2026 IDSA Clinical Practice Guidelines on Prevention of Invasive Aspergillosis in Adult Solid Organ Transplant Recipients – Lung and Heart Transplant Recipients

Shahid M. Husain[1]*, Nitipong Permpalung[2]*, M. Hong Nguyen[3], Jo-Anne H. Young[4], Aadith Ashok[5], Miranda M. So[6], David R. Andes[7], Monica I. Ardura[8], Antonio C. Arrieta[9], Eric J. Bow[10], Pranatharthi H. Chandrasekar[11], Sharon C-A. Chen[12], Sarah P. Hammond[13], Sophia A. Koo[14], Thomas F. Patterson[15], George R. Thompson[16], C. Orla Morrissey[17], Mindy G. Schuster**[18], Valéry Lavergne**[19]**

[1]Department of Medicine, Division of Infectious Diseases, University Health Network, University of Toronto, Toronto, Canada; [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [3]Department of Medicine, Division of Infectious Diseases, Transplant Infectious Diseases and Antimicrobial Management Program, University of Pittsburgh, Pennsylvania, USA; [4]Department of Medicine, Division of Infectious Diseases and International Diseases, University of Minnesota, Minnesota, USA; [5]Department of Infectious Diseases, Bayside Health (Alfred Care Group),Monash University, Melbourne, Australia; [6]University Health Network, Toronto, Canada, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada, Department of Infectious Diseases, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne Australia; [7]Division of Infectious Disease and the Department of Medical Microbiology and Immunology, University of Wisconsin-Madison, Wisconsin, USA; [8]Pediatric Infectious Diseases, Host Defense, Nationwide Children's Hospital, Columbus, Ohio, USA, Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio, USA; [9]Division of Infectious Diseases, Children's Hospital of Orange County, University of California Irvine, California, USA. Department of Pediatrics, University of California Irvine, California, USA; [10]Departments of Medical Microbiology and Infectious Diseases and Internal Medicine, Sections of Infectious Diseases and Haematology/Oncology, Max Rady College of Medicine, University of Manitoba, Manitoba, Canada, Department of Medical Oncology and Haematology and Infection Control Services, CancerCare Manitoba, Manitoba, Canada; [11]Division of Infectious Diseases, Karmanos Cancer Center, Wayne State University, Detroit, Michigan, USA; [12]Department of Infectious Diseases and Microbiology Laboratory Services, Westmead Hospital, Westmead, Australia; [13]Divisions of Infectious Diseases and Hematology Oncology, Massachusetts General Hospital, Massachusetts, USA, Department of Medical Oncology, Dana-Farber Cancer Institute, Massachusetts, USA, Harvard Medical School, Massachusetts, USA; [14]Division of Infectious Diseases, Brigham and Women's Hospital, Massachusetts, USA, Department of Medical Oncology, Dana-Farber Cancer Institute, Massachusetts, USA, Harvard Medical School, Massachusetts, USA; [15]Department of Medicine, Division of Infectious Diseases, University of Texas Health San Antonio, Texas, USA; [16]Departments of Medicine and Department of Medical Microbiology and Immunology, Division of Infectious Diseases, University of California-Davis Medical Center, California, USA ; [17]Department of Infectious Diseases, Bayside Health (Alfred Care Group), Melbourne, Victoria, Australia, Department of Infectious Diseases, School of Translational Medicine, Monash University, Melbourne, Victoria, Australia, Centre to Impact AMR, Monash University, Clayton, Victoria, Australia; [18]Department of Medicine, Division of Infectious Diseases, Hospital of the University of Pennsylvania, Pennsylvania, USA; [19]Division of Medical Microbiology and Infection Control, Department of Pathology & Laboratory Medicine, Vancouver General Hospital, University of British Columbia, Vancouver, Canada, Department of Clinical Affairs and Practice Guidelines, Infectious Diseases Society of America, Virginia, USA

*co first authors
**co last authors

Lung Transplant Recipients

Clinical question A: In lung transplant recipients, what is the optimal anti-*Aspergillus* prophylaxis strategy (universal prophylaxis, targeted prophylaxis, or pre-emptive therapy)?

Recommendations:

1) **In lung transplant recipients, we make no recommendation for or against universal anti-*Aspergillus* prophylaxis (*no recommendation, knowledge gap*).**

Comments:

-The panel concluded that the potential benefits of the universal as compared to no anti-*Aspergillus* prophylaxis remain unclear. There are critical risks of bias in existing studies, unexplored sources of heterogeneity between studies, and serious concerns regarding their lack of generalizability to current clinical practice. Further studies are needed to evaluate the effectiveness and safety of antifungal agents particularly in respect to potential harms such as serious adverse events, drug-drug interactions, costs and challenges related to antimicrobial stewardship.
-The role of antifungal prophylaxis in lung transplantation remains complex due to the lack of high-quality evidence supporting a standardized approach, leading to significant variability in practice. Please refer to the "Considerations when implementing a prophylactic strategy" section.

2) **In lung transplant recipients, we make no recommendation for or against any targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy rather than universal anti-*Aspergillus* prophylaxis (*no recommendation, knowledge gap*).**

Comments:

-The panel concluded that the potential benefits of the different anti-*Aspergillus* prophylactic strategies (universal prophylaxis, targeted prophylaxis, and pre-emptive therapy) remain unclear. There are critical risks of bias in existing studies, unexplored sources of heterogeneity between studies, and serious concerns regarding their lack of generalizability to current clinical practice. Further studies are needed to evaluate the effectiveness and safety of antifungal agents in this setting, particularly in respect to potential harms such as serious adverse events, drug-drug interactions, costs and challenges related to antimicrobial stewardship.
-The role of antifungal prophylaxis in lung transplantation remains complex due to the lack of high-quality evidence supporting a standardized approach, leading to significant variability in practice. Please refer to the "Considerations when implementing a prophylactic strategy" section.

Clinical question B: In lung transplant recipients in whom anti-*Aspergillus* prophylaxis or pre-emptive therapy is considered, is there an optimal choice of antifungal agent(s)?

