Rezafungin (CD101-IV) is a novel echinocandin with distinctive pharmacokinetic properties that allow once-weekly dosing, and has potent *in-vitro* activity and *in-vivo* efficacy against a broad range of *Aspergillus* species[291]. E1210/APX001 is a broad-spectrum antifungal with a novel mechanism of action -inhibition of fungal glycosylphosphatidylinositol biosynthesis- and reported efficacy in animal models of IA[292, 293]. Ibrexafungerp (SCY-078) is another investigational antifungal agent, first representative of a novel class of structurally-distinct glucan synthase inhibitors, triterpenoids[294]. Clinical trials with these new agents are ongoing.

The development of ECVs/breakpoints for isavuconazole against *Aspergillus* will aid in the interpretation of isavuconazole MICs. A recent survey of US infectious diseases physicians found that 21% of respondents lacked access to antifungal susceptibility testing[295]. Thus, access to antifungal susceptibility testing should be improved[173].

Although a number of potential genetic and immune correlates of protection in IA have been identified[1], the clinical utility of these biomarkers remains largely unexplored. In a recent

study, the levels of pentraxin-3 (PTX-3) in BAL samples were significantly higher among lung transplant patients with IA[89].

The role of combination antifungals for primary therapy of IA remains controversial and further research in this area is needed. Finally, pharmacokinetics studies are necessary to determine the optimal dosing of antifungals in patients on ECMO/cardiovascular support and special populations such as children and patients with CF.

ACKNOWLEDGEMENTS

We thank Mark Richmond for excellent assistance with editing of the manuscript. This manuscript was modified from the Guideline included in the 3rd Edition of the AST Infectious Diseases Guidelines written by N. Singh and S. Husain published in the American Journal of Transplantation 2013; 13 Suppl 4: 228 - 241, and endorsed by the American Society of Transplantation.

Table 1: Risk factors for invasive aspergillosis in organ transplant recipients.

Transplant Type	Risk Factor
Liver transplant recipients	
Early (0- 3months)	– Re-transplantation – Renal failure, particularly requiring renal replacement therapy – Fulminant hepatic failure – MELD >30 – Reoperation involving thoracic or intra-abdominal cavity
Late (> 3 months)	– Cytomegalovirus infection – Creatinine greater than 3.3gm/dl
Lung transplant recipients	
	– Single lung transplant – Early airway ischemia – Cytomegalovirus infection – Rejection and augmented immunosuppression within last 3 months, particularly in CF patients – Pre-transplant *Aspergillus* colonization – Post-transplant *Aspergillus* colonization within a year of transplant – Positive intraoperative *Aspergillus* culture in CF patients – Acquired hypogammaglobulinemia (IgG <400mg/dl)
Heart transplant recipients	
	– *Aspergillus* colonization – Airborne *Aspergillus* spores in ICU – Reoperation (thoracic) – CMV disease – Post-transplant hemodialysis – Existence of an episode of IA in the program 2 months before or after heart transplant
Kidney transplant recipients	
	– Pre-transplant diagnosis of COPD – Acute rejection episode in last three months – Graft failure – High and prolonged duration of corticosteroids

Table 2: Antifungal therapy for IA in adult organ transplant recipients

Drug	Dosing (adult)	TDM	Comments
Primary therapy			
Voriconazole	6 mg/kg IV/PO* every 12 h for 1 day, followed by 4 mg/kg IV/PO every 12 h	Target trough level for treatment is >1 mg/L[180, 181, 185]. A level of 1-5.5 mg/L is considered adequate for most patients. A higher target (e.g. 2-6 mg/L) should be used if there is disease with a poor prognosis (e.g. CNS infection, bulky disease, multifocal infection); infections with pathogen with elevated MICs (e.g. an MIC of 2 mg/L)[129]	Due to accumulation of the IV vehicle (cyclodextrin), the manufacturer recommends the use of oral voriconazole in patients with CrCl<50 mL/min. In clinical practice, however, IV voriconazole has been safely administered to patients with different degrees of renal failure[210, 211]
		Once steady-state levels have been reached, repeat sampling is warranted every 3–5 days[185] in unstable patients and when there is uncertainty about voriconazole concentrations	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended
		Measurement of serum trough concentration within 5-7 days	Non-linear (i.e., highly variable) pharmacokinetics
Alternative therapies			
Isavuconazole	372 mg (isavuconazole 200 mg) IV/PO* every 8 hours for 6 doses, followed by 372 mg (isavuconazole 200 mg) IV/PO once daily	Trough level in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 suggests adequate drug exposure[129]	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended
		No apparent relationship between exposure and efficacy to support routine TDM for isavuconazole[184] Has 130 hour half life – long clearance after discontinuation	Dose adjustment is not required in renal impairment
			Linear pharmacokinetics with low interpatient variability[137]
Liposomal amphotericin B (AmBisome®)	3–5 mg/kg/day IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, renal and hepatic function is recommended
			Higher dosages are not more effective
			Better tolerated than Abelcet®
Amphotericin B Lipid Complex (Abelcet®)	5 mg/ kg/day IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, renal and hepatic function is recommended
			Higher dosages are not more effective
Other therapies*			
Anidulafungin	200 mg IV on day 1 and 100 mg IV daily thereafter	There is currently insufficient evidence to support the routine use of TDM	It has been evaluated only as salvage therapy. Its role as single agent therapy is controversial. It does not require dosage adjustments in patients with renal or hepatic dysfunction
Caspofungin	70 mg IV on day 1 and 50 mg IV/day thereafter	There is currently insufficient evidence to support the routine use of TDM	It has been evaluated only as salvage therapy. Its role as single agent therapy is controversial.

			Monitoring of hepatic function is recommended
			Dose adjustment is not required in renal impairment
			Drug interactions are less clinically important
Micafungin	100-150 mg IV daily	There is currently insufficient evidence to support the routine use of TDM	Monitoring of hepatic function is recommended
			Non-FDA approved use (for treatment of IA)
			Dose adjustment is not required in renal impairment
			Drug interactions are less clinically important
Posaconazole	300 mg PO (delayed release tablets))/IV twice daily on day 1 followed by 300 mg PO (delayed release tablets))/IV once daily on day 2 and thereafter	Target trough level for treatment is >1 mg/L[185] (preferably >1.25 mg/L)	Although the delayed-release tablet can be taken without food, a high-fat meal (~70 g fat) can increase its serum concentration by ~1.5-fold[296]
	When using suspension 200mg PO every 8 h or 400 mg PO every 12 h	Measurement of serum trough concentration within 7 days of initiation of therapy or following dose adjustment[185]	Dose adjustment is not required in renal impairment. Dose after HD in patients on RRT
			Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended
			Non-FDA approved use (for treatment of IA)
Itraconazole	200 mg PO 3 times daily for the first 3 days of therapy, followed by 200-400 PO mg/day	Target trough level is >0.5–1 mg/L[179] *Hydroxy-itraconazole is an active metabolite with antifungal activity similar to itraconazole. Assays that measure total (itraconazole + hydroxy-itraconazole) concentration of itraconazole are preferred.	Itraconazole capsules are poorly orally bioavailable, and absorption is both food-and acid-dependent. In contrast, the oral solution has better bioavailability and there is no significant food or acid effect
		Measurement of serum trough concentration within 5-7 days	Use with caution in patients with renal impairment; some recommend decreasing dose by 50% in CrCl<10mL/min
			Use should be considered only in mild cases intolerant to other therapies

* IV loading favored in patients with CNS infection, bulky disease, and multifocal infection.

**Agents listed here can be considered when first line antifungals are contraindicated, or for salvage therapy in patients who are intolerant to, or whose infections are refractory to standard therapy. Echinocandins are frequently use as second agent in patients receiving combination therapy.

