



Is universal antifungal prophylaxis mandatory in lung transplant patients?

Joanna M. Schaenman

Purpose of review

Lung transplantation remains the major therapy for patients with end-stage lung disease, yet survival remains limited by infection and chronic rejection. Invasive fungal infection, especially invasive aspergillosis, continues to cause a high rate of mortality after lung transplantation, and there is evidence that fungal colonization in itself may have a negative impact as well. This article reviews clinical trials in primary antifungal prophylaxis to determine whether antifungal prophylaxis after lung transplantation is indicated.

Recent findings

A variety of antifungal regimens have been tested after lung transplantation including itraconazole or voriconazole monotherapy, inhaled amphotericin B products, and combination therapy. Studies using a historical cohort that has not received antifungal prophylaxis show a decrease in the incidence of invasive fungal disease and/or invasive aspergillosis with antifungal prophylaxis, with relatively few safety concerns. Both systemic azoles and inhaled amphotericin B products appear to provide benefit.

Summary

Despite multiple reports of antifungal prophylaxis efficacy, a randomized, controlled, multicenter trial has yet to be performed. The optimal agent or agents for prophylaxis and length of therapy posttransplantation remain unknown. However, sufficient evidence exists for the utility of some type of antifungal prophylaxis posttransplantation for the majority of lung transplant recipients.

Keywords

aerosolized amphotericin, aspergillosis, invasive fungal infection, itraconazole, lung transplantation, posaconazole, prophylaxis, voriconazole

INTRODUCTION

This review will survey the evidence for use of antifungal prophylaxis with a focus on prevention of invasive aspergillosis in the adult lung transplant population, including the most recent literature reporting data on incidence of fungal disease, surveys of regimens in use, and the efficacy of antifungal prophylaxis in the current era of transplantation, updating a previous review from 2005 [1,2]. There is a growing number of patients with end-stage lung disease, and the rate of lung transplantation in the US continues to grow as well [3,4]. However, bronchiolitis obliterans and opportunistic infections continue to contribute to morbidity and mortality in this patient group, and remain two of the most common causes of death, with a 5-year survival of about 50% after lung transplantation, even in the most recent cohort of transplant recipients [4–18]. Amongst infections, invasive fungal infections are one of the most important post-transplant complications, causing 15–35% of all

infections after lung transplantation, and both associated with a direct mortality risk from infection as well as contributing to development of bronchiolitis obliterans [19,20,21^a,22].

Therefore, the question of possibly a meliorating these effects via antifungal prophylaxis is a very important one in this patient population. Unfortunately, there is a dearth of large-scale clinical trials addressing this topic, and a lack of consensus concerning which approach and what duration of prophylaxis is best [23,24]. The epidemiology of

Department of Medicine, Division of Infectious Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Correspondence to Joanna M. Schaenman, MD, PhD, Department of Medicine, Division of Infectious Diseases, David Geffen School of Medicine at UCLA, 10833 LeConte Ave. 37–121 CHS, Los Angeles, CA 90095, USA. Tel: +1 310 825 7225; fax: +1 310 825 3632; e-mail: jschaenman@mednet.ucla.edu

Curr Opin Infect Dis 2013, 26:000–000

DOI:10.1097/QCO.0b013e3283630e67

KEY POINTS

- Invasive fungal infections, especially invasive aspergillosis, continue to cause significant morbidity after lung transplantation. Colonization with *Aspergillus* may predispose to infection as well as to the development of bronchiolitis obliterans.
- Surveys of lung transplant centers worldwide reveal a wide diversity of antifungal prophylaxis practices. A consensus does not exist on whether universal prophylaxis is needed, and what the ideal agent and length of treatment should be.
- Cohort studies using itraconazole, voriconazole, and inhaled amphotericin B products show a decrease in invasive aspergillosis as compared with historical controls. Use of inhaled amphotericin B products alone does not protect against systemic fungal infection including invasive candidiasis.
- A multicenter, randomized, controlled trial is needed. Although universal prophylaxis posttransplant is recommended, with an extended course in high-risk patients, future improvements in diagnosis and screening may make a pre-emptive approach more feasible.

invasive fungal infections including invasive aspergillosis will be reviewed and results of surveys of practice and society recommendations will be summarized, followed by a review of the English-language literature for fungal prophylaxis in lung transplant recipients, highlighting modern antifungal agents. Because there have been few new studies in the past 12 months, this review will extend to all evaluable studies with a focus on the last 5 years. Endemic fungi and *Pneumocystis jirovecii* pneumonia will not be discussed as they are outside the scope of this review.

EPIDEMIOLOGY OF FUNGAL INFECTIONS IN LUNG TRANSPLANTATION

The increased incidence of fungal infection in lung transplant recipients as compared to other solid organ transplant recipients has been well described, especially for invasive mold infections including aspergillosis [25^{••},26,27,28^{••}]. As many fungal infections are transmitted by environmental exposure from the air, the lung allograft is uniquely vulnerable to fungal infection. In addition, other factors increasing risk after lung transplant include decreased ciliary clearance of pathogens, decreased cough reflex due to denervation, compromised blood supply to the tracheal anastomosis, lifelong requirement for immunosuppression often at higher levels than some other transplant recipients,

and the risk of donor-derived infections in the allograft itself, including endemic fungal infections [6,29].