Recommendation:

In lung transplant recipients in whom anti-*Aspergillus* prophylaxis or pre-emptive therapy is being considered, clinicians should select agent(s) based on the following factors: adverse events profile, drug-drug interactions, ease of administration and tolerability, associated costs and resources, availability, as well as local epidemiology (*good practice statement*).

Comments:

-In absence of direct comparisons between different classes of agents in the reviewed evidence, the panel judged that an individualized approach for selecting anti-*Aspergillus* prophylaxis (if considered) is preferable.

-Comparison between triazoles is presented in **Table 3** and between different formulations of aerosolized amphotericin B in **Table 4**.

Background

Lung transplant recipients are at increased risk for invasive mold infections (IMIs), particularly invasive aspergillosis (IA), due to multiple predisposing factors. These include profound immunosuppression, diminished airway defenses due to impaired mucociliary clearance and cough reflex, and environmental exposures. In addition, airway ischemia plays a critical role as bronchial arteries are typically not re-anastomosed during transplantation, leading to compromised blood supply to the airway, and further weakening of local immune defenses. This ischemia can result in bronchial wall injury and necrosis, which are well-recognized predisposing factors for fungal invasion, particularly by *Aspergillus* [1-4]. Specific risk factors for IA include pre-transplant *Aspergillus* colonization, post-transplant colonization within the first year, cytomegalovirus virus (CMV) infection, and in single lung transplantation [5-7]. IA is associated with higher mortality [7, 8] and contributes to the development of chronic lung allograft dysfunction (CLAD) [9, 10].

Several prophylactic antifungal strategies can be considered, including universal prophylaxis, targeted prophylaxis, and pre-emptive therapy during the post-transplant period [11, 12] (See Introduction, Table 1 on Definitions of the different types of antifungal prophylaxis). There is currently no consensus on the optimal prophylactic strategies, antifungal agent(s), duration, or criteria for patient selection [13]. Alternative strategies, such as risk-targeted prophylaxis or pre-emptive therapy based on bronchoalveolar lavage (BAL) cultures and/or fungal biomarkers have been proposed but remain less defined due to variability in clinical practice and inconsistent data [12].

To address key knowledge gaps, the IDSA panel conducted a systematic review of the literature to determine the optimal anti-*Aspergillus* prophylactic strategy (universal prophylaxis, targeted prophylaxis or pre-emptive therapy) and optimal choice of antifungal agent(s), including regimen and duration of therapy. In addition, the panel also conducted a comprehensive literature review to assess the incidence and risk of IA during the first year following lung transplantation in recipients not receiving post-transplant anti-*Aspergillus* prophylaxis. The primary objectives of this document are to evaluate the effectiveness and limitations of current prophylactic approaches, to define the baseline risk of IA, identify key clinical risk factors and provide evidence-based, patient-centered recommendations for IA prevention in lung transplant recipients. Notably, the current recommendations represent a significant shift from the universal antifungal prophylaxis previously recommended in the 2016 version of the Society's Practice Guidelines for the Diagnosis and Management of Aspergillosis [14].

Clinical question A: In lung transplant recipients, what is the optimal anti-*Aspergillus* prophylaxis strategy?

Clinical question A1: In lung transplant recipients, should universal anti-*Aspergillus* prophylaxis be used rather than no anti-*Aspergillus* prophylaxis?

Recommendation: In lung transplant recipients, we make no recommendation for or against universal anti-*Aspergillus* prophylaxis (*no recommendation, knowledge gap*).

Comments:

-The panel concluded that the potential benefits of the universal as compared to no anti-*Aspergillus* prophylaxis remain unclear. There are critical risks of bias in existing studies, unexplored sources of heterogeneity between studies, and serious concerns regarding their lack of generalizability to current clinical practice. Further studies are needed to evaluate the effectiveness and safety of antifungal agents particularly in respect to potential harms such as serious adverse events, drug-drug interactions, costs and challenges related to antimicrobial stewardship.

-The role of antifungal prophylaxis in lung transplantation remains complex due to the lack of high-quality evidence supporting a standardized approach, leading to significant variability in practice. Please refer to the "Considerations when implementing a prophylactic strategy" section.

Summary of the evidence

Our systematic review of the literature (spanning from 2000-2025) identified four observational studies [15-18] comparing universal anti-*Aspergillus* prophylaxis (utilizing either voriconazole or aerosolized amphotericin B with or without itraconazole) to the absence of anti-*Aspergillus* prophylaxis.

Studied populations and clinical settings:

A total of 656 lung transplant recipients were included across four retrospective "before-and-after" cohort studies conducted post-transplantation. In these studies, the "before" periods corresponded to the comparator groups without anti-*Aspergillus* prophylaxis, while the "after" periods corresponded to the intervention groups with universal anti-*Aspergillus* prophylaxis using either voriconazole or aerosolized amphotericin B with or without itraconazole.

Enrollment spanned from 1990 to 2006 in three studies [15-17] and from 2013 to 2022 in a more contemporary study [18]. Studies were performed in North America (USA, from 2002 to 2006) and Europe (Denmark, from 1990 to 1999, Spain, from 1990 to 1997, and the Netherlands, from 2013-2022). Two of these studies date back more than three decades, with relatively small cohorts [16, 17]. Among the 656 lung transplant recipients, 249 had single lung transplants, 399 had bilateral lung transplants, and eight had heart-lung transplants (see Supplementary material, Table A1.2 Characteristics of the included studies). Routine surveillance bronchoscopy was performed only in Tofte 2012 study [15], while in the van Gemert 2025 study, a protocolized bronchoscopy was performed once 1 to 3 months after transplant (including galactomannan and *Aspergillus* PCR), with subsequent bronchoscopies being performed based on clinical indication [18]. The reported rates of IA in the no prophylaxis control groups were very high and ranged from 17.1 to 72.1%. One-year all-cause mortality rate in the no-prophylaxis control group was reported in the van Gemert 2025 and Tofte 2012, and ranged from 10.4 to 29.2%, respectively [15, 18].