CNI, calcineurin inhibitor; CrCL, creatinine clearance; FDA, US Food and Drug Administration; h, hours; HD, hemodialysis; IA, invasive aspergillosis; IV, intravenous; kg, kilograms; mg, milligrams; mTOR, mammalian target of rapamycin; PO, by mouth; RRT, renal replacement therapy; TDM, therapeutic drug monitoring;

Table 3: Antifungal Agents for Potential Use in Children with IA*

Drug	Dosing (children)	Comments
Voriconazole	*Children 2 to <12 years (regardless of weight), and 12-14 years (<50kg)*	Voriconazole, while only FDA approved for children 12 years and older, is the mainstay of pediatric aspergillosis treatment in all ages
	9 mg/kg IV every 12 h for 2 doses on day 1, followed by 8 mg/kg every 12 h	In children, there is still considerable pharmacokinetic variability, but (pseudo)-linear pharmacokinetics are observed[167]
	Oral suspension: 9 mg/kg every 12 h	
	12-14 years (>50kg) and ≥15 years (regardless of weight)	
	6 mg/kg IV every 12 h for 2 doses; followed by 4 mg/kg every 12 h	
	Oral: 200-300 mg every 12 h or 3-4 mg/kg every 12 h	
Isavuconazole	No pediatric information available	
Amphotericin B deoxycholate	1.0–1.5 mg/kg; infuse as a single dose over 2 h	
Liposomal amphotericin B (AmBisome®)	3–5 mg/kg/day IV	Acceptable front-line therapy. Monitoring of electrolytes, renal and hepatic function is recommended
Amphotericin B Lipid Complex (Abelcet®)	5 mg/ kg/day IV	Higher dosages are not more effective
		Monitoring of electrolytes, renal and hepatic function is recommended
Caspofungin	Loading dose of 70 mg/m^2, followed by 50 mg/m^2 daily thereafter, not to exceed 70 mg	Not for CNS disease
		FDA approved for children 3 months and older
Micafungin	2–3 mg/kg/day	Not for CNS disease FDA approved for children 4 months and older.
	Higher doses might be needed in infants	
	Patients >40 kg use the adult dose (100 mg)	
Anidulafungin	Loading dose of 1.5-3 mg/kg once, followed by 0.75-1.5 mg/kg/day	Not FDA approved for children
		Limited pediatric data; not for CNS disease
Posaconazole	Pediatric dosing has not yet been fully defined. See adult dosage for children 13 years and older	FDA approved for children ≥13 years for the PO formulations, and ≥ 18 years for the IV formulation
		Limited pediatric data
Itraconazole	5-10 mg/kg PO divided into 2 doses	Mild infections in selected older individuals

*See **Table 2** for additional information on each agent

Adapted from: Recommended doses of parental and oral antifungal Drugs, and Drugs for Invasive and Other Serious Fungal Infections [297,188,72].

References

1. Camargo JF, Husain S. Immune Correlates of Protection in Human Invasive Aspergillosis. *Clinical Infectious Diseases* 2014; **59**(4): 569-77.

2. Segal BH. Aspergillosis. *New England Journal of Medicine* 2009; **360**(18): 1870-84.

3. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *ClinInfectDis* 2010; **50**(8): 1101-11.

4. Steinbach WJ, Marr KA, Anaissie EJ, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. *The Journal of infection* 2012; **65**(5): 453-64.

5. Husain S, Silveira FP, Azie N, Franks B, Horn D. Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance® registry analysis. *Medical mycology* 2017; **55**(3): 269-77.

6. Gavalda J, Len O, San Juan R, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005; **41**(1): 52-9.

7. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. *Medicine (Baltimore)* 1999; **78**(2): 123-38.

8. Brown RS, Jr., Lake JR, Katzman BA, et al. Incidence and significance of Aspergillus cultures following liver and kidney transplantation. *Transplantation* 1996; **61**(4): 666-9.

9. Briegel J, Forst H, Spill B, et al. Risk factors for systemic fungal infections in liver transplant recipients. *EurJClinMicrobiolInfectDis* 1995; **14**(5): 375-82.

10. Kusne S, Torre-Cisneros J, Manez R, et al. Factors associated with invasive lung aspergillosis and the significance of positive Aspergillus culture after liver transplantation. *JInfectDis* 1992; **166**(6): 1379-83.

11. Pappas PG. Amphotericin B lipid complex in the treatment of invasive fungal infections: results of the Collaborative Exchange of Antifungal Research (CLEAR), an industry-supported patient registry. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005; **40** (Suppl 6): S379-83.

12. Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005-2007). *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2011; **17**(12): 1882-9.

13. Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. *Pediatrics* 2006; **117**(4): e711-6.

14. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. *ClinInfectDis* 2003; **36**(1): 46-52.

15. Fortun J, Martin-Davila P, Moreno S, et al. Risk factors for invasive aspergillosis in liver transplant recipients. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2002; **8**(11): 1065-70.

16. Saliba F, Delvart V, Ichai P, et al. Fungal infections after liver transplantation: outcomes and risk factors revisited in the MELD era. *Clinical transplantation* 2013; **27**(4): E454-61.

17. Singh N, Paterson DL. Aspergillus infections in transplant recipients. *Clinical microbiology reviews* 2005; **18**(1): 44-69.

18. Singh N, Paterson DL, Gayowski T, Wagener MM, Marino IR. Preemptive prophylaxis with a lipid preparation of amphotericin B for invasive fungal infections in liver

transplant recipients requiring renal replacement therapy. *Transplantation* 2001; **71**(7): 910-3.

19. Osawa M, Ito Y, Hirai T, et al. Risk factors for invasive aspergillosis in living donor liver transplant recipients. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2007; **13**(4): 566-70.

20. Singh N, Arnow PM, Bonham A, et al. Invasive aspergillosis in liver transplant recipients in the 1990s. *Transplantation* 1997; **64**(5): 716-20.

21. Selby R, Ramirez CB, Singh R, et al. Brain abscess in solid organ transplant recipients receiving cyclosporine-based immunosuppression. *ArchSurg* 1997; **132**(3): 304-10.

22. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. *Transplantation* 2006; **81**(3): 320-6.

23. Altiparmak MR, Apaydin S, Trablus S, et al. Systemic fungal infections after renal transplantation. *ScandJInfectDis* 2002; **34**(4): 284-8.

24. Cofan F, Ricart MJ, Oppenheimer F, et al. Study of kidney rejection following simultaneous kidney-pancreas transplantation. *Nephron* 1996; **74**(1): 58-63.

25. Weiland D, Ferguson RM, Peterson PK, Snover DC, Simmons RL, Najarian JS. Aspergillosis in 25 renal transplant patients. Epidemiology, clinical presentation, diagnosis, and management. *AnnSurg* 1983; **198**(5): 622-9.

26. Gustafson TL, Schaffner W, Lavely GB, Stratton CW, Johnson HK, Hutcheson RH, Jr. Invasive aspergillosis in renal transplant recipients: correlation with corticosteroid therapy. *JInfectDis* 1983; **148**(2): 230-8.

27. Peterson PK, Ferguson R, Fryd DS, Balfour HH, Jr., Rynasiewicz J, Simmons RL. Infectious diseases in hospitalized renal transplant recipients: a prospective study of a complex and evolving problem. *Medicine (Baltimore)* 1982; **61**(6): 360-72.

28. Gallis HA, Berman RA, Cate TR, Hamilton JD, Gunnells JC, Stickel DL. Fungal infection following renal transplantation. *ArchInternMed* 1975; **135**(9): 1163-72.

29. Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, et al. Multinational case-control study of risk factors for the development of late invasive pulmonary aspergillosis following kidney transplantation. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2018; **24**(2): 192-8.

30. Panackal AA, Dahlman A, Keil KT, et al. Outbreak of invasive aspergillosis among renal transplant recipients. *Transplantation* 2003; **75**(7): 1050-3.

31. Husain S, Paterson DL, Studer S, et al. Voriconazole prophylaxis in lung transplant recipients. *AmJTransplant* 2006; **6**(12): 3008-16.

32. Doligalski CT, Benedict K, Cleveland AA, et al. Epidemiology of invasive mold infections in lung transplant recipients. *AmJTransplant* 2014; **14**(6): 1328-33.

33. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transplant infectious disease : an official journal of the Transplantation Society* 2010; **12**(3): 220-9.

34. Grossi P, Farina C, Fiocchi R, Dalla Gasperina D. Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: a multicenter retrospective study. Italian Study Group of Fungal Infections in Thoracic Organ Transplant Recipients. *Transplantation* 2000; **70**(1): 112–6.

35. Aguilar-Guisado M, Givalda J, Ussetti P, et al. Pneumonia after lung transplantation in the RESITRA Cohort: a multicenter prospective study. *AmJTransplant* 2007; **7**(8): 1989-96.

36. Aguilar CA, Hamandi B, Fegbeutel C, et al. Clinical Risk Factors for Invasive Aspergillosis in Lung Transplant Recipients: Results of an International Cohort Study. *The Journal of Heart and Lung Transplantation* 2018; **36**(4): S24.

37. Higgins R, McNeil K, Dennis C, et al. Airway stenoses after lung transplantation: management with expanding metal stents. *JHeart Lung Transplant* 1994; **13**(5): 774-8.

38. Westney GE, Kesten S, De Hoyos A, Chapparro C, Winton T, Maurer JR. Aspergillus infection in single and double lung transplant recipients. *Transplantation* 1996; **61**(6): 915-9.

39. Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. *Transplantation* 2001; **71**(2): 242-6.

40. Husni RN, Gordon SM, Longworth DL, et al. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 1998; **26**(3): 753-5.

41. Cahill BC, Hibbs JR, Savik K, et al. Aspergillus airway colonization and invasive disease after lung transplantation. *Chest* 1997; **112**(5): 1160-4.

42. Nunley DR, Ohori P, Grgurich WF, et al. Pulmonary aspergillosis in cystic fibrosis lung transplant recipients. *Chest* 1998; **114**(5): 1321-9.

43. Helmi M, Love RB, Welter D, Cornwell RD, Meyer KC. Aspergillus infection in lung transplant recipients with cystic fibrosis: risk factors and outcomes comparison to other types of transplant recipients. *Chest* 2003; **123**(3): 800-8.