Individual patient factors in lung transplantation that increase infection risk include history of pretransplant fungal infection or colonization (especially in patients with cystic fibrosis), airway ischemia, receipt of single-lung transplantation in which the native lung can serve as a reservoir for infection, development of fungal sinusitis, neutropenia or hypogammaglobulinemia, anti-thymocyte globulin (ATG) or OKT3 use, treatment for episodes of rejection, other intercurrent infections most notably cytomegalovirus (CMV), renal failure requiring dialysis, diabetes mellitus, and mechanical interventions including stenting or ballooning of the airways [29–33]. A recent abstract suggests that community-acquired respiratory virus infection may also increase risk of invasive fungal infection in lung transplantation [34^{••},35].

A multicenter observational study described the 12-month cumulative incidence of invasive fungal infection after lung or heart–lung transplant to be 8.6%, although this figure was seen to vary greatly between reporting sites (0–25.9%), with aspergillosis the most common type of fungal infection [10–16,26]. Recent studies have estimated incidence of invasive aspergillosis to be between 6 and 8% after lung transplant, although this has ranged from 2.2 to 20% in published series [13,16,32,36]. Although invasive aspergillosis is arguably the most important type of fungal infection after lung transplantation, candidiasis can also cause serious disease including candidemia, mediastinitis, pleural space infection, pneumonia, and disseminated disease [17,18,26,27,36,37]. Invasive candidiasis tends to occur early after transplant, within 6 months or less, while invasive aspergillosis was diagnosed at a mean of 382 days posttransplant in a survey of fungal infections after solid organ transplant [27,38]. Interestingly, earlier studies reported *Aspergillus* infection at a median of 3.2 months after lung transplantation with a longer time to infection in single lung recipients [32,38]. Invasive aspergillosis includes tracheobronchitis, infection of the bronchial anastomosis, and invasive pulmonary infection, as distinguished from colonization [21[•],39]. Rates of colonization are reported to be as high as 25%, and colonization was associated with increased mortality despite the absence of invasive fungal disease [39,40].

Mortality rates in invasive aspergillosis in lung transplant depends on the site of involvement, with 23–29% mortality in tracheobronchitis and 67–82% in patients with invasive pulmonary disease [20,28^{••}]. An increased mortality rate up to 80% has been reported in non-*Aspergillus* mold infections,

such as *Scedosporium*, *Fusarium*, and the agents of mucormycosis, which have been increasingly recognized as important pathogens in lung transplantation and may be increasing over time [33,41–44]. Patient specific factors associated with increased mortality in invasive aspergillosis in a range of immunocompromised patients included steroid therapy, neutropenia, renal impairment, disseminated infection, and the presence of diffuse pulmonary lesions [45,46]. Approaches to diagnosis and treatment continue to evolve over time, and have been well reviewed in previous publications [28²²,33,47–53].

INDIRECT DELETERIOUS EFFECTS OF FUNGAL INFECTION AND/OR COLONIZATION

In addition to direct impact on patient mortality described above, there is evidence of increased mortality rates in patients with *Aspergillus* colonization in the absence of invasive infection [40,54,55]. In addition, positive cultures for *Aspergillus* are associated with the development of bronchiolitis obliterans [22,56,57], especially colonization with those species whose conidia are small enough to penetrate to the small airways in which bronchiolitis occurs [47,58]. The mechanism for this association is postulated to be via stimulation of chemokine expression, leading to migration of lymphocytes bearing chemokine receptors to the lung, amplifying the inflammatory signal within the lung allograft [59]. Ligands for CCR1, CCR5, CXCR2, and CXCR3 have all been implicated in contributing to this mechanism of disease [60].

ANTIFUNGAL PROPHYLAXIS: SURVEY DATA AND SOCIETY RECOMMENDATIONS

The current field of lung transplantation is marked by a large degree of variability across centers in terms of whether to initiate antifungal prophylaxis, either empirically or in selected high-risk patients, as well as which agent or agents to use as well as the optimal length of prophylaxis [61]. The American Society of Transplantation Infectious Diseases Community of Practice recommends antifungal prophylaxis for patients with pretransplant *Aspergillus* colonization or posttransplant colonization within the first year posttransplant as well as for patients with more than one risk factor including ATG or alemtuzumab induction, single lung transplant, *Aspergillus* colonization after CMV infection, rejection and augmentation of immunosuppression, and hypogammaglobulinemia. Recommended regimens are inhaled amphotericin B products (deoxycholate, Abelcet, or Ambisome) or systemic azole therapy

with itraconazole or voriconazole [28²²]. These updated recommendations are similar to those previously published by this organization [62]. The International Society for Heart and Lung Transplantation has not issued formal guidelines for antifungal prophylaxis after lung transplantation.

The most recent published survey of lung transplant centers worldwide revealed a rate of 58.6% universal prophylaxis, with voriconazole as the most commonly reported monotherapy followed by itraconazole and inhaled amphotericin B deoxycholate [34²²]. Nineteen per cent of reporting centers used combination therapy, with voriconazole and inhaled amphotericin B deoxycholate as the most common agents used. Universal prophylaxis was most often given for 6 months post-transplant. 36.2% of centers used pre-emptive prophylaxis, most commonly with voriconazole, and 5.2% of centers reported not using antifungal prophylaxis [34²²]. Echinocandin use for primary prophylaxis was also reported in a minority of centers. Another worldwide survey administered between 2002 and 2003 revealed a rate of 69% for universal primary prophylaxis with an additional 31% utilizing pre-emptive antifungal prophylaxis; 70% of centers reported prophylaxis during periods of augmented immunosuppression [63]. Agents used in this survey included aerosolized amphotericin B, itraconazole, or combination therapy for a median of 90 days.