Studied comparison:

The antifungal regimens and duration of prophylaxis in the intervention groups varied considerably among the four studies. In the Monforte study, recipients received lifelong aerosolized amphotericin B alone [17]. The Minari 2002 study implemented a regimen of aerosolized amphotericin B for two weeks followed by lifelong itraconazole [16], while the Tofte 2012 study used voriconazole for 3 months [15] and the van

Gemert 2025 study used aerosolized amphotericin B for the duration of the hospital stay (for a median of 26 days). None of the studies used posaconazole, isavuconazole, or echinocandins for prophylaxis. Comparator groups across all four studies did not receive antifungal prophylaxis. Therapeutic drug monitoring (TDM) was performed in one of the two studies that used triazole agents, i.e. TDM for itraconazole in Minari 2002 [16].

Studied outcomes:

All studies focused on the incidence of IA during the post-transplant period. The most contemporary study (van Gemert 2025) applied the 2020 European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORCT/MSG) criteria and the 2015 International Society for Heart and Lung Transplantation (ISHLT) criteria to define probable and proven IA. Although the three older studies predate the EORTC/MSG [19] and ISHLT [20] IA definitions, their criteria are well aligned, except for the omission of galactomannan (GM). Monforte's study broadly categorized tracheobronchitis, ulcerative tracheobronchitis, and invasive pulmonary aspergillosis (IPA) as "*Aspergillus* infection," potentially reducing specificity. Minari's study, despite a vague description of ulcerative bronchitis, confirmed IPA in all 24 patients. Tofte's 2012 study used strict criteria for proven infection, requiring hyphal evidence in transbronchial biopsy samples to define invasive tracheobronchitis and bronchial anastomotic infection, emphasizing histopathological confirmation [15]. Few studies reported *Aspergillus* colonization, mortality (all-cause), or serious adverse events (SAE) leading to antifungal discontinuation. No study reported attributable mortality, graft loss, graft rejection, or non-serious adverse events (AE). The follow-up period was similar between groups and ranged from 14 to 56 months [15, 17, 18], except for the control group in the Minari 2002 study where follow-up was extended up to 9 years [16].

Study design, risk of bias, and other considerations:

The overall risk of bias of the identified evidence was judged to be critical, which precludes drawing meaningful conclusions. All three studies were single-center retrospective “before-and-after” cohort studies, a design inherently prone to biases. The inclusion of patients from older studies may compromise the validity of the conclusions, as evolving clinical practice, patient demographics, and healthcare standards could affect the findings’ generalizability to current clinical settings. Small sample sizes (55 to 274 patients) were prone to residual confounding and selection bias, undermining reliability. Moreover, the absence of critical baseline characteristics, such as *Aspergillus* colonization at transplant and use of anti-lymphocyte therapies, maintenance immunosuppressive regimens precluded meaningful comparisons. Similarly, Tofte 2012 noted significant mortality changes across two time periods, likely driven by shifts in clinical practices or inclusion of higher-risk patients rather than prophylaxis effects [15]. Additional limitations included the absence of surveillance bronchoscopies in two studies [16, 17], lack of TDM for azoles in one study [15], and incomplete reporting on AE and adherence to the intended prophylaxis. Finally, the very high incidence of IA (>17%) in all four studies raises further concerns about their generalizability to current practice (See discussion below).

Our review revealed significant heterogeneity among the studies, but the small number of studies limited exploration of its sources. Potential contributors include differences in eras (patients enrolled in the 1990s vs later), population IA risk profiles, surveillance protocols (routine surveillance bronchoscopies and newer diagnostic tools), standards of care, prophylaxis types (agents, dosage, route of administration, and duration), or durations of follow-up. Without addressing these factors, the panel could not draw meaningful conclusions about the impact of antifungal prophylactic strategies on IA incidence. Consequently, the panel was unable to draw meaningful or definitive conclusions regarding the impact of antifungal prophylaxis on IA incidence.

Conclusion:

Given the critical risk of bias, limited generalizability to current clinical practice, and unresolved sources of heterogeneity between studies, the panel concluded that the potential benefits of universal prophylaxis as compared to no anti-*Aspergillus* prophylaxis in lung transplant recipients remain uncertain.

Other supporting evidence

Incidence of invasive aspergillosis in lung transplant recipients

To understand the true burden of IA in lung transplant recipients, a mapping review of the literature was performed to determine the incidence of IA in different settings (i.e. with or without anti-*Aspergillus* prophylaxis).

Incidence of Invasive Aspergillosis in lung transplant recipients not receiving anti-*Aspergillus* prophylaxis

The overall incidence of IA among lung transplant recipients who did not receive anti-*Aspergillus* prophylaxis was 19.0% (95% confidence interval (CI): 8.4-37.2%) [15-17, 21-23] (See Supplementary material, Figure A4.2 Forest plot of incidence of IA in lung transplant recipients not receiving anti-*Aspergillus* prophylaxis). To accurately estimate the baseline IA incidence in this population, it is essential to exclude patients who received universal prophylaxis, targeted prophylaxis, or pre-emptive antifungal therapy, as their inclusion could underestimate the true IA risk. A review of selected studies meeting these criteria revealed substantial variability in reported IA rates [15-17, 21-23]. Monforte et al. documented a notably high IA incidence of 73% (8/11) [17]; however, this study involved an older cohort, patients treated with orthoclone marumonab-CD3 (OKT3) induction therapy, and extended follow-up of up to 41 months. In contrast, a non-comparative study in lung transplant recipients without antifungal prophylaxis reported a substantially lower IA rate of 4.5% (11/242) over a 12-year period, with a median follow-up of 20 months after transplantation highlighting the confounding due to geography [21]. Intermediate incidence rates were observed by Tofte et al. at 17% (14/82) over more than 24 months [15], and Minari et al. at 20% (16/88) over a period exceeding five years [16].