44. Vadnerkar A, Clancy CJ, Celik U, et al. Impact of mold infections in explanted lungs on outcomes of lung transplantation. *Transplantation* 2010; **89**(2): 253-60.

45. Kanj SS, Tapson V, Davis RD, Madden J, Browning I. Infections in patients with cystic fibrosis following lung transplantation. *Chest* 1997; **112**(4): 924-30.

46. Tofte N, Jensen C, Tvede M, Andersen CB, Carlsen J, Iversen M. Use of prophylactic voriconazole for three months after lung transplantation does not reduce infection with Aspergillus: a retrospective study of 147 patients. *ScandJInfectDis* 2012; **44**(11): 835-41.

47. Shitrit D, Ollech JE, Ollech A, et al. Itraconazole prophylaxis in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. *JHeart Lung Transplant* 2005; **24**(12): 2148-52.

48. Dhar D, Dickson JL, Carby MR, Lyster HS, Hall AV, Banner NR. Fungal infection in cardiothoracic transplant recipients: outcome without systemic amphotericin therapy. *Transplant International* 2012; **25**(7): 758-64.

49. Iversen M, Burton CM, Vand S, et al. Aspergillus infection in lung transplant patients: incidence and prognosis. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2007; **26**(12): 879-86.

50. Peghin M, Hirsch HH, Len Ó, et al. Epidemiology and Immediate Indirect Effects of Respiratory Viruses in Lung Transplant Recipients: A 5-Year Prospective Study. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2017; **17**(5): 1304-12.

51. Luong ML, Chaparro C, Stephenson A, et al. Pretransplant Aspergillus colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. *Transplantation* 2014; **97**(3): 351-7.

52. Husain S, Zaldonis D, Kusne S, Kwak EJ, Paterson DL, McCurry KR. Variation in antifungal prophylaxis strategies in lung transplantation. *TransplInfectDis* 2006; **8**(4): 213-8.

53. Neoh CF, Snell GI, Kotsimbos T, et al. Antifungal prophylaxis in lung transplantation--a world-wide survey. *American journal of transplantation : official journal*

of the American Society of Transplantation and the American Society of Transplant Surgeons 2011; **11**(2): 361-6.

54. Munoz P, Singh N, Bouza E. Treatment of solid organ transplant patients with invasive fungal infections: should a combination of antifungal drugs be used? *CurrOpinInfectDis* 2006; **19**(4): 365-70.

55. Neofytos D, Chatzis O, Nasioudis D, et al. Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss Transplant Cohort Study. *Transplant Infectious Disease* 2018; **0**(0): e12898.

56. Berenguer J, Munoz P, Parras F, Fernandez-Baca V, Hernandez-Sampelayo T, Bouza E. Treatment of deep mycoses with liposomal amphotericin B. *EurJClinMicrobiolInfectDis* 1994; **13**(6): 504-7.

57. Munoz P, Rodriguez C, Bouza E, et al. Risk factors of invasive aspergillosis after heart transplantation: protective role of oral itraconazole prophylaxis. *AmJTransplant* 2004; **4**(4): 636-43.

58. Munoz P, Alcala L, Sanchez CM, et al. The isolation of Aspergillus fumigatus from respiratory tract specimens in heart transplant recipients is highly predictive of invasive aspergillosis. *Transplantation* 2003; **75**(3): 326-9.

59. Pelaez T, Munoz P, Guinea J, et al. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **54**(3): e24-31.

60. Cook JC, Cook A, Tran RH, Chang PP, Rodgers JE. A case control study of the risk factors for developing aspergillosis following cardiac transplant. *Clinical transplantation* 2018; **32**(9): e13367.

61. Munoz P, Ceron I, Valerio M, et al. Invasive aspergillosis among heart transplant recipients: a 24-year perspective. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2014; **33**(3): 278-88.

62. Saxena S, Gee J, Klieger S, et al. Invasive Fungal Disease in Pediatric Solid Organ Transplant Recipients. *Journal of the Pediatric Infectious Diseases Society* 2018; **7**(3): 219-25.

63. Camargo JF. Donor-derived infections in solid organ transplant recipients: Challenging the 30-day paradigm. *Transplant Infectious Disease* 2017; **19**(2): e12665.

64. Linden E, Restrepo D, Dikman S, Murphy B, Huprikar S. Aspergillus infection limited to renal allograft: case report and review of literature. *Transplant infectious disease : an official journal of the Transplantation Society* 2006; **8**(3): 177-81.

65. Keating MR, Guerrero MA, Daly RC, Walker RC, Davies SF. Transmission of invasive aspergillosis from a subclinically infected donor to three different organ transplant recipients. *Chest* 1996; **109**(4): 1119-24.

66. Mueller NJ, Weisser M, Fehr T, et al. Donor-derived aspergillosis from use of a solid organ recipient as a multiorgan donor. *Transplant infectious disease : an official journal of the Transplantation Society* 2010; **12**(1): 54-9.

67. N.J. M, M. W, T. F, et al. Donor-derived aspergillosis from use of a solid organ recipient as a multiorgan donor. *Transplant Infectious Disease* 2010; **12**(1): 54-9.

68. Valerio M, Machado M, Cedeno S, et al. Donor-derived invasive aspergillosis after kidney transplant. *Medical mycology case reports* 2018; **22**: 24-6.

69. Garrido J, Lerma JL, Heras M, et al. Pseudoaneurysm of the iliac artery secondary to Aspergillus infection in two recipients of kidney transplants from the same donor. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2003; **41**(2): 488-92.

70. Fernandez-Ruiz M, Silva JT, San-Juan R, et al. Aspergillus tracheobronchitis: report of 8 cases and review of the literature. *Medicine (Baltimore)* 2012; **91**(5): 261-73.

71. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. *AmRevRespirDis* 1991; **144**(3 Pt 1): 552-6.

72. Patterson TF, Thompson GR, 3rd, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; **63**(4): e1-e60.

73. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. *Future microbiology* 2012; **7**(5): 639-55.

74. Baddley JW, Andes DR, Marr KA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2010; **50**(12): 1559-67.

75. Mehrad B, Paciocco G, Martinez FJ, Ojo TC, Iannettoni MD, Lynch JP, 3rd. Spectrum of Aspergillus infection in lung transplant recipients: case series and review of the literature. *Chest* 2001; **119**(1): 169-75.

76. Hoyo I, Sanclemente G, de la Bellacasa JP, et al. Epidemiology, clinical characteristics, and outcome of invasive aspergillosis in renal transplant patients. *Transplant infectious disease : an official journal of the Transplantation Society* 2014; **16**(6): 951-7.

77. Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, et al. Clinical Presentation and Determinants of Mortality of Invasive Pulmonary Aspergillosis in Kidney Transplant Recipients: A Multinational Cohort Study. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2016; **16**(11): 3220-34.

78. Fortun J, Martin-Davila P, Alvarez ME, et al. ASPERGILLUS ANTIGENEMIA SANDWICH-ENZYME IMMUNOASSAY TEST AS A SERODIAGNOSTIC METHOD FOR INVASIVE ASPERGILLOSIS IN LIVER TRANSPLANT RECIPIENTS1. *Transplantation* 2001; **71**(1): 145-9.

79. Kwak EJ, Husain S, Obman A, et al. Efficacy of Galactomannan Antigen in the Platelia Aspergillus Enzyme Immunoassay for Diagnosis of Invasive Aspergillosis in Liver Transplant Recipients. *Journal of clinical microbiology* 2004; **42**(1): 435-8.

80. Singh N, Winston DJ, Limaye AP, et al. Performance Characteristics of Galactomannan and beta-d-Glucan in High-Risk Liver Transplant Recipients. *Transplantation* 2015; **99**(12): 2543-50.

81. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia Aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2004; **4**(5): 796-802.

82. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *ClinInfectDis* 2006; **42**(10): 1417-27.

83. Avcu G, Karapinar DY, Akinci AB, et al. Utility of the serum galactomannan assay for the diagnosis of invasive aspergillosis in children with acute lymphoblastic leukemia. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2017; **54**: 8-12.

84. Clancy CJ, Jaber RA, Leather HL, et al. Bronchoalveolar lavage galactomannan in diagnosis of invasive pulmonary aspergillosis among solid-organ transplant recipients. *Journal of clinical microbiology* 2007; **45**(6): 1759-65.

85. Husain S, Paterson DL, Studer SM, et al. Aspergillus galactomannan antigen in the bronchoalveolar lavage fluid for the diagnosis of invasive aspergillosis in lung transplant recipients. *Transplantation* 2007; **83**(10): 1330-6.

86. Husain S, Clancy CJ, Nguyen MH, et al. Performance characteristics of the platelia Aspergillus enzyme immunoassay for detection of Aspergillus galactomannan antigen in bronchoalveolar lavage fluid. *Clinical and vaccine immunology : CVI* 2008; **15**(12): 1760-3.