In contrast, an earlier survey of US lung transplant centers revealed a 76% frequency of antifungal prophylaxis for at least some subgroup of high-risk patients while 24% of centers reported no prophylaxis [1]. Duration of prophylaxis was most commonly in the 1–3 month posttransplant range, with inhaled deoxycholate amphotericin B as the most commonly administered agent and itraconazole as the second most commonly used agent. In 2002, a survey of US and Canadian centers revealed the use of primary prophylaxis in 80% of centers, primarily with aerosolized amphotericin B, itraconazole, and fluconazole [3]. These surveys are inherently limited by their voluntary nature, with a range of 54–86% of centers who received questionnaires submitting responses.

DATA REGARDING EFFICACY OF PROPHYLAXIS REGIMENS

The data regarding effectiveness and tolerability of antifungal prophylaxis targeting invasive aspergillosis after lung transplantation is limited. Studies reporting sufficient data for analysis of study inclusion criteria and invasive aspergillosis rates in adult lung transplant recipients are summarized in Table 1. Studies cited are notable for the variable

Table 1. Antifungal prophylaxis studies in adult lung transplant recipients by regimen type

Study name, location	n	% Single lung/ double lung/HL	% CF	Anticellular induction	Immuno suppres- sion regimen	Dose	Length of prophylaxis	IA Rate ^a	Reference IA	Length of follow-up
Itraconazole										
Shitrit [5,28 [■]]	40	50%/37%/13%	0%	None	TAC, MMF, pred	200 mg po bid	6 months	5%	N/A	1 year
Cadena [6,33,42–44]	32	UNK	6%	UNK	UNK	200 mg po bid	3 months	12.5%	N/A	1 year
Voriconazole										
Cadena [6,46]	35	UNK	9%	UNK	UNK	200 mg po bid	3 months	0%	12.5% (itracona- zole)	1 year
Husain [7,28 [■] ,33,48,51]	30	47%/53%/0%	20%	ATG or Campath	TAC, pred	6 mg/kg IV q12 then 200 mg po bid	4 months	1.5%	23% (preemptive treatment)	1 year
Mitsani [8,40,55]	93	19%/80%/1%	13%	Campath	CNI, MMF, pred	6 mg/kg IV q12 then 200 mg po bid	3 months	4.3% ^a	N/A	1 year
Tofte [9,22,57]	147	60%/39%/1%	21%	ATG	CyA, AZA, pred	200 mg po bid	3 months	19%	10% (no prophy- laxis)	3 year
Inhaled amphotericin										
Reichenspurner [10,58]	126 ^b	UNK	UNK	UNK	UNK	d-AmB 5→20 mg tid	Posttx hosp.	10%	25% (no prophy- laxis)	1 year
Calvo [11,59]	52	17%/83%/0%	23%	Some ATG	CyA, AZA, pred	d-AmB 0.2 mg/kg tid	Posttx hosp.	7.7%	N/A	3 year
Monforte [12,60]	55	45%/55%/0%	7%	None	CyA, AZA, pred	d-AmB 6 mg tid	4 months	33%	N/A	Mean 14 months
Drew [13,61]	51	12%/82%/0%	20%	None	CNI, AZA, pred	ABLC 50 mg qd × 4 days then weekly	2 months ^c	2%	2% d-AmB	2 months
Lowry [14,28 [■]]	38	68%/32%/0%	21%	UNK	UNK	L-AmB 5–20 mg bid OR d-AmB 2.5–10 mg bid	Posttx hosp. ^c	3%	N/A	UNK
Borro [15,62]	60	42%/57%/2%	UNK	Some Simulect	CNI, AZA or MMF, pred	ABLC 50 mg qod × 2 weeks then weekly	3 months	0	N/A	6 months
Monforte [16,34 [■]]	104	28%/68%/4%	15%	ATG or Simulect	CNI, AZA, pred	L-AmB 25 mg 3×/week × 2 months then weekly × 4 months then q 2 weeks	Indefinite	2%	4% (d-AmB)	12 months
Combination antimold therapy										
Minari [17,34 [■]]	183	61%/36%/3%	UNK	None	CyA, AZA, pred	d-AmB 5–10 mg bid × 2 weeks AND itracona- zole 200 mg po bid indefinitely	Indefinite (itraconazole)	12.8%	N/A	Average of 3 year
Eriksson [18,63]	76	7%/93%/0%	9%	None	CNI, MMF, pred	d-AmB 25 mg bid or ABLC 50 mg qd × 4 days then weekly plus short course caspofun- gin for high-risk patients ^d	Median 2 months aeroso- lized AmB; variable length of therapy for caspofungin	1.3%	N/A	2 year

ABLC, amphotericin B lipid complex (Abelcet); ATG, anti-thymocyte globulin; AZA, azathioprine; CF, cystic fibrosis; CNI, calcineurin inhibitor; CyA, cyclosporine; d-AmB, amphotericin B deoxycholate; HL, heart–lung; IA, invasive aspergillosis; L-AmB, liposomal amphotericin B (Ambisome); MMF, mycophenolate mofetil; Posttx hosp., posttransplant hospitalization; pred, prednisone; TAC, tacrolimus; UNK, unknown.

^aIf rate of invasive aspergillosis not indicated, rate of invasive mold infections reported. When only overall incidence of fungal infection reported by authors rate of aspergillosis calculated from reported data where possible.