Although studies using pre-emptive antifungal strategy were largely excluded from the incidence analysis due to potential underestimation bias, one study [22] provided sufficiently detailed data to merit inclusion. In this study, among 519 consecutive lung transplant recipients followed for one-year post-transplant, 370 patients did not receive anti-*Aspergillus* prophylaxis. This subgroup included 259 patients who were both GM and culture-negative, and 111 patients who had positive GM or *Aspergillus* cultures from BAL yet did not receive treatment. The one-year IA incidence in this cohort was 9.7% (36/370). More recently, van Gemert et al. reported a 32% incidence (43/136), with follow-up extending beyond four years [23].

This variability is not unexpected and reflects both methodological and clinical heterogeneity. Longer follow-up periods capture more IA events, inflating cumulative incidence. However, this data should not be dismissed as noise. Rather, it highlights the complex and multifactorial nature of IA risk in lung transplant populations. Risk of IA is shaped by factors such as pre/ post-transplant colonization, underlying disease, transplant type (single vs. double lung transplants), induction and maintenance immunosuppression, and center-specific practices. Variability in airway management, and local epidemiology further contribute to observed differences.

Given the significant methodological variability (including differences in diagnostic techniques, surveillance protocols, and follow-up durations) determining a precise incidence rate remains challenging. These findings underscore the importance of interpreting published IA rates within their clinical context and with awareness of one's own local center's baseline incidence. Local data, accounting for patient mix, diagnostic approaches and clinical protocols, are vital for guiding prophylaxis strategies and risk-benefit decisions. While this literature provides a useful framework, individualized and institution-specific approaches remain essential for optimizing IA prevention in lung transplant recipients. Taken together, despite the variability in reported rates, these studies consistently demonstrate the substantial burden of IA incidence in the absence of prophylaxis and reinforce the need for personalized risk-based prevention strategies.

Rate of Breakthrough Infection

Breakthrough aspergillosis, defined as infection occurring despite ongoing anti-*Aspergillus* fungal prophylaxis, varies significantly based on the prophylactic strategy employed. Universal prophylaxis, targeted prophylaxis, and pre-emptive therapy approaches differ in timing, patient selection, and initial fungal burden, influencing the observed breakthrough infection rates and outcomes. Aggregating data across these approaches risks obscuring critical distinctions. For instance, universal prophylaxis strategies may appear more effective due to the inclusion of lower-risk individuals, whereas pre-emptive strategies could appear less effective due to the delayed initiation of antifungal therapy in higher-risk patients.

The overall rate of breakthrough IA was 6.4% (95% CI: 3.3-12.1%) [4, 7, 17, 22-25]. Among studies employing universal prophylaxis, the reported breakthrough rates vary due to the use of a variety of antifungal agents (See Supplementary material, Figure A4.3 and narrative). Note that none of the studies involving systemic azoles for prophylaxis or pre-emptive therapy routinely performed TDM, which may have impacted drug exposure and breakthrough. These observations highlight that breakthrough infection rates may be influenced by antifungal selection, adherence to TDM, and host-specific factors (poor drug penetration in ischemic areas), emphasizing the importance of interpreting outcomes within the context of the specific prophylactic strategy employed.

Mortality Associated with Invasive Aspergillosis

Overall, mortality among lung transplant recipients with IA averages around 32.8% (95% CI: 22.5-45.1%) across published studies [7, 8, 16, 17, 21-39] The highest rates were reported by Arthurs et al. (100%) [30], Iversen et al. (59.1%) [29], and Aguilar et al. (40.5%) [7], underscoring the historically lethal nature of the infection. In contrast, Husain et al. (4.2%) and Linder et al. (0%) reported the lowest mortality [22, 25], suggesting improved survival in more contemporary cohorts. Indeed, studies conducted in the 1990s to early 2000s consistently demonstrated markedly higher mortality, reflecting limited diagnostic tools and antifungal options at the time. By comparison, more recent cohorts published after 2015 show substantially lower mortality rates, typically ranging from 0% to 22%, a trend that likely reflects earlier diagnosis, effective prophylactic strategies, and advances in antifungal therapy (See Supplementary material, Figure A4.4 and narrative).

Post-Transplant *Aspergillus* Colonization

Post-transplan*t Aspergillus* colonization is a unique clinical syndrome noted in lung transplant recipients and is an established risk factor for IA. The rate of *Aspergillus* colonization was reported as 23.8% (95% CI: 15.1%–35.4%) among 5,099 lung transplant recipients in 22 studies [7, 8, 15, 17, 22-24, 26, 28, 29, 31, 33, 34, 38-46] (See Supplementary material, Figure A4.5 Rate of *Aspergillus* colonization in lung transplant recipients). The variability in reported incidence rates of *Aspergillus* colonization may be attributed to several factors, including the choice of prophylactic agent (e.g., aerosolized amphotericin B or azoles),duration of anti-*Aspergillus* prophylaxis the prophylactic strategy employed (universal or targeted), or pre-emptive therapy differences in the frequency of BAL surveillance protocols at centers, the inclusion of biomarkers (such as GM) alongside *Aspergillus* culture, and varying durations of follow-up across studies. and the fact that reported rates included both patients receiving antifungal therapy and those not receiving prophylaxis for any reason

Clinical question A2: In lung transplant recipients, should targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy be used rather than universal prophylaxis?

Recommendation: In lung transplant recipients, we make no recommendation for or against any targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy rather than universal anti-*Aspergillus* prophylaxis (*no recommendation, knowledge gap*).

Comments:

-The panel concluded that the potential benefits of the different anti-*Aspergillus* prophylactic strategies (universal prophylaxis, targeted prophylaxis, and pre-emptive therapy) remain unclear. There are critical risks of bias in existing studies, unexplored sources of heterogeneity between studies, and serious concerns regarding their lack of generalizability to current clinical practice. Further studies are needed to evaluate the effectiveness and safety of antifungal agents in this setting, particularly in respect to potential harms such as serious adverse events, drug-drug interactions, costs and challenges related to antimicrobial stewardship.