87. Luong ML, Clancy CJ, Vadnerkar A, et al. Comparison of an Aspergillus real-time polymerase chain reaction assay with galactomannan testing of bronchoalvelolar lavage fluid for the diagnosis of invasive pulmonary aspergillosis in lung transplant recipients. *ClinInfectDis* 2011; **52**(10): 1218-26.

88. Pasqualotto AC, Xavier MO, Sanchez LB, et al. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. *Transplantation* 2010; **90**(3): 306-11.

89. Kabbani D, Bhaskaran A, Singer LG, et al. Pentraxin 3 levels in bronchoalveolar lavage fluid of lung transplant recipients with invasive aspergillosis. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2017; **36**(9): 973-9.

90. Tortorano AM, Esposto MC, Prigitano A, et al. Cross-reactivity of Fusarium spp. in the Aspergillus Galactomannan enzyme-linked immunosorbent assay. *Journal of clinical microbiology* 2012; **50**(3): 1051-3.

91. Swanink CM, Meis JF, Rijs AJ, Donnelly JP, Verweij PE. Specificity of a sandwich enzyme-linked immunosorbent assay for detecting Aspergillus galactomannan. *JClinMicrobiol* 1997; **35**(1): 257-60.

92. Xu H, Fan SG. [Possible mechanisms of the action of lymphocyte proliferation-inhibitory factor(s) in rat serum receiving electroacupuncture stimulation]. *Sheng li xue bao : [Acta physiologica Sinica]* 1990; **42**(6): 555-61.

93. Capoor MR, Agarwal P, Goel M, et al. Invasive pulmonary mycosis due to Chaetomium globosum with false-positive galactomannan test: a case report and literature review. *Mycoses* 2016; **59**(3): 186-93.

94. Xavier MO, Pasqualotto AC, Cardoso IC, Severo LC. Cross-reactivity of Paracoccidioides brasiliensis, Histoplasma capsulatum, and Cryptococcus species in the commercial Platelia Aspergillus enzyme immunoassay. *Clinical and vaccine immunology : CVI* 2009; **16**(1): 132-3.

95. Dalle F, Charles PE, Blanc K, et al. Cryptococcus neoformans Galactoxylomannan Contains an Epitope(s) That Is Cross-Reactive with Aspergillus Galactomannan. *Journal of clinical microbiology* 2005; **43**(6): 2929-31.

96. Mohammadi S, Khalilzadeh S, Goudarzipour K, et al. Bronchoalveolar galactomannan in invasive pulmonary aspergillosis: a prospective study in pediatric patients. *Medical mycology* 2015; **53**(7): 709-16.

97. de Mol M, de Jongste JC, van Westreenen M, et al. Diagnosis of invasive pulmonary aspergillosis in children with bronchoalveolar lavage galactomannan. *Pediatric pulmonology* 2013; **48**(8): 789-96.

98. Levesque E, Rizk F, Noorah Z, et al. Detection of (1,3)-beta-d-Glucan for the Diagnosis of Invasive Fungal Infection in Liver Transplant Recipients. *International journal of molecular sciences* 2017; **18**(4).

99. Akamatsu N, Sugawara Y, Kaneko J, Tamura S, Makuuchi M. Preemptive treatment of fungal infection based on plasma (1 --> 3)beta-D-glucan levels after liver transplantation. *Infection* 2007; **35**(5): 346-51.

100. Alexander BD, Smith PB, Davis RD, Perfect JR, Reller LB. The (1,3)beta-D-glucan test as an aid to early diagnosis of invasive fungal infections following lung transplantation. *Journal of clinical microbiology* 2010; **48**(11): 4083-8.

101. Bhaskaran A, Kabbani D, Singer LG, et al. (1,3) beta-D-Glucan in Bronchoalveolar Lavage of Lung Transplant Recipients for the Diagnosis of Invasive Pulmonary Aspergillosis. *Medical mycology* 2017; **55**(2): 173-9.

102. Avni T, Levy I, Sprecher H, Yahav D, Leibovici L, Paul M. Diagnostic accuracy of PCR alone compared to galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis: a systematic review. *JClinMicrobiol* 2012; **50**(11): 3652-8.

103. Arvanitis M, Ziakas PD, Zacharioudakis IM, Zervou FN, Caliendo AM, Mylonakis E. PCR in diagnosis of invasive aspergillosis: a meta-analysis of diagnostic performance. *Journal of clinical microbiology* 2014; **52**(10): 3731-42.

104. White PL, Wingard JR, Bretagne S, et al. Aspergillus Polymerase Chain Reaction: Systematic Review of Evidence for Clinical Use in Comparison With Antigen Testing. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; **61**(8): 1293-303.

105. Haidar G, Falcione BA, Nguyen MH. Diagnostic Modalities for Invasive Mould Infections among Hematopoietic Stem Cell Transplant and Solid Organ Recipients: Performance Characteristics and Practical Roles in the Clinic. *J Fungi (Basel)*, 2015. http://europepmc.org/abstract/MED/29376911

http://europepmc.org/articles/PMC5753113?pdf=render

http://europepmc.org/articles/PMC5753113

https://doi.org/10.3390/jof1020252 (accessed 2015/09//).

106. White PL, Perry MD, Moody A, Follett SA, Morgan G, Barnes RA. Evaluation of analytical and preliminary clinical performance of Myconostica MycAssay Aspergillus when testing serum specimens for diagnosis of invasive Aspergillosis. *Journal of clinical microbiology* 2011; **49**(6): 2169-74.

107. Guinea J, Padilla C, Escribano P, et al. Evaluation of MycAssay™ Aspergillus for diagnosis of invasive pulmonary aspergillosis in patients without hematological cancer. *PloS one* 2013; **8**(4): e61545.

108. Gupta P, Ahmad A, Khare V, et al. Comparative evaluation of pan-fungal real-time PCR, galactomannan and (1-3)-beta-D-glucan assay for invasive fungal infection in paediatric cancer patients. *Mycoses* 2017; **60**(4): 234-40.

109. White PL, Posso RB, Barnes RA. Analytical and Clinical Evaluation of the PathoNostics AsperGenius Assay for Detection of Invasive Aspergillosis and Resistance to Azole Antifungal Drugs during Testing of Serum Samples. *Journal of clinical microbiology* 2015; **53**(7): 2115-21.

110. Willinger B, Lackner M, Lass-Flörl C, et al. Bronchoalveolar lavage lateral-flow device test for invasive pulmonary aspergillosis in solid organ transplant patients: a semiprospective multicenter study. *Transplantation* 2014; **98**(8): 898-902.

111. Pan Z, Fu M, Zhang J, Zhou H, Fu Y, Zhou J. Diagnostic accuracy of a novel lateral-flow device in invasive aspergillosis: a meta-analysis. *Journal of Medical Microbiology* 2015; **64**(7): 702-7.

112. Koo S, Thomas HR, Daniels SD, et al. A breath fungal secondary metabolite signature to diagnose invasive aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **59**(12): 1733-40.

113. Marr KA, Datta K, Mehta S, et al. Urine Antigen Detection as an Aid to Diagnose Invasive Aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018; **67**(11): 1705-11.

114. Page ID, Richardson M, Denning DW. Antibody testing in aspergillosis--quo vadis? *Medical mycology* 2015; **53**(5): 417-39.

115. Du C, Wingard JR, Cheng S, Nguyen MH, Clancy CJ. Serum IgG responses against Aspergillus proteins before hematopoietic stem cell transplantation or chemotherapy identify patients who develop invasive aspergillosis. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2012; **18**(12): 1927-34.

116. Page ID, Baxter C, Hennequin C, et al. Receiver operating characteristic curve analysis of four Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis. *Diagnostic microbiology and infectious disease* 2018; **91**(1): 47-51.

117. Page ID, Richardson MD, Denning DW. Siemens Immulite Aspergillus-specific IgG assay for chronic pulmonary aspergillosis diagnosis. *Medical mycology* 2018; **Epub ahead of print**.

118. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *ClinInfectDis* 2007; **44**(3): 373-9.

119. Greene R. The radiological spectrum of pulmonary aspergillosis. *Medical mycology* 2005; **43**(Suppl 1): S147-54.

120. Caillot D, Latrabe V, Thiebaut A, et al. Computer tomography in pulmonary invasive aspergillosis in hematological patients with neutropenia: an useful tool for diagnosis and assessment of outcome in clinical trials. *European journal of radiology* 2010; **74**(3): e172-5.

121. Prasad A, Agarwal K, Deepak D, Atwal SS. Pulmonary Aspergillosis: What CT can Offer Before it is too Late! *Journal of clinical and diagnostic research : JCDR* 2016; **10**(4): TE01-TE5.

122. Park SY, Kim SH, Choi SH, et al. Clinical and radiological features of invasive pulmonary aspergillosis in transplant recipients and neutropenic patients. *TransplInfectDis* 2010; **12**(4): 309-15.

123. Singh N, Suarez JF, Avery R, et al. Risk factors and outcomes in lung transplant recipients with nodular invasive pulmonary aspergillosis. *JInfect* 2013; **67**(1): 72-8.