^bIncludes heart transplant recipients.

^cContinued for longer period and/or other therapy administered if evidence colonization with *Aspergillus*.

^dHigh risk defined as delay in aerosolized amphotericin B start, history of *Aspergillus* colonization, mycetoma in explanted lung, necrotizing tracheobronchitis, cystic fibrosis, elderly.

types and durations of antifungal prophylaxis regimens as well as the variability of reported invasive aspergillosis rates for each study [5–18]. These studies are characteristically limited by the small sample size, single center structure, and lack of blinded randomization, and are additionally difficult to compare because of variations in immunosuppression induction and maintenance regimens, percentages of single lung, double lung, and cystic fibrosis patients, and differences in surveillance bronchoscopy practices. In addition, although improved since the creation of published guidelines on definitions of invasive fungal infection [19,21[¶]], there remain differences in the definition of fungal colonization, infection, and invasive disease between studies. A recent abstract at the International Society for Heart and Lung Transplantation 2013 meeting reports a meta-analysis of eight retrospective studies suggesting that antifungal prophylaxis reduces the risk of invasive aspergillosis (RR, 0.45; CI, 0.21–0.97) but not colonization [23].

Both itraconazole and voriconazole have been used for primary prophylaxis, and it is difficult to state definitively which azole is superior in efficacy as a randomized trial does not exist [25^{¶¶}]. However, a decrease in incidence of invasive aspergillosis after programmatic switch from itraconazole to voriconazole was observed by Cadena *et al.* [6], suggesting possible superiority of voriconazole for prophylaxis. Although difficult to compare with solid organ transplantation, there is head-to-head data from the blood and marrow transplant population suggesting superiority of voriconazole as compared with itraconazole for prevention of invasive fungal infection [30]. There is no reported data on efficacy of posaconazole, although surveys report use of this agent in patients intolerant of voriconazole [34^{¶¶}]. Although there are many reports on both aerosolized deoxycholate and lipid-conjugated amphotericin B agents, the reported length of therapy of these drugs is notably quite variable, ranging from the posttransplant hospitalization to lifelong therapy, with a range of frequencies of administration [10–16].

Single versus double agent therapy is another unanswered question in antifungal prophylaxis. Aerosolized preparations offer the advantage of targeted delivery of drug to the lungs, but leave patients at risk for the development of extrapulmonary fungal infection including candidemia and pleural candida infection [13,16,36]. Therefore, strategies of either systemic azole or echinocandin and inhaled amphotericin B agent have been utilized [17,18].

The studies cited above report universal prophylaxis regimens, but it is possible that pre-emptive therapy might also be used to prevent invasive

fungal disease, with notable report on pre-emptive therapy in lung transplant by Hamacher *et al.* [38]. In this study of 31 patients treated from 1993 to 1997, antifungal therapy was started if surveillance bronchoscopy showed either *Candida* (with fluconazole) or mold (with itraconazole) until fungal cultures became negative. During a mean follow-up time of 19 months, 84% of patients had positive respiratory specimens for fungi at some point, and the incidence of invasive aspergillosis was 6.5% [38].

One US study using neither empiric prophylaxis nor preemptive therapy for fungal colonization in patients reported a rate of invasive fungal infection similar to reported historical rates [39]. This review of 242 patients without cystic fibrosis transplanted from 1994 to 2006 used only clotrimazole oral troche and 3–5 days of inhaled deoxycholate amphotericin B for patients with history of *Aspergillus* colonization receiving ATG induction with frequent monitoring by surveillance bronchoscopy and measurement of forced expiratory volume in 1 s (FEV1) and found an invasive fungal infection rate of 9.1% (4.5% invasive aspergillosis) with a median time to infection of 247 days posttransplant [39]. Of note, the infection-related mortality rate was 55%, and the 1 year survival of 77% in cases of fungal infection compared with 83% in uninfected controls and 3 year survival of 35% in cases of fungal infection compared with 49% in uninfected controls suggested the possibility of decreased overall graft function without antifungal prophylaxis despite rates of invasive aspergillosis comparable to historical controls [20].

As mentioned above, the optimal length of time for both primary and secondary prophylaxis is unknown. An important recent development in the modern transplant era of is the appearance of late onset invasive aspergillosis, presumably related to changes in antifungal prophylaxis patterns [41].

REVIEW OF ANTIFUNGAL AGENTS AND RISKS OF USE

Azoles

The systemically absorbed azoles itraconazole and voriconazole are inhibitors of the CYP3A4 isoenzyme and have well described drug–drug interactions with calcineurin inhibitors as well as risk for hepatotoxicity. There is reported increased risk in patients with cystic fibrosis as well as with early initiation of azoles posttransplantation, with 51% of lung transplant recipients demonstrating evidence of hepatotoxicity in one study, defined as an elevation of AST, ALT, alkaline phosphatase, or bilirubin three times the upper limit of normal [45]. Other side effects associated with voriconazole

include visual changes, mental status changes, dermatitis, skin cancer, and periostitis [47,49,50,52,53]. Cost is another important factor to consider as well, especially with prolonged use.

The importance of therapeutic drug monitoring for voriconazole is now generally accepted, and is associated with increased efficacy as well as mitigation of some drug concentration associated side effects [54], and monitoring of azole drug levels is especially important in patients with cystic fibrosis [64]. Breakthrough mold infections with azole-resistant organisms are another potential limitation of itraconazole or voriconazole prophylaxis [56]. However, the effective absorption after oral administration of voriconazole and its ability to provide prophylaxis against both yeast and molds makes it an attractive agent for use posttransplant [47].