-The role of antifungal prophylaxis in lung transplantation remains complex due to the lack of high-quality evidence supporting a standardized approach, leading to significant variability in practice. Please refer to the “Considerations when implementing a prophylactic strategy” section.

Background

Targeted prophylaxis is limited to patients identified as high-risk based on clinical or microbiological criteria, such as prior fungal colonization, prolonged mechanical ventilation, CMV infection, or re-transplantation. In contrast, pre-emptive therapy relies on intensive serial surveillance using diagnostic tools—such as BAL cultures or GM assays—to guide early antifungal intervention before the onset of clinical disease. Despite these definition distinctions, the literature often uses the terms interchangeably which complicates comparative analyses across studies.

Summary of the evidence

Our systematic review of the literature (spanning from 2000-2025) identified three observational studies reported across four publications [25, 28, 46, 47] that compared universal anti-*Aspergillus* prophylaxis with targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy.

Studied populations and clinical settings:

A total of 495 lung transplant recipients were enrolled in these three studies in the peri-transplantation period. The timeframe of enrollment spanned from 2010 to 2019 for the two most recent studies [25, 46] and from 2001 to 2004 in the older study [28]. Studies were performed in North America (USA) [25, 28] and Europe (Denmark) [46, 47].

All three studies were retrospective “before-and-after” cohort design. In two studies [25, 46, 47], the “before” periods corresponded to the comparator groups who received universal antifungal prophylaxis, and the “after” periods corresponded to the intervention groups who received targeted anti-*Aspergillus* prophylaxis and/or pre-emptive therapy, while the third study [28] the “before” period corresponded to the intervention groups who received targeted anti-*Aspergillus* prophylaxis / pre-emptive therapy, and the “after” period corresponded to the intervention groups who received universal anti-*Aspergillus* prophylaxis.

Among the 495 patients, 396 were bilateral lung transplants, 97 were single lung transplants, and two heart-lung transplants (see Supplementary material, Table A1.2 Characteristics of the included studies). Routine surveillance bronchoscopy with biopsies and cultures were performed in all three studies, but the timing and frequency of surveillance varied. The reported rates of IA in the comparator groups (patients who receiving universal anti-*Aspergillus* prophylaxis) varied from 8.5 to 14.0% [25, 46] and 23.3% in patients receiving pre-emptive prophylaxis [28].

Studied comparisons:

Although the terminology used across studies blurs the distinction between pre-emptive and targeted prophylaxis, each of the three studies used different anti-*Aspergillus* prophylaxis strategies. Crone et al. implemented a strictly targeted prophylaxis approach, limiting antifungal prophylaxis to lung transplant recipients at high-risk for IA [46]. High-risk criteria included one or more of the following within the first 3 months after transplant: cystic fibrosis, sarcoidosis, re-transplantation, hypogammaglobulinemia, impaired ciliary function, CMV infection, high-dose steroids, anti-lymphocyte treatment, older age, renal insufficiency, previous mold infection). Linder et al. combined targeted criteria (e.g., anti-thymocyte globulin therapy, pre-transplant colonization with *Aspergillus*, or prior IPA, or donor respiratory culture positive for *Aspergillus*) with pre-emptive measures (e.g., post-transplant BAL cultures positive for *Aspergillus*) under a framework labeled as targeted prophylaxis [25]. Husain et al. implemented a pre-emptive strategy guided by surveillance cultures [28].

In all three studies, the agents used for anti-*Aspergillus* prophylaxis changed between the comparator and the intervention groups: Crone et al. changed from universal prophylaxis with voriconazole to targeted posaconazole and aerosolized Amphotericin B Lipid Complex (ABLC), Linder et al. shifted from universal itraconazole with or without aerosolized amphotericin B to targeted / pre-emptive voriconazole, while Husain et al. transitioned from targeted itraconazole with or without aerosolized amphotericin B to universal voriconazole [25, 28, 46, 47]. TDM was not systematically performed.

Furthermore, the duration of prophylaxis also changed between the before-and-after periods, for example, the Linder study varied the duration of prophylaxis: six months in the universal group versus three months in the pre-emptive group.

Studied outcomes:

All studies focused on the incidence of IA during the post-transplant period, employing acceptable diagnostic criteria. Linder et al. utilized the 2008 EORTC/MSG [19] definitions to identify proven or probable IFIs, while Husain et al. applied the earlier 2002 EORTC/MSG criteria [48]. Crone et al. adopted the ISHLT criteria, which included specific definitions for *Aspergillus* tracheobronchitis and anastomotic infection [20].

All studies reported on the incidence of IA and breakthrough IA. Most studies reported on post-transplant *Aspergillus* colonization, all-cause mortality, SAE (generally defined as severe AE leading to antifungal discontinuation), while only one of the three studies reported on graft rejection and non-serious AE. The follow-up period to assess the outcomes ranged from 12 to 18 months post-transplant.

Study design, risk of bias and other considerations:

The overall risk of bias of the identified evidence was judged to be critical, severely limiting the ability to draw meaningful conclusions. All three studies were single-center retrospective “before-and-after” cohort studies, each enrolling a relatively small number of participants, ranging from 95 to 295 enrolled patients. The most important methodological limitation across these studies was the simultaneous alterations of multiple variables, including the antifungal prophylactic strategy, the agent used, and the duration of prophylaxis. These concurrent changes precluded valid comparisons and attribution of outcomes to any one intervention component.

Many other factors further limited the interpretation of the effects of prophylaxis on IA such as 1) the incomplete reporting on AE and adherence to the intended prophylaxis in two studies [25, 28] and significant non-adherence and interruption of prophylaxis in the universal prophylaxis group in Crone 2023 study [46, 47], 2) serious concerns about dose of itraconazole used in Linder 2021 study [25], 3) the lack of TDM for azoles in the three studies, and 4) missing data on pertinent baseline clinical characteristics of the studied populations in two studies [25, 28], precluded any meaningful comparison between the before-and-after periods.