124. Lim C, Seo JB, Park SY, et al. Analysis of initial and follow-up CT findings in patients with invasive pulmonary aspergillosis after solid organ transplantation. *Clinical radiology* 2012; **67**(12): 1179-86.

125. Stanzani M, Sassi C, Lewis RE, et al. High resolution computed tomography angiography improves the radiographic diagnosis of invasive mold disease in patients with hematological malignancies. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; **60**(11): 1603-10.

126. Stanzani M, Battista G, Sassi C, et al. Computed tomographic pulmonary angiography for diagnosis of invasive mold diseases in patients with hematological malignancies. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **54**(5): 610-6.

127. Fernandez Rde L, Fischer FM. Irregular work schedule: a case of a steward. *Progress in clinical and biological research* 1990; **341B**: 317-25.

128. Kim JY, Yoo JW, Oh M, et al. (18)F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography findings are different between invasive and noninvasive pulmonary aspergillosis. *Journal of computer assisted tomography* 2013; **37**(4): 596-601.

129. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2018; **24** (Suppl 1): e1-e38.

130. Hachem RY, Langston AA, Graybill JR, Perfect JR, Patino H, Raad II. Posaconazole as salvage treatment of invasive fungal infections in patients with underlying renal impairment. *The Journal of antimicrobial chemotherapy* 2008; **62**(6): 1386-91.

131. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *The New England journal of medicine* 2002; **347**(6): 408-15.

132. Fortun J, Martin-Davila P, Sanchez MA, et al. Voriconazole in the treatment of invasive mold infections in transplant recipients. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2003; **22**(7): 408-13.

133. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2002; **34**(5): 563-71.

134. Veroux M, Corona D, Gagliano M, et al. Voriconazole in the treatment of invasive aspergillosis in kidney transplant recipients. *Transplantation proceedings* 2007; **39**(6): 1838-40.

135. Baddley JW, Andes DR, Marr KA, et al. Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis. *Medical mycology* 2013; **51**(2): 128-35.

136. Kramer M, Kramer MR, Blau H, Bishara J, Axer-Siegel R, Weinberger D. Intravitreal voriconazole for the treatment of endogenous Aspergillus endophthalmitis. *Ophthalmology* 2006; **113**(7): 1184-6.

137. Maertens JA, Raad, II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016; **387**(10020): 760-9.

138. Trang TP, Hanretty AM, Langelier C, Yang K. Use of isavuconazole in a patient with voriconazole-induced QTc prolongation. 2017; **19**(4).

139. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007; **44**(1): 2-12.

140. Durani U, Tosh PK, Barreto JN, Estes LL, Jannetto PJ, Tande AJ. Retrospective Comparison of Posaconazole Levels in Patients Taking the Delayed-Release Tablet versus the Oral Suspension. *Antimicrobial agents and chemotherapy* 2015; **59**(8): 4914-8.

141. D. S, A. W, F. I, et al. Posaconazole liquid vs tablet formulation in lung transplant recipients. *Mycoses* 2018; **61**(3): 186-94.

142. Conant MM, Sha BE, Proia LA. Use of posaconazole delayed-release tablets for treatment of invasive aspergillosis. *Mycoses* 2015; **58**(5): 313-4.

143. Carby MR, Hodson ME, Banner NR. Refractory pulmonary aspergillosis treated with caspofungin after heart-lung transplantation. *Transplant international : official journal of the European Society for Organ Transplantation* 2004; **17**(9): 545-8.

144. Aguado JM, Varo E, Usetti P, et al. Safety of anidulafungin in solid organ transplant recipients. *Liver transplantation : official publication of the American Association for the*

Study of Liver Diseases and the International Liver Transplantation Society 2012; **18**(6): 680-5.

145. Wadi J, Al-kawasmeh SI, Kamel MT, AlJayyousi BB. Disseminated invasive aspergillosis successfully treated with micafungin in a renal transplant recipient. *Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia* 2010; **21**(5): 914-8.

146. Heinz WJ, Buchheidt D, Ullmann AJ. Clinical evidence for caspofungin monotherapy in the first-line and salvage therapy of invasive Aspergillus infections. *Mycoses* 2016; **59**(8): 480-93.

147. Cleary JD. Echinocandins: pharmacokinetic and therapeutic issues. *Current medical research and opinion* 2009; **25**(7): 1741-50.

148. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Annals of internal medicine* 2015; **162**(2): 81-9.

149. Denning DW, Marr KA, Lau WM, et al. Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *JInfect* 2006; **53**(5): 337-49.

150. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2000; **31**(5): 1155-63.

151. Fleming RV, Kantarjian HM, Husni R, et al. Comparison of amphotericin B lipid complex (ABLC) vs. ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. *Leukemia & lymphoma* 2001; **40**(5-6): 511-20.

152. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. *Clinical microbiology reviews* 2014; **27**(1): 68-88.

153. Martin-Pena A, Aguilar-Guisado M, Espigado I, Cisneros JM. Antifungal combination therapy for invasive aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **59**(10): 1437-45.

154. Garbati MA, Alasmari FA, Al-Tannir MA, Tleyjeh IM. The role of combination antifungal therapy in the treatment of invasive aspergillosis: a systematic review. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2012; **16**(2): e76-81.

155. Barchiesi F, Mazzocato S, Mazzanti S, et al. Invasive aspergillosis in liver transplant recipients: epidemiology, clinical characteristics, treatment, and outcomes in 116 cases. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2015; **21**(2): 204-12.

156. Seroy J, Antiporta P, Grim SA, Proia LA, Singh K, Clark NM. Aspergillus calidoustus case series and review of the literature. *Transplant infectious disease : an official journal of the Transplantation Society* 2017; **19**(5): e12755.

157. Singh N, Wagener MM, Cacciarelli TV, Levitsky J. Antifungal management practices in liver transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2008; **8**(2): 426-31.

158. Wattier RL, Dvorak CC, Hoffman JA, et al. A Prospective, International Cohort Study of Invasive Mold Infections in Children. *Journal of the Pediatric Infectious Diseases Society* 2015; **4**(4): 313-22.

159. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. *Infection* 2011; **39**(3): 201-10.

160. Panackal AA, Parisini E, Proschan M. Salvage combination antifungal therapy for acute invasive aspergillosis may improve outcomes: a systematic review and meta-analysis. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2014; **28**: 80-94.

161. Arendrup MC, Cuenca-Estrella M, Lass-Florl C, Hope WW. Breakpoints for antifungal agents: an update from EUCAST focussing on echinocandins against Candida spp. and triazoles against Aspergillus spp. *Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy* 2013; **16**(6): 81-95.

162. Espinel-Ingroff A, Chowdhary A, Gonzalez GM, et al. Multicenter study of isavuconazole MIC distributions and epidemiological cutoff values for Aspergillus spp. for the CLSI M38-A2 broth microdilution method. *Antimicrobial agents and chemotherapy* 2013; **57**(8): 3823-8.

163. Howard SJ, Lass-Florl C, Cuenca-Estrella M, Gomez-Lopez A, Arendrup MC. Determination of isavuconazole susceptibility of Aspergillus and Candida species by the EUCAST method. *Antimicrobial agents and chemotherapy* 2013; **57**(11): 5426-31.

164. Espinel-Ingroff A, Fothergill A, Fuller J, Johnson E, Pelaez T, Turnidge J. Wild-type MIC distributions and epidemiological cutoff values for caspofungin and Aspergillus spp. for the CLSI broth microdilution method (M38-A2 document). *Antimicrobial agents and chemotherapy* 2011; **55**(6): 2855-9.

165. Andes DR, Ghannoum MA, Mukherjee PK, et al. Outcomes by Minimum Inhibitory Concentrations for Patients Treated with Isavuconazole or Voriconazole for Invasive

Aspergillosis in the Phase 3 SECURE and VITAL Trials. *Antimicrobial agents and chemotherapy* 2018; **63**(1): e01634-18.

166. Lockhart SR, Zimbeck AJ, Baddley JW, et al. In Vitro Echinocandin Susceptibility of Aspergillus Isolates from Patients Enrolled in the Transplant-Associated Infection Surveillance Network. *Antimicrobial agents and chemotherapy* 2011; **55**(8): 3944-6.

167. Hope WW, Cuenca-Estrella M, Lass-Florl C, Arendrup MC. EUCAST Technical Note on Voriconazole and Aspergillus spp. *Clinical Microbiology and Infection* 2013; **19**(6): E278-E80.

168. C. AM, M. C-E, C. L-F, W. HW. EUCAST Technical Note on Aspergillus and amphotericin B, itraconazole, and posaconazole. *Clinical Microbiology and Infection* 2012; **18**(7): E248-E50.

169. Gregson L, Goodwin J, Johnson A, et al. In vitro susceptibility of Aspergillus fumigatus to isavuconazole: correlation with itraconazole, voriconazole, and posaconazole. *Antimicrobial agents and chemotherapy* 2013; **57**(11): 5778-80.