Aerosolized amphotericin B products

Systemic amphotericin B is not a good option in solid organ transplant recipients because of potential nephrotoxicity and electrolyte wasting, as well as the need for intravenous administration [2,65]. Aerosolized versions, however, are an attractive alternative for targeted lung treatment, and there is no evidence for systemic absorption of nebulized products [4,66,67]. Lipid-based formulations including aerosolized Abelcet (ABLC) and Ambisome (L-AmB) are considered superior to amphotericin B deoxycholate because of ease of drug delivery given the products are already in solution, the potential for better tissue penetration, a longer half-life, and the observation of fewer side effects in clinical practice [4,13,68,69]. Technetium-labeling of these drugs demonstrates good distribution throughout the lungs, although distribution is preferential in the transplanted lung after single lung transplant [20,22,70], and sampling of aerosolized lipid-conjugated amphotericin in the lung by bronchoscopy has demonstrated sufficient levels for inhibition of *Aspergillus* growth [24,67,69]. Minimal rates of patient intolerance due to bronchospasm or significant decline in FEV1 or changes in lipid content of pulmonary surfactant have been observed with lipid-based formulations [26,27,28^{***},68,71], although possible side-effects of long-term use have not been completely excluded. As mentioned above, one limitation of this prophylaxis modality is its targeting of the lung and respiratory tree alone, leading to the possibility of extrapulmonary fungal disease including pleural space infections [25^{***},29,36].

Echinocandins

There is only limited data on the use of echinocandins in lung transplantation, although they have

become a common modality for posttransplant prophylaxis in the liver transplant population with good efficacy and minimal safety issues [29,31–33,72]. Limited data from one trial of combination therapy with aerosolized amphotericin B with addition of caspofungin in high-risk patients suggested that this regimen is well tolerated and can decrease the incidence of both invasive mold and candida infections in lung transplantation [18,35]. The major limitation of this therapy is the need for intravenous administration, making it best suited to the posttransplant hospitalization period.

RECOMMENDATIONS

Although randomized, controlled trial data is still lacking, evidence exists that antifungal prophylaxis can decrease the incidence of invasive aspergillosis after lung transplantation. In addition to decreasing morbidity and mortality related to fungal infection, the likely decrease in fungal colonization with this treatment may offer benefits in decreasing propensity for development of bronchiolitis obliterans. Therefore, the use of universal primary prophylaxis after lung transplantation is recommended, although the optimal agent and length of therapy is unknown. Prophylaxis should begin as soon as possible after transplant before potential fungal inoculates have the opportunity to penetrate into the respiratory epithelium, and because of the risk of candidal disease, inhaled amphotericin B products should not be used as monotherapy in the early posttransplant period [18,26]. In addition, evidence of pre or posttransplant colonization with *Aspergillus* or other molds should prompt extension of prophylaxis after completion of primary prophylaxis, as should identification of other risk factors, namely, cystic fibrosis, hypogammaglobulinemia, leukopenia, CMV viremia or disease, and treatment for rejection. Although a total course of 3 months prophylaxis may well be insufficient for high-risk patients given the evidence of late onset invasive aspergillosis [32,41], the long-term consequences of indefinite treatment courses are not known at this time.

A reasonable approach for empiric prophylaxis for all patients would be oral itraconazole solution 200 mg by mouth twice daily, voriconazole 200 mg by mouth twice daily (with monitoring of liver function tests and drug levels), aerosolized ABLC 50 mg every other day for 2 weeks then weekly thereafter, or aerosolized liposomal amphotericin B 25 mg three times weekly for 2 months then weekly for a total of 4 months posttransplant. For patient using aerosolized amphotericin B products only, either fluconazole or a mold-active azole

should be used concurrently to decrease risk of invasive candidal disease. For high-risk patients as defined above, after an initial period of empiric prophylaxis, longer term therapy should be administered using either voriconazole or lipid-conjugated aerosolized amphotericin B product for a total of 6 months posttransplant. For both low-risk and high-risk patients, prophylaxis should be reinstated after treatment for rejection, and prophylaxis should be reinstated or extended if there is evidence of fungal colonization [26,27,36,37,73]. Posaconazole would be an option for voriconazole-intolerant patients, or for those with higher than usual risk for skin cancer.

FUTURE DIRECTIONS

In the current era, our ability to diagnosis invasive fungal disease and colonization is primarily dependent on detection of positive fungal cultures, a methodology with low sensitivity, making universal prophylaxis necessary. It is possible that as non-invasive diagnostic modalities improve, targeted pre-emptive therapy could become more well tolerated and practical. Currently available diagnostic tests such as serum *Aspergillus* galactomannan and fungal PCR have not been sufficiently robust to allow for this approach [27,74–76], however other approaches including galactomannan detection from bronchoalveolar lavage fluid may in the future allow for a greater adoption of pre-emptive therapy [32,77,78]. There is clearly an unmet need for prospective, multicenter, randomized clinical trials to better determine risks for fungal infection and assess the optimal therapeutic approach in both adults and children. In addition, for aerosolized amphotericin B, the ideal frequency, dose, and delivery system remain unclear. Other nebulizable antifungal agents such as aerosolized voriconazole, which has been used in animal models, may also alter the standard prophylaxis regimens [21[■],79], and newer azoles under development such as isavuconazole may also change recommendations for prophylaxis [40,80]. These changes in choice of prophylaxis agent as well as possible trends towards longer courses of prophylaxis, on top of likely evolution in immunosuppression regimens and treatment of rejection, will continue to alter the observed patterns of fungal infection after lung transplantation.