Our review of the literature highlighted the large heterogeneity between the different studies identified. Sources of heterogeneity could not be explored due to the small number of studies identified, but may have been caused by a multitude of factors such as difference in eras (patients enrolled in the 2000s vs 2020s), included populations, baseline risk of IA, surveillance protocols (timing of surveillance newer diagnostic tools), standards of care, types of prophylaxis use (class of agents, dosage, route of administration, and duration), or durations of follow-up. Without further exploration of the potential sources of heterogeneity, the panel could not come to a meaningful conclusion on the potential effect of any type of antifungal prophylactic strategies on the incidence of IA.

Conclusion:

Due to critical risk of bias of the studies identified and unexplorable sources of heterogeneity between studies, the panel concluded that no reliable inferences could be made regarding the relative effectiveness of the different prophylactic strategies and thus the potential benefits and harms of the different prophylactic strategies (universal or targeted prophylaxis) and pre-emptive therapy remain unknown.

Other supporting evidence

Targeted Prophylaxis

A systematic review and meta-analysis conducted on studies published from 2001 to 2020 identified key risk factors for IA among lung transplant recipients [6]. The meta-analysis included eight studies involving 2,163 individual patients. Significant independent risk factors included previous fungal colonization (odds ratio [OR]: 2.44; 95% CI: 1.72-3.45), CMV infection (OR: 1.96; 95% CI: 1.08-3.56), and single lung transplantation (OR: 1.77; 95% CI: 1.08-2.91). Conversely, pre-emptive antifungal therapy was found to be protective (OR: 0.20; 95% CI: 0.08-0.47). The certainty of evidence ranged from moderate to high for most identified risk factors, although the effectiveness of antifungal prophylaxis exhibited lower certainty due to inconsistent findings across studies [6].

Two recent studies further examined the potential role of statin therapy in mitigating the risk of IA among lung transplant recipients, with mixed outcomes. Villalobos et al., in a retrospective analysis of 785 recipients on pre-emptive therapy protocol, reported that statin use significantly reduced the risk of IA and lowered post-transplant *Aspergillus* colonization rates [45]. They proposed that statins exert antifungal effects through inhibition of ergosterol biosynthesis, essential for fungal cell membrane integrity. Notably, statins administered for at least two weeks post-transplant resulted in approximately a 70% reduction in IA incidence. Van Gemert et al.'s observational study involving 274 recipients with or without nebulized amphotericin initially suggested a protective effect from statins, but this association lost significance upon performing a matched case-control sensitivity analysis, suggesting that confounding factors may have influenced the initial results [23].

Overall, these collective findings underline critical risk factors—including fungal colonization, CMV infection, single lung transplantation, prolonged mechanical ventilation, and acute cellular rejection—that heighten the susceptibility of lung transplant recipients to *Aspergillus* infections [6]. Additionally, renal replacement therapy (RRT) and extracorporeal membrane oxygenation (ECMO) were identified as risk factors for IMI, which includes IA [49, 50] (See Supplementary material, Risk factors for IMI narrative section). They also indicate potential beneficial roles for pre-emptive antifungal therapies and possibly statins, both warrant further confirmation through rigorous randomized controlled trials. Tailored prophylactic strategies and meticulous clinical monitoring remain paramount to managing the risk of invasive fungal infections (IFIs) in this vulnerable patient population.

Pre-emptive Therapy

There is significant overlap between targeted prophylaxis and pre-emptive therapy strategies in the post-transplant setting. For the purposes of this evaluation, studies employing surveillance cultures or biomarker-based approaches will be categorized as pre-emptive therapy, even if they also incorporate targeted criteria.

Our systematic review of the literature identified only two studies [25, 28] that directly compared universal prophylaxis with pre-emptive therapy using pre- and post-intervention analyses. While both studies reported less IA with universal prophylaxis, drawing direct comparisons and definitive conclusions is challenging, as both studies simultaneously altered the prophylactic strategy (from universal to pre-emptive or vice versa), the antifungal agent and the duration of prophylaxis.

Two additional studies [22, 42] examined pre-emptive therapy guided by surveillance BAL cultures, either alone or in combination with GM assay. Conducted at the same center but at different times, these studies identified a positive BAL culture or a BAL GM index ≥1 as risk factors for IA and suggested some protective effects of pre-emptive therapy. Pre-emptive therapy did not reduce mortality [22]. Pre-emptive therapy was overall associated with lower risk of IA compared to no pre-emptive therapy (adjusted HR 0.23, 95% CI 0.09 to 0.58) [22]. Additionally, within the positive surveillance group, the IA incidence remained high at 14%, and the IA rate among those receiving pre-emptive therapy (11.3%; 6/53) was not significantly different from those not receiving it (5.8%; 5/86). These findings raise questions about the efficacy of pre-emptive therapy in reducing IA incidence. Several significant limitations render the findings difficult to interpret. These include the studies' descriptive and observational design, potential selection bias, confounding-by-indication, small sample sizes, and lack of randomization. Delays in initiating pre-emptive therapy may have further diminished its effectiveness, while the complexity and resource demands of implementing such strategies may have posed additional barriers to timely intervention.

Timing of surveillance is another critical issue. Husain et al. reported that surveillance was most frequent during the early post-transplant period (up to 3 months) but decreased thereafter [22]. Given that the median time to IA onset

was 105 days post-transplant, this approach may fail to capture late IA cases. Consistent with the limitations of current pre-emptive strategies, Linder et al. found that none of the patients who developed IA met the criteria for pre-emptive antifungal therapy, suggesting that reliance solely on BAL cultures may be insufficient [25]. Incorporating additional clinical or immunologic risk factors could improve patient stratification for pre-emptive treatment.

In conclusion, while the studies identified risk factors for IA and some benefits of pre-emptive therapy, the evidence does not robustly demonstrate its efficacy in reducing IA incidence or improving outcomes. The timing and methodology of surveillance, as well as patient selection criteria, are critical areas requiring refinement. Future research should address the limitations of current studies through larger sample sizes, randomized designs, and broader evaluation of risk factors to optimize the utility of pre-emptive therapy.