170. Heo ST, Tatara AM, Jimenez-Ortigosa C, et al. Changes in In Vitro Susceptibility Patterns of Aspergillus to Triazoles and Correlation With Aspergillosis Outcome in a Tertiary Care Cancer Center, 1999-2015. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2017; **65**(2): 216-25.

171. Alanio A, Cabaret O, Sitterle E, et al. Azole preexposure affects the Aspergillus fumigatus population in patients. *Antimicrobial agents and chemotherapy* 2012; **56**(9): 4948-50.

172. Benoit P, Dea G-H, Alexandre A, et al. Failure of voriconazole therapy due to acquired azole resistance in Aspergillus fumigatus in a kidney transplant recipient with chronic necrotizing aspergillosis. *American Journal of Transplantation* 2018; **18**(9): 2352–5.

173. Schwartz IS, Patterson TF. The Emerging Threat of Antifungal Resistance in Transplant Infectious Diseases. *Current infectious disease reports* 2018; **20**(3): 2.

174. Baddley JW, Marr KA, Andes DR, et al. Patterns of susceptibility of Aspergillus isolates recovered from patients enrolled in the Transplant-Associated Infection Surveillance Network. *Journal of clinical microbiology* 2009; **47**(10): 3271-5.

175. van der Linden JWM, Arendrup MC, Warris A, et al. Prospective Multicenter International Surveillance of Azole Resistance in Aspergillus fumigatus. *Emerging infectious diseases* 2015; **21**(6): 1041-4.

176. Shalhoub S, Luong ML, Howard SJ, et al. Rate of cyp51A mutation in Aspergillus fumigatus among lung transplant recipients with targeted prophylaxis. *Journal of Antimicrobial Chemotherapy* 2015; **70**(4): 1064-7.

177. Balajee SA, Kano R, Baddley JW, et al. Molecular identification of Aspergillus species collected for the Transplant-Associated Infection Surveillance Network. *Journal of clinical microbiology* 2009; **47**(10): 3138-41.

178. Egli A, Fuller J, Humar A, et al. Emergence of Aspergillus calidoustus infection in the era of posttransplantation azole prophylaxis. *Transplantation* 2012; **94**(4): 403-10.

179. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *Journal of Antimicrobial Chemotherapy* 2014; **69**(5): 1162-76.

180. Luong ML, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *The Journal of antimicrobial chemotherapy* 2016; **71**(7): 1786-99.

181. Hamada Y, Seto Y, Yago K, Kuroyama M. Investigation and threshold of optimum blood concentration of voriconazole: a descriptive statistical meta-analysis. *Journal of*

infection and chemotherapy : official journal of the Japan Society of Chemotherapy 2012; **18**(4): 501-7.

182. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrobial agents and chemotherapy* 2011; **55**(10): 4782-8.

183. Mitsani D, Nguyen MH, Shields RK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. *Antimicrobial agents and chemotherapy* 2012; **56**(5): 2371-7.

184. Desai AV, Kovanda LL, Hope WW, et al. Exposure-Response Relationships for Isavuconazole in Patients with Invasive Aspergillosis and Other Filamentous Fungi. *Antimicrobial agents and chemotherapy* 2017; **61**(12): e01034-17.

185. Stott KE, Hope WW. Therapeutic drug monitoring for invasive mould infections and disease: pharmacokinetic and pharmacodynamic considerations. *Journal of Antimicrobial Chemotherapy* 2017; **72**(Suppl 1): i12-i8.

186. Red Book, 30th Edition (2015); 2015.

187. Driscoll TA, Yu LC, Frangoul H, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. *Antimicrobial agents and chemotherapy* 2011; **55**(12): 5770-9.

188. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. *Antimicrobial agents and chemotherapy* 2012; **56**(6): 3032-42.

189. Walsh TJ, Driscoll T, Milligan PA, et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrobial agents and chemotherapy* 2010; **54**(10): 4116-23.

190. Timpone JG, Jr., Girlanda R, Rudolph L, Fishbein TM. Infections in intestinal and multivisceral transplant recipients. *Infectious disease clinics of North America* 2013; **27**(2): 359-77.

191. Florescu DF, Sandkovsky U. Fungal infections in intestinal and multivisceral transplant recipients. *Current opinion in organ transplantation* 2015; **20**(3): 295-302.

192. Kubak BM, Huprikar SS. Emerging & Rare Fungal Infections in Solid Organ Transplant Recipients. *American Journal of Transplantation* 2009; **9**(Suppl 4): S208-S26.

193. Bharadwaj S, Tandon P, Gohel TD, et al. Current status of intestinal and multivisceral transplantation. *Gastroenterology Report* 2017; **5**(1): 20-8.

194. Kohler S, Gerlach U, Guckelberger O, et al. Successful treatment of invasive sphenoidal, pulmonary and intracerebral aspergillosis after multivisceral transplantation. *Transplant international : official journal of the European Society for Organ Transplantation* 2009; **22**(5): 589-91.

195. Vianna R, Misra V, Fridell JA, Goldman M, Mangus RS, Tector J. Survival after disseminated invasive aspergillosis in a multivisceral transplant recipient. *Transplantation proceedings* 2007; **39**(1): 305-7.

196. Valenza G, Tappe D, Turnwald D, et al. Prevalence and antimicrobial susceptibility of microorganisms isolated from sputa of patients with cystic fibrosis. *Journal of Cystic Fibrosis* 2008; **7**(2): 123-7.

197. Bargon J, Dauletbaev N, Köhler B, Wolf M, Posselt HG, Wagner TO. Prophylactic antibiotic therapy is associated with an increased prevalence of Aspergillus colonization in adult cystic fibrosis patients. *Respiratory medicine* 1999; **93**(11): 835-8.

198. N. B, V. R, J. B, G. J-N. Prevalence of Aspergillus fumigatus and other fungal species in the sputum of adult patients with cystic fibrosis. *Mycoses* 2003; **46**(1-2): 19-23.

199. Burgel PR, Baixench MT, Amsellem M, et al. High prevalence of azole-resistant Aspergillus fumigatus in adults with cystic fibrosis exposed to itraconazole. *Antimicrobial agents and chemotherapy* 2012; **56**(2): 869-74.

200. Billaud EM, Guillemain R, Berge M, et al. Pharmacological considerations for azole antifungal drug management in cystic fibrosis lung transplant patients. *Medical mycology* 2010; **48**(Suppl 1): S52-9.

201. Han K, Capitano B, Bies R, et al. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. *Antimicrobial agents and chemotherapy* 2010; **54**(10): 4424-31.

202. Kabulski GM, MacVane SH. Isavuconazole pharmacokinetics in a patient with cystic fibrosis following bilateral orthotopic lung transplantation. *Transplant infectious disease : an official journal of the Transplantation Society* 2018; **20**(3): e12878.

203. Husain S, Sole A, Alexander BD, et al. 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. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2016; **35**(3): 261-82.

204. Watt KM, Cohen-Wolkowiez M, Williams DC, et al. Antifungal Extraction by the Extracorporeal Membrane Oxygenation Circuit. *The journal of extra-corporeal technology* 2017; **49**(3): 150-9.

205. Aguilar G, Ferriols R, Carbonell JA, et al. Pharmacokinetics of anidulafungin during venovenous extracorporeal membrane oxygenation. *Critical Care* 2016; **20**(1): 325.

206. Koch BC, Wildschut ED, Goede AL, Hoog M, Bruggemann RJ. Insufficient serum caspofungin levels in a paediatric patient on ECMO. *Medical mycology case reports* 2012; **2**: 23-4.

207. Ruiz S, Papy E, Da Silva D, et al. Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation. *Intensive Care Med* 2009; **35**(1): 183-4.

208. Spriet I, Annaert P, Meersseman P, et al. Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. *The Journal of antimicrobial chemotherapy* 2009; **63**(4): 767-70.

209. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy* 2006; **26**(12): 1730-44.

210. Neofytos D, Lombardi LR, Shields RK, et al. Administration of Voriconazole in Patients With Renal Dysfunction. *Clinical Infectious Diseases* 2012; **54**(7): 913-21.

211. Oude Lashof AM, Sobel JD, Ruhnke M, et al. Safety and tolerability of voriconazole in patients with baseline renal insufficiency and candidemia. *Antimicrobial agents and chemotherapy* 2012; **56**(6): 3133-7.

212. von Mach MA, Burhenne J, Weilemann LS. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. *BMC clinical pharmacology* 2006; **6**: 6.

213. Alvarez-Lerma F, Allepuz-Palau A, Garcia MP, et al. Impact of intravenous administration of voriconazole in critically ill patients with impaired renal function. *Journal of chemotherapy (Florence, Italy)* 2008; **20**(1): 93-100.

214. Weiler S, Seger C, Pfisterer H, et al. Pharmacokinetics of caspofungin in critically ill patients on continuous renal replacement therapy. *Antimicrobial agents and chemotherapy* 2013; **57**(8): 4053-7.