CONCLUSION

Invasive fungal infection and especially invasive aspergillosis remain an important complication of lung transplantation affecting both graft function and patient mortality. Despite the fact that the

majority of lung transplant centers worldwide utilize some type of antifungal prophylaxis, there is a lack of consensus within the field in terms of empiric prophylaxis and choice of antifungal agent. Studies of antifungal prophylaxis with antimold azoles as well as inhaled amphotericin B formulations overall demonstrate decreased rates of invasive fungal infection and invasive aspergillosis as compared with historical controls; however, a multicenter, randomized, controlled trial is lacking. Despite the lack of definitive data, enough evidence has accumulated to recommend the use of universal antifungal prophylaxis of some type, especially for patients at higher risk for fungal infection, both in the initial posttransplant period as well as after treatment for rejection or detection of colonization with molds. Improvements in ability to detect presence of invasive fungal disease or colonization with higher sensitivity may affect these recommendations. Hopefully, future studies will bring more clarity as to the optimal agent and duration of antifungal prophylaxis after lung transplantation.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Dummer JS, Lazariashvili N, Barnes J, *et al.* A survey of antifungal management in lung transplantation. *J Heart Lung Transplant* 2004; 23:1376–1381.
2. Covarrubias MB, Millstone AP. An overview of fungal prophylaxis in lung transplantation. *Curr Opin Organ Transplant* 2005; 10:227–232.
3. Levine SM. Transplant/Immunology Network of the American College of Chest Physicians: a survey of clinical practice of lung transplantation in North America. *Chest* 2004; 125:1224–1238.
4. Christie JD, Edwards LB, Kucheryavaya AY, *et al.* The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report–2012. *J Heart Lung Transplant* 2012; 31:1073–1086.
5. Shitrit D, Ollech JE, Ollech A, *et al.* Itraconazole prophylaxis in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. *J Heart Lung Transplant* 2005; 24:2148–2152.
6. Cadena J, Levine DJ, Angel LF, *et al.* Antifungal prophylaxis with voriconazole or itraconazole in lung transplant recipients: hepatotoxicity and effectiveness. *Am J Transplant* 2009; 9:2085–2091.
7. Husain S, Paterson DL, Studer S, *et al.* Voriconazole prophylaxis in lung transplant recipients. *Am J Transplant* 2006; 6:3008–3016.
8. 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. *Antimicrob Agents Chemother* 2012; 56:2371–2377.
9. Tofte N, Jensen C, Tvede M, *et al.* Use of prophylactic voriconazole for three months after lung transplantation does not reduce infection with *Aspergillus*: a retrospective study of 147 patients. *Scand J Infect Dis* 2012; 44:835–841.