Rationale for recommendation

Balance of benefits and harms / Other considerations

When comparing the different anti-*Aspergillus* prophylaxis strategies in lung transplant recipients, the panel judges that the balance of benefits and harms remains unknown. More specifically, potential benefits were not fully evaluable due to critical risk of bias (multiple study limitations), serious inconsistency (i.e. heterogeneity between studies), and indirectness (lack of generalizability).

Furthermore, potential harms are very heterogenous and agent-specific: 1) specific safety profile (toxicities, such as hepatotoxicity, bronchospasm), 2) specific drug interactions with immunosuppressive agents, 3) mode of administration, 4) availability of TDM, 5) total duration of prophylaxis (duration of immediate post-transplantation to life), 6) costs of agents and resources needed for administration, as well as 7) stewardship considerations. See the section on choice of agent(s) for more information.

Conclusion

The guideline panel makes no recommendation for or against anti-*Aspergillus* prophylactic strategies or for or against any specific anti-*Aspergillus* pre-emptive treatment strategies for lung transplant recipients in the post-transplantation period.

Considerations when implementing a prophylactic strategy

The role of antifungal prophylaxis in lung transplantation remains complex due to the lack of high-quality evidence supporting a standardized approach, leading to significant variability in practice. Four main approaches—universal prophylaxis, targeted prophylaxis, pre-emptive therapy, and no prophylaxis and no pre-emptive therapy—are commonly employed, each with distinct advantages and limitations (See **Table 1**). Transplant centers must carefully balance clinical efficacy, toxicity, drug interactions, cost, and feasibility to determine the most practical prophylaxis strategy for use in their own center.

Table 1. Comparative antifungal prophylaxis strategies in lung transplantation

Strategy	Advantages	Limitations
Universal prophylaxis	- Aimed at preventing IA for all patients - Standardized so easier to implement - May reduce IA incidence and mortality during high-risk periods	- Increased antifungal exposure - Higher risk of toxicity and resistance - Higher cost of antifungal agents - Potential overtreatment
Targeted prophylaxis	- Limits antifungal exposure to high-risk recipients - Potentially lowers toxicity and cost	- Requires accurate risk stratification - Risk of missing early IA in patients not meeting criteria
Pre-emptive therapy	- Antifungal use based on early microbiologic or biomarker detection - Avoids unnecessary treatment	- Relies on frequent bronchoscopies and reliable surveillance testing - Risk of delayed therapy - Operational complexity and higher diagnostic cost

No prophylaxis and no pre-emptive therapy	- Avoid antifungal drug exposure, drug costs, and associated adverse events - Operational simplicity - May reduce selection pressure for antifungal resistance - Avoids concerns about false negative diagnostic tests for IA	- Higher risk of IA during the early post-transplant period, especially among patients with established risk factors - Potential for increased IA-associated morbidity and mortality - Higher downstream costs related to treatment of established infection

While **Table 1** highlights the advantages and limitations of various antifungal prophylaxis strategies, it is important to emphasize that antifungal prophylaxis is not a one-size-fits-all approach. Instead, the choice should be tailored to transplant institutional factors, including local epidemiology, patient characteristics, immunosuppression protocols, diagnostic capabilities and available resources (See **Table 2**).

Table 2. Summary table for selecting antifungal prophylaxis strategies

Factors	Considerations
Local epidemiology	Centers with baseline high IA rates may benefit from universal prophylaxis; targeted prophylaxis may be appropriate in centers with well-defined high-risk cohorts (e.g., fungal colonization, pre-transplant IA, etc.).
Institutional immunosuppression protocols	High-risk regimen (e.g. lymphocyte-depleting agents) may benefit from universal or targeted strategies; lower-intensity protocols may permit pre-emptive strategies.
Diagnostic capabilities	Centers with reliable diagnostics (e.g. GM or other fungal biomarkers) may adopt a pre-emptive approach; limited diagnostic access favors universal prophylaxis.
Resource availability	Universal prophylaxis requires significant resources but is simpler to implement; pre-emptive approaches demand diagnostic and staffing investments.

By carefully weighing these factors, transplant centers can design antifungal prophylaxis protocols that optimize patient outcomes while adapting to local conditions. If a prophylactic strategy is selected, continuous monitoring with regular assessment of IA rates, mortality, drug tolerability, and resistance patterns is essential. Stable IA infection rates and minimal toxicities support maintaining the current strategy. However, increase in breakthrough IA, toxicity, or resistance warrants a strategic evaluation and adjustment. A practical example of such adaptability is from a center that identified a 9.8% IA rate, primarily early surgical site infections, despite employing universal aerosolized amphotericin B prophylaxis [32]. Bilateral lung transplantation and positive respiratory cultures on the day of transplant were identified as risk factors. In response, the center implemented an enhanced universal prophylaxis by adding systemic antifungal therapy for high-risk patients: micafungin was administered for 7–10 days in bilateral lung transplant recipients, and voriconazole was prescribed for 3–6 months for patients with positive fungal cultures. This modification reduced the IA rate to 2.4%, with only 8% of patients requiring voriconazole, illustrating the potential value of a tailored, risk-based strategy informed by ongoing surveillance and local epidemiology.

Although the outlined antifungal prophylaxis strategies provide a practical framework tailored to current clinical needs and institutional circumstances, they are temporary solutions in the absence of evidence-based guidelines. The absence of large, randomized clinical trials leaves significant gaps in knowledge, contributing to variability in practice and uncertainty about the optimal approach. As such, it is crucial for the transplant community to prioritize and support additional research, particularly well-designed clinical trials, to establish standardized prophylaxis protocols that can improve patient outcomes. Until such evidence becomes available, transplant centers must continue to adapt their strategies based on ongoing monitoring, evolving institutional data, and advances in diagnostic and therapeutics.

Clinical question B: In lung transplant recipients in whom anti-*Aspergillus* prophylaxis or pre-emptive therapy is considered, is there an optimal choice of antifungal agent(s)?