215. Vossen MG, Knafl D, Haidinger M, et al. Micafungin Plasma Levels Are Not Affected by Continuous Renal Replacement Therapy: Experience in Critically Ill Patients. *Antimicrobial agents and chemotherapy* 2017; **61**(8).

216. Fischer JJ, Walker DH. Invasive pulmonary aspergillosis associated with influenza. *Jama* 1979; **241**(14): 1493-4.

217. Wauters J, Baar I, Meersseman P, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. *Intensive Care Medicine* 2012; **38**(11): 1761-8.

218. van de Veerdonk FL, Kolwijck E, Lestrade PP, et al. Influenza-Associated Aspergillosis in Critically Ill Patients. *Am J Respir Crit Care Med* 2017; **196**(4): 524–7.

219. Alshabani K, Haq A, Miyakawa R, Palla M, Soubani AO. Invasive pulmonary aspergillosis in patients with influenza infection: report of two cases and systematic review of the literature. *Expert Rev Respir Med* 2015; **9**(1): 89-96.

220. Shah MM, Hsiao EI, Kirsch CM, Gohil A, Narasimhan S, Stevens DA. Invasive pulmonary aspergillosis and influenza co-infection in immunocompetent hosts: case reports and review of the literature. *Diagnostic microbiology and infectious disease* 2018; **91**(2): 147-52.

221. Crum-Cianflone NF. Invasive Aspergillosis Associated With Severe Influenza Infections. *Open forum infectious diseases* 2016; **3**(3): ofw171.

222. Garcia-Vidal C, Barba P, Arnan M, et al. Invasive aspergillosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; **53**(6): e16-9.

223. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. *The Lancet Infectious diseases* 2007; **7**(6): 395-401.

224. Singh N, Suarez JF, Avery R, et al. Immune reconstitution syndrome-like entity in lung transplant recipients with invasive aspergillosis. *Transpl Immunol* 2013; **29**(1-4): 109-13.

225. Mellinghoff SC, Bassetti M, Dorfel D, et al. Isavuconazole shortens the QTc interval. *Mycoses* 2018; **61**(4): 256-60.

226. Baxter CG, Marshall A, Roberts M, Felton TW, Denning DW. Peripheral neuropathy in patients on long-term triazole antifungal therapy. *The Journal of antimicrobial chemotherapy* 2011; **66**(9): 2136-9.

227. Cowen EW, Nguyen JC, Miller DD, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *Journal of the American Academy of Dermatology* 2010; **62**(1): 31-7.

228. Hamandi B, Fegbeutel C, Silveira FP, et al. Voriconazole and squamous cell carcinoma after lung transplantation: A multicenter study. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2018; **18**(1): 113-24.

229. Wermers RA, Cooper K, Razonable RR, et al. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; **52**(5): 604-11.

230. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. *Transplant infectious disease : an official journal of the Transplantation Society* 2017; **19**(5).

231. J. T-C, T.L. L. Interactions Between Anti-Infective Agents and Immunosuppressants in Solid Organ Transplantation. *American Journal of Transplantation* 2013; **13**(Suppl 4): 318-26.

232. Marty FM, Bryar J, Browne SK, et al. Sirolimus-based graft-versus-host disease prophylaxis protects against cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation: a cohort analysis. *Blood* 2007; **110**(2): 490-500.

233. Mathis AS, Shah NK, Friedman GS. Combined use of sirolimus and voriconazole in renal transplantation: a report of two cases. *Transplantation proceedings* 2004; **36**(9): 2708-9.

234. Groll AH, Desai A, Han D, et al. Pharmacokinetic Assessment of Drug-Drug Interactions of Isavuconazole With the Immunosuppressants Cyclosporine, Mycophenolic Acid, Prednisolone, Sirolimus, and Tacrolimus in Healthy Adults. *Clinical pharmacology in drug development* 2017; **6**(1): 76-85.

235. Rivosecchi RM, Clancy CJ, Shields RK, et al. Effects of Isavuconazole on the Plasma Concentrations of Tacrolimus among Solid-Organ Transplant Patients. *Antimicrobial agents and chemotherapy* 2017; **61**(9).

236. Rea F, Marulli G, Loy M, et al. Salvage right pneumonectomy in a patient with bronchial-pulmonary artery fistula after bilateral sequential lung transplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2006; **25**(11): 1383-6.

237. Scherer M, Fieguth HG, Aybek T, Ujvari Z, Moritz A, Wimmer-Greinecker G. Disseminated Aspergillus fumigatus infection with consecutive mitral valve endocarditis in a lung transplant recipient. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2005; **24**(12): 2297-300.

238. Hummel M, Schuler S, Weber U, et al. Aspergillosis with Aspergillus osteomyelitis and diskitis after heart transplantation: surgical and medical management. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 1993; **12**(4): 599-603.

239. Loria KM, Salinger MH, Frohlich TG, Gendelman MD, Cook FV, Arentzen CE. Primary cutaneous aspergillosis in a heart transplant recipient treated with surgical excision and oral itraconazole. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 1992; **11**(1 Pt 1): 156-9.

240. Lodge BA, Ashley ED, Steele MP, Perfect JR. Aspergillus fumigatus empyema, arthritis, and calcaneal osteomyelitis in a lung transplant patient successfully treated with posaconazole. *Journal of clinical microbiology* 2004; **42**(3): 1376-8.

241. Shlobin OA, Dropulic LK, Orens JB, et al. Mediastinal mass due to Aspergillus fumigatus after lung transplantation: a case report. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2005; **24**(11): 1991-4.

242. Sandur S, Gordon SM, Mehta AC, Maurer JR. Native lung pneumonectomy for invasive pulmonary aspergillosis following lung transplantation: a case report. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 1999; **18**(8): 810-3.

243. Nivoix Y, Velten M, Letscher-Bru V, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2008; **47**(9): 1176-84.

244. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (2). *The New England journal of medicine* 1992; **327**(2): 99-106.

245. Dale DC, Liles WC, Summer WR, Nelson S. Review: granulocyte colony-stimulating factor--role and relationships in infectious diseases. *The Journal of infectious diseases* 1995; **172**(4): 1061-75.

246. Gaviria JM, van Burik JA, Dale DC, Root RK, Liles WC. Comparison of interferon-gamma, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor for priming leukocyte-mediated hyphal damage of opportunistic fungal pathogens. *The Journal of infectious diseases* 1999; **179**(4): 1038-41.

247. Roilides E, Blake C, Holmes A, Pizzo PA, Walsh TJ. Granulocyte-macrophage colony-stimulating factor and interferon-gamma prevent dexamethasone-induced immunosuppression of antifungal monocyte activity against Aspergillus fumigatus hyphae. *Journal of medical and veterinary mycology : bi-monthly publication of the International Society for Human and Animal Mycology* 1996; **34**(1): 63-9.

248. Nagai H, Guo J, Choi H, Kurup V. Interferon-gamma and tumor necrosis factor-alpha protect mice from invasive aspergillosis. *The Journal of infectious diseases* 1995; **172**(6): 1554-60.

249. Rex JH, Bennett JE, Gallin JI, Malech HL, DeCarlo ES, Melnick DA. In vivo interferon-gamma therapy augments the in vitro ability of chronic granulomatous disease neutrophils to damage Aspergillus hyphae. *The Journal of infectious diseases* 1991; **163**(4): 849-52.

250. Summers SA, Dorling A, Boyle JJ, Shaunak S. Cure of disseminated cryptococcal infection in a renal allograft recipient after addition of gamma-interferon to anti-fungal therapy. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2005; **5**(8): 2067-9.

251. Mamishi S, Zomorodian K, Saadat F, Gerami-Shoar M, Tarazooie B, Siadati SA. A case of invasive aspergillosis in CGD patient successfully treated with Amphotericin B and INF-gamma. *Annals of clinical microbiology and antimicrobials* 2005; **4**: 4.

252. Saulsbury FT. Successful treatment of aspergillus brain abscess with itraconazole and interferon-gamma in a patient with chronic granulomatous disease. *Clinical infectious*

diseases : an official publication of the Infectious Diseases Society of America 2001; **32**(10): E137-9.

253. Pasic S, Abinun M, Pistignjat B, et al. Aspergillus osteomyelitis in chronic granulomatous disease: treatment with recombinant gamma-interferon and itraconazole. *The Pediatric infectious disease journal* 1996; **15**(9): 833-4.

254. Avery RK, Michaels MG. Strategies for safe living after solid organ transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2013; **13**(Suppl 4): 304-10.

255. (CDC) CfDCaP. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports* 2000; **49**(Rr-10): 1-125, ce1-7.

256. Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. *Liver Transpl* 2006; **12**(5): 850-8.

257. Playford EG, Webster AC, Sorrell TC, Craig JC. Systematic review and meta-analysis of antifungal agents for preventing fungal infections in liver transplant recipients. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2006; **25**(9): 549-61.

258. Evans JD, Morris PJ, Knight SR. Antifungal prophylaxis in liver transplantation: a systematic review and network meta-analysis. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2014; **14**(12): 2765-76.