10. 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. *Transplant Proc* 1997; 29:627–628.
 11. Calvo V, Borro JM, Morales P, *et al*, the Valencia Lung Transplant Group. Antifungal prophylaxis during the early postoperative period of lung transplantation. *Chest* 1999; 115:1301–1304.
 12. Monforte V, Román A, Gavalda J, *et al*. Nebulized amphotericin B prophylaxis for Aspergillus infection in lung transplantation: study of risk factors. *J Heart Lung Transplant* 2001; 20:1274–1281.
 13. Drew RH, Dodds Ashley E, Benjamin DK Jr, *et al*. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. *Transplantation* 2004; 77:232–237.
 14. Lowry CM, Marty FM, Vargas SO, *et al*. Safety of aerosolized liposomal versus deoxycholate amphotericin B formulations for prevention of invasive fungal infections following lung transplantation: a retrospective study. *Transplant Infect Dis* 2007; 9:121–125.
 15. Borro JM, Solé A, la Torre de M, *et al*. Efficiency and safety of inhaled amphotericin B lipid complex (Abelcet) in the prophylaxis of invasive fungal infections following lung transplantation. *Transplant Proc* 2008; 40:3090–3093.
 16. Monforte V, Ussetti P, Gavalda J, *et al*. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for Aspergillus infection prevention in lung transplantation. *J Heart Lung Transplant* 2010; 29:523–530.
 17. 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. *Transpl Infect Dis* 2002; 4:195–200.
 18. Eriksson M, Lemström K, Suojaranta-Ylinen R, *et al*. Control of early aspergillus mortality after lung transplantation: outcome and risk factors. *Transplant Proc* 2010; 42:4459–4464.
 19. De Pauw B, Walsh TJ, Donnelly JP, *et al*. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; 46:1813–1821.
 20. Solé A, Morant P, Salavert M, *et al*, the Valencia Lung Transplant Group. Aspergillus infections in lung transplant recipients: risk factors and outcome. *Clin Microbiol Infect* 2005; 11:359–365.
 21. Husain S, Mooney ML, Danziger-Isakov L, *et al*. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. *J Heart Lung Transplant* 2011; 30:361–374.
- Clear explanation of the diagnostic classes of infection including fungal infections in the heart and lung transplant recipient.
22. Weigt SS, Elshoff RM, Huang C, *et al*. Aspergillus colonization of the lung allograft is a risk factor for bronchiolitis obliterans syndrome. *Am J Transplant* 2009; 9:1903–1911.
 23. Bhaskaran A, Mumtaz K, Singer LG, Rotstein C, Husain S. Anti-fungal prophylaxis in lung transplant recipients (LTRs): a meta-analysis of cohort studies. *J Heart Lung Transplant* 2013; 32:S130.
 24. Magill SS, Dropulic LK. Antifungal prophylaxis in transplant recipients: where do we go from here? *Transpl Infect Dis* 2006; 8:187–189.
 25. Avery R. Antifungal prophylaxis in lung transplantation. *Semin Respir Crit Care Med* 2011; 32:717–726.
- Excellent review of risk factors, pathogens, and antifungal agents used for prophylaxis after lung transplantation.
26. Pappas PG, Alexander BD, Andes DR, *et al*. Invasive fungal infections among organ transplant recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 2010; 50:1101–1111.
 27. Neofytos D, Fishman JA, Horn D, *et al*. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transplant Infect Dis* 2010; 12:220–229.
 28. Singh NM, Husain S, the AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. *Am J Transplant* 2013; 13:228–241.
- Excellent up-to-date but concise review of the epidemiology, diagnosis, treatment, and prophylaxis of invasive fungal infections in solid organ transplant including the latest American Society of Transplantation guidelines for treatment and prophylaxis.
29. Gordon SM, Avery RK. Aspergillosis in lung transplantation: incidence, risk factors, and prophylactic strategies. *Transpl Infect Dis* 2001; 3:161–167.
 30. Marks DI, Pagliuca A, Kibbler CC, *et al*. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol* 2011; 155:318–327.
 31. Husni RN, Gordon SM, Longworth DL, *et al*. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. *Clin Infect Dis* 1998; 26:753–755.
 32. Singh N, Husain S. Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management. *J Heart Lung Transplant* 2003; 22:258–266.
 33. Solé A, Salavert M. Fungal infections after lung transplantation. *Transplant Rev* 2008; 22:89–104.
 34. Neoh CF, Snell GI, Kotsimbos T, *et al*. Antifungal prophylaxis in lung transplantation: a world-wide survey. *Am J Transplant* 2011; 11:361–366.
- Broad survey of antifungal prophylaxis practices in lung transplant centers world-wide illustrates the diversity of approaches in current practice.
35. Chambers DC, Yerkovich ST, Maliyasena V, *et al*. Risk factors for invasive fungal infection after lung transplantation. *J Heart Lung Transplant* 2012; 31:S143–S144.
 36. Wahidi MM. Diagnosis and outcome of early pleural space infection following lung transplantation. *Chest* 2009; 135:484.
 37. Schaenman JM, Rosso F, Austin JM, *et al*. Trends in invasive disease due to Candida species following heart and lung transplantation. *Transplant Infect Dis* 2009; 11:112–121.
 38. Hamacher J, Spiliopoulos A, Kurt AM, Nicod LP. Preemptive therapy with azoles in lung transplant patients. Geneva Lung Transplantation Group. *Eur Respir J* 1999; 13:180–186.
 39. Pinney MF, Rosenberg AF, Hampp C, *et al*. Invasive fungal infections in lung transplant recipients not receiving routine systemic antifungal prophylaxis: 12-year experience at a university lung transplant center. *Pharmacotherapy* 2011; 31:537–545.
 40. Iversen M, Burton CM, Vand S, *et al*. Aspergillus infection in lung transplant patients: incidence and prognosis. *Eur J Clin Microbiol Infect Dis* 2007; 26:879–886.
 41. Singh N, Limaye AP, Forrest G, *et al*. Late-onset invasive aspergillosis in organ transplant recipients in the current era. *Med Mycol* 2006; 44:445–449.
 42. Kubak BM, Huprikar SS, the AST Infectious Diseases Community of Practice. Emerging & rare fungal infections in solid organ transplant recipients. *Am J Transplant* 2009; 9:S208–S226.
 43. Nucci M. Emerging moulds: Fusarium, Scedosporium and Zygomycetes in transplant recipients. *Curr Opin Infect Dis* 2003; 16:607–612.
 44. Hosseini-Moghaddam SM, Husain S. Fungi and molds following lung transplantation. *Semin Respir Crit Care Med* 2010; 31:222–233.
 45. Luong M-L, Hosseini-Moghaddam SM, Singer LG, *et al*. Risk factors for voriconazole hepatotoxicity at 12 weeks in lung transplant recipients. *Am J Transplant* 2012; 12:1929–1935.
 46. Nivoix Y, Velten M, Letscher Bru V, *et al*. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis* 2008; 47:1176–1184.
 47. Mikulska M, Novelli A, Aversa F, *et al*. Voriconazole in clinical practice. *J Chemother* 2012; 24:311–327.
 48. Segal BH, Walsh TJ. Current approaches to diagnosis and treatment of invasive aspergillosis. *Am J Respir Crit Care Med* 2006; 173:707–717.
 49. Feist A, Lee R, Osborne S, *et al*. Increased incidence of cutaneous squamous cell carcinoma in lung transplant recipients taking long-term voriconazole. *J Heart Lung Transplant* 2012; 31:1177–1181.
 50. Zwald FO, Spratt M, Lemos BD, *et al*. Duration of voriconazole exposure: an independent risk factor for skin cancer after lung transplantation. *Dermatol Surg* 2012; 38:1369–1374.
 51. Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. *Curr Opin Pulm Med* 2010; 16:242–250.
 52. Singer JP, Boker A, Metchnikoff C, *et al*. High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. *J Heart Lung Transplant* 2012; 31:694–699.
 53. Chen L, Mulligan ME. Medication-induced periostitis in lung transplant patients: periostitis deformans revisited. *Skeletal Radiol* 2010; 40:143–148.
 54. Han K, Capitano B, Bies R, *et al*. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. *Antimicrob Agents Chemother* 2010; 54:4424–4431.
 55. Felton TW, Roberts SA, Isalca B, *et al*. Isolation of Aspergillus species from the airway of lung transplant recipients is associated with excess mortality. *J Infect* 2012; 65:350–356.
 56. Singh N, Aguado JM, Bonatti H, *et al*. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. *J Infect Dis* 2009; 200:1002–1011.
 57. Garantziotis S, Palmer SM. An unwelcome guest: aspergillus colonization in lung transplantation and its association with bronchiolitis obliterans syndrome. *Am J Transplant* 2009; 9:1705–1706.
 58. Weigt SS, Copeland CAF, Derhovanessian A, *et al*. Colonization with small conidia aspergillus species is associated with bronchiolitis obliterans syndrome: a two-center validation study. *Am J Transplant* 2013; 13:919–927.
 59. Belperio JA, Keane MP, Burdick MD, *et al*. Critical role for CXCR3 chemokine biology in the pathogenesis of bronchiolitis obliterans syndrome. *J Immunol* 2002; 169:1037–1049.
 60. Belperio JA, Weigt SS, Fishbein MC, Lynch JP. Chronic lung allograft rejection: mechanisms and therapy. *Proc Am Thorac Soc* 2009; 6:108–121.
 61. Husain S, Raza K, Pilewski JM, *et al*. Experience with immune monitoring in lung transplant recipients: correlation of low immune function with infection. *Transplantation* 2009; 87:1852–1857.
 62. Singh N, Husain S, the AST Infectious Diseases Community of Practice. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant* 2009; 9:S180–S191.
 63. Husain S, Zaldonis D, Kusne S, *et al*. Variation in antifungal prophylaxis strategies in lung transplantation. *Transplant Infect Dis* 2006; 8:213–218.
 64. Billaud EM, Guillemin R, Berge M, *et al*. Pharmacological considerations for azole antifungal drug management in cystic fibrosis lung transplant patients. *Med Mycol* 2010; 48:S52–S59.