Recommendation: In lung transplant recipients in whom anti-*Aspergillus* prophylaxis or pre-emptive therapy is being considered, clinicians should select agent(s) based on the following factors: adverse events profile, drug-drug interactions, ease of administration and tolerability, associated costs and resources, availability, as well as local epidemiology (*good practice statement*).

Background

The selection of an optimal antifungal agent for prophylaxis or pre-emptive therapy in lung transplant recipients remains challenging due to a lack of high-quality, comparative studies. While mold-active azoles (itraconazole, voriconazole, isavuconazole, and posaconazole) and aerosolized amphotericin B are commonly used, direct head-to-head evidence comparing their efficacy is limited. Our systematic review of literature from 2000 to 2025 identified no randomized controlled trials comparing antifungal classes and only a small number of observational studies evaluating specific agents or formulations. Most available evidence is with older agents, such as itraconazole, voriconazole and earlier formulations of posaconazole, while data on newer antifungal options, including isavuconazole and newer posaconazole formulations, remain sparse. As a result, current decision-making is guided largely by observational data, individual patient factors, safety profiles, and institutional practices. This review synthesizes the available evidence to assess whether an optimal choice of agent(s) can be recommended for anti-*Aspergillus* prophylaxis in lung transplant recipients.

Summary of the evidence

Our systematic review of the literature (spanning from 2000-2025) did not identify any study directly comparing different classes of antifungal agents used for universal anti-*Aspergillus* prophylaxis but identified one study comparing different anti-mold triazoles [4] and four studies comparing different formulations of aerosolized amphotericin B [51-54].

Anti-mold triazoles

Summary of the evidence: Isavuconazole vs Voriconazole

Our systematic review of the literature (spanning from 2000-2025) identified one observational study comparing universal anti-*Aspergillus* prophylaxis with isavuconazole with aerosolized amphotericin B to voriconazole with or without aerosolized amphotericin B [4].

Studied population and clinical setting:

This retrospective single-center “before-and-after” cohort study [4] included 300 lung transplant recipients in North America receiving at least 5 days of anti-*Aspergillus* prophylaxis post-transplantation. During the “before” period (between 2013-2015), patients received voriconazole, while in the “after” period (2015-2018), isavuconazole was used as the universal prophylactic agent. The transition was prompted by a cluster of mucormycosis cases in solid organ transplant recipients.

Of the 300 patients, 164 underwent bilateral lung transplants (See Supplementary material, Table B1.2 Characteristics of the included study). Routine surveillance bronchoscopy was performed at 14 days and then every 2 months during the first year. The reported incidence of IA was 4.5% in the voriconazole group and 2.1 % in the isavuconazole, and respective one-year all-cause mortality rates were 11.5% and 9.7%.

Studied comparison:

Both groups received antifungal prophylaxis for a similar duration, with a median of 3.1 months for isavuconazole and 3.4 months for voriconazole. TDM was not performed in either arm. Adjunctive

aerosolized amphotericin B was systematically co-administered in only 40% of patients in the voriconazole group, introducing a potential confounding factor in the comparative assessment of outcomes [4].

Studied outcomes:

The study primarily assessed the incidence of IA and IFI during the post-transplant period, including breakthrough infection and those occurring within 12 months, based on 2020 EORTC/MSG [55]. Additional outcomes included SAE, defined as those leading to discontinuation of prophylaxis, and one-year all-cause mortality. Non-serious AE, graft rejection or graft loss were not reported.

Study design, risk of bias, and other considerations:

The overall risk of bias was assessed as "serious", primarily due to the single-center retrospective "before-and-after" design. In addition, the routine use of aerosolized amphotericin B in the isavuconazole group (compared to partial use in the voriconazole group) may have confounded examining isavuconazole efficacy, though it likely did not affect comparative tolerability. Additionally, the absence of TDM for azoles further limits the strength of the findings, although the clinical utility of TDM for isavuconazole has not been fully established.

Benefits and harms

Based on the panel's decision threshold (see Methods), isavuconazole as universal anti-*Aspergillus* prophylaxis in lung transplant recipients may result in comparable rates of IA, breakthrough IA, IFI and one-year all-cause mortality as voriconazole (See Supplementary material, Table B1.1 GRADE Evidence Profile). However, patients receiving isavuconazole may experience SAE less frequently (risk difference (RD): -24.7%; 95% CI: -33.9% to -15.4%; very low Certainty of Evidence (CoE)).

Other direct evidence

Two observational studies comparing posaconazole to voriconazole were initially considered [56, 57] but were excluded due to critical risk of bias. In both studies, posaconazole was selectively prescribed to patients at higher risk for AE (such as hepatotoxicity and cutaneous squamous cell carcinoma (cSCC)) or in the setting of limited drug availability. This confounding-by-indication introduced selection bias, precluding a valid comparison between antifungal agents.

Other supporting evidence

The absence of high-quality controlled trials and inherent methodological limitations complicates the selection of mold-active azoles for *Aspergillus* prophylaxis in lung transplant recipients. Current recommendations rely on limited evidence, patient-specific factors, AE and cost considerations. A more detailed description of AE is provided in the Pharmacology Tables (See Appendix).

Voriconazole

Voriconazole is the most extensively studied azole for *Aspergillus* prophylaxis in lung transplant recipients. It has shown potential in reducing IA [4, 28] and is commonly preferred for its *Aspergillus* coverage, and lower cost relative to newer mold-active azoles [57]. However, its use is significantly limited by adverse effects, such as hepatotoxicity, phototoxicity, visual disturbances and QTc prolongation, which frequently lead to discontinuation, [4, 15, 58]. Among mold-active azoles, voriconazole is most strongly associated with cSCC, presenting a notable concern for lung transplant recipients who are already at elevated risk of skin malignancy due to chronic immunosuppression [59, 60]. Studies have demonstrated a 1.7- to 2.6-fold increased risk of cSCC with voriconazole use, with the absolute risk rising substantially within five years post-transplant [58, 61-63]. This risk appears to be cumulative, as each additional month of exposure incrementally increases the likelihood of