259. Eschenauer GA, Kwak EJ, Humar A, et al. Targeted versus universal antifungal prophylaxis among liver transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2015; **15**(1): 180-9.

260. Balogh J, Gordon Burroughs S, Boktour M, et al. Efficacy and cost-effectiveness of voriconazole prophylaxis for prevention of invasive aspergillosis in high-risk liver transplant recipients. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2016; **22**(2): 163-70.

261. Winston DJ, Limaye AP, Pelletier S, et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2014; **14**(12): 2758-64.

262. Verma A, Auzinger G, Kantecki M, et al. Safety and Efficacy of Anidulafungin for Fungal Infection in Patients With Liver Dysfunction or Multiorgan Failure. *Open forum infectious diseases*, 2017. http://europepmc.org/abstract/MED/28480239

http://europepmc.org/articles/PMC5414057?pdf=render

http://europepmc.org/articles/PMC5414057

https://doi.org/10.1093/ofid/ofw241 (accessed 2017).

263. Saliba F, Pascher A, Cointault O, et al. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; **60**(7): 997-1006.

264. Fortun J, Muriel A, Martin-Davila P, et al. Caspofungin versus fluconazole as prophylaxis of invasive fungal infection in high-risk liver transplantation recipients: A propensity score analysis. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2016; **22**(4): 427-35.

265. Fortun J, Martin-Davila P, Moreno S, et al. Prevention of invasive fungal infections in liver transplant recipients: the role of prophylaxis with lipid formulations of amphotericin B in high-risk patients. *The Journal of antimicrobial chemotherapy* 2003; **52**(5): 813-9.

266. Hellinger WC, Bonatti H, Yao JD, et al. Risk stratification and targeted antifungal prophylaxis for prevention of aspergillosis and other invasive mold infections after liver transplantation. *Liver Transpl* 2005; **11**(6): 656-62.

267. Reed A, Herndon JB, Ersoz N, et al. Effect of prophylaxis on fungal infection and costs for high-risk liver transplant recipients. *Liver Transpl* 2007; **13**(12): 1743-50.

268. Singhal S, Ellis RW, Jones SG, et al. Targeted prophylaxis with amphotericin B lipid complex in liver transplantation. *Liver Transpl* 2000; **6**(5): 588-95.

269. Borro JM, Sole A, de la TM, et al. Efficiency and safety of inhaled amphotericin B lipid complex (abelcet) in the prophylaxis of invasive fungal infections following lung transplantation. *TransplantProc* 2008; **40**(9): 3090-3.

270. Drew RH, Dodds AE, Benjamin DK, Jr., Duane DR, Palmer SM, Perfect JR. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. *Transplantation* 2004; **77**(2): 232-7.

271. Minari A, Husni R, Avery RK, et al. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. *TransplInfectDis* 2002; **4**(4): 195-200.

272. Monforte V, Roman A, Gavalda J, et al. Nebulized amphotericin B prophylaxis for Aspergillus infection in lung transplantation: study of risk factors. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2001; **20**(12): 1274-81.

273. Monforte V, Roman A, Gavalda J, Ussetti P, Bravo C, Pou L. Nebulized liposomal amphotericin B (n-LAB) prophylaxis for aspergillus infection in lung transplantation (LT): Pharmacokinetics, safety and efficacy. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2005; **24**(2): S108-S9.

274. Calvo V, Borro JM, Morales P, et al. Antifungal prophylaxis during the early postoperative period of lung transplantation. Valencia Lung Transplant Group. *Chest* 1999; **115**(5): 1301-4.

275. Reichenspurner H, Gamberg P, Nitschke M, et al. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. *TransplantProc* 1997; **29**(1-2): 627-8.

276. Peghin M, Monforte V, Martin-Gomez MT, et al. 10 years of prophylaxis with nebulized liposomal amphotericin B and the changing epidemiology of Aspergillus spp. infection in lung transplantation. *Transplant international : official journal of the European Society for Organ Transplantation* 2016; **29**(1): 51-62.

277. Bhaskaran A, Mumtaz K, Husain S. Anti-Aspergillus Prophylaxis in Lung Transplantation: A Systematic Review and Meta-analysis. *CurrInfectDisRep* 2013; **15**(6): 514-25.

278. Pilarczyk K, Haake N, Heckmann J, et al. Is universal antifungal prophylaxis mandatory in adults after lung transplantation? A review and meta-analysis of observational studies. *Clinical transplantation* 2016; **30**(12): 1522-31.

279. Hamacher J, Spiliopoulos A, Kurt AM, Nicod LP. Pre-emptive therapy with azoles in lung transplant patients. Geneva Lung Transplantation Group. *EurRespirJ* 1999; **13**(1): 180-6.

280. Jeong W, Snell GI, Levvey BJ, et al. Clinical effectiveness of early posaconazole suspension pre-emptive therapy in lung transplant recipients: The Alfred's experience. *Journal of Antimicrobial Chemotherapy* 2017; **72**(7): 2089-92.

281. Neoh CF, Snell GI, Levvey B, et al. Preemptive treatment with voriconazole in lung transplant recipients. *TransplInfectDis* 2013; **15**(4): 344-53.

282. Hosseini-Moghaddam SM, Chaparro C, Luong ML, et al. The Effectiveness of Culture-Directed Preemptive Anti-Aspergillus Treatment in Lung Transplant Recipients at One Year After Transplant. *Transplantation* 2015; **99**(11): 2387-93.

283. Husain S, Bhaskaran A, Rotstein C, et al. A strategy for prevention of fungal infections in lung transplantation: Role of bronchoalveolar lavage fluid galactomannan and fungal culture. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2018.

284. Palmer SM, Drew RH, Whitehouse JD, et al. Safety of aerosolized amphotericin B lipid complex in lung transplant recipients. *Transplantation* 2001; **72**(3): 545-8.

285. Monforte V, Roman A, Gavalda J, et al. Nebulized amphotericin B concentration and distribution in the respiratory tract of lung-transplanted patients. *Transplantation* 2003; **75**(9): 1571-4.

286. Wahidi MM, Willner DA, Snyder LD, Hardison JL, Chia JY, Palmer SM. Diagnosis and Outcome of Early Pleural Space Infection Following Lung Transplantation. *Chest* 2009; **135**(2): 484-91.

287. Cadena J, Levine DJ, Angel LF, et al. Antifungal prophylaxis with voriconazole or itraconazole in lung transplant recipients: hepatotoxicity and effectiveness. *American journal*

of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009; **9**(9): 2085-91.

288. Munoz P, Guinea J, Pelaez T, Duran C, Blanco JL, Bouza E. Nosocomial invasive aspergillosis in a heart transplant patient acquired during a break in the HEPA air filtration system. *Transplant infectious disease : an official journal of the Transplantation Society* 2004; **6**(1): 50-4.

289. Munoz P, Valerio M, Palomo J, et al. Targeted antifungal prophylaxis in heart transplant recipients. *Transplantation* 2013; **96**(7): 664-9.

290. Kabbani D, Goldraich L, Ross H, Rotstein C, Husain S. Outbreak of invasive aspergillosis in heart transplant recipients: The role of screening computed tomography scans in asymptomatic patients and universal antifungal prophylaxis. *Transplant infectious disease : an official journal of the Transplantation Society* 2018; **20**(1).

291. Sandison T, Ong V, Lee J, Thye D. Safety and Pharmacokinetics of CD101 IV, a Novel Echinocandin, in Healthy Adults. *Antimicrobial agents and chemotherapy* 2017; **61**(2).

292. Hata K, Horii T, Miyazaki M, et al. Efficacy of oral E1210, a new broad-spectrum antifungal with a novel mechanism of action, in murine models of candidiasis, aspergillosis, and fusariosis. *Antimicrobial agents and chemotherapy* 2011; **55**(10): 4543-51.

293. Gebremariam T, Alkhazraji S, Alqarihi A, et al. APX001 is Effective in the Treatment of Murine Invasive Pulmonary Aspergillosis. *Antimicrobial agents and chemotherapy* 2018; **Epub ahead of print**.

294. Ghannoum M, Long L, Larkin EL, et al. Evaluation of the Antifungal Activity of the Novel Oral Glucan Synthase Inhibitor SCY-078, Singly and in Combination, for the Treatment of Invasive Aspergillosis. *Antimicrobial agents and chemotherapy* 2018; **62**(6).

295. Walker TA, Lockhart SR, Beekmann SE, et al. Recognition of Azole-Resistant Aspergillosis by Physicians Specializing in Infectious Diseases, United States. *Emerging infectious diseases* 2018; **24**(1): 111-3.

296. Kersemaekers WM, Dogterom P, Xu J, et al. Effect of a high-fat meal on the pharmacokinetics of 300-milligram posaconazole in a solid oral tablet formulation. *Antimicrobial agents and chemotherapy* 2015; **59**(6): 3385-9.

297. Diseases ACoI. Red Book, 29th Edition (2012); 2012.