65. Safdar A, Ma J, Saliba F, *et al*. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B. *Medicine* 2010; 89:236–244.
66. Solé A. Invasive fungal infections in lung transplantation: role of aerosolised amphotericin B. *Int J Antimicrob Agents* 2008; 32:S161–S165.
67. Monforte V, Ussetti P, López R, *et al*. Nebulized liposomal amphotericin B prophylaxis for Aspergillus infection in lung transplantation: pharmacokinetics and safety. *J Heart Lung Transplant* 2009; 28:170–175.
68. Drew R. Potential role of aerosolized amphotericin B formulations in the prevention and adjunctive treatment of invasive fungal infections. *Int J Antimicrob Agents* 2006; 27 (Suppl 1):36–44.
69. Husain S, Capitano B, Corcoran T, *et al*. Intrapulmonary disposition of amphotericin B after aerosolized delivery of amphotericin B lipid complex (Abelcet; ABLC) in lung transplant recipients. *Transplantation* 2010; 90:1215–1219.
70. Monforte V, Román A, Gavalda J, *et al*. Nebulized amphotericin B concentration and distribution in the respiratory tract of lung-transplanted patients. *Transplantation* 2003; 75:1571–1574.
71. Monforte V, López-Sánchez A, Zurbano F, *et al*. Prophylaxis with nebulized liposomal amphotericin B for Aspergillus infection in lung transplant patients does not cause changes in the lipid content of pulmonary surfactant. *J Heart Lung Transplant* 2013; 32:313–319.
72. Salavert M. Prophylaxis, preemptive or empirical antifungal therapy: which is best in nonlung transplant recipients? *Int J Antimicrob Agents* 2008; 32:S149–S153.
73. Kubak BM. Fungal infection in lung transplantation. *Transpl Infect Dis* 2002; 4 (Suppl 3):24–31.
74. 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. *Am J Transplant* 2004; 4:796–802.
75. Leeflang MM, Debets-Ossenkopp YJ, Visser CE, *et al*. Galactomannan detection for invasive aspergillosis in immunocompromized patients. *Cochrane Database Syst Rev* 2008; 4:CD007394.
76. Lass-Flörl C, Gunsilius E, Gastl G, *et al*. Diagnosing invasive aspergillosis during antifungal therapy by PCR analysis of blood samples. *J Clin Microbiol* 2004; 42:4154–4157.
77. 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; 83:1330–1336.
78. Bhaskaran A, Singer LG, Yinka A, *et al*. Efficacy of BAL galactomannan (GM) and culture based pre-emptive antifungal therapy (PET) in lung transplant recipients (LTRs). *J Heart Lung Transplant* 2013; 32:S49.
79. Tolman JA, Wiederhold NP, McConville JT, *et al*. Inhaled voriconazole for prevention of invasive pulmonary aspergillosis. *Antimicrob Agents Chemother* 2009; 53:2613–2615.
80. Thompson GR, Wiederhold NP. Isavuconazole: a comprehensive review of spectrum of activity of a new triazole. *Mycopathologia* 2010; 170:291–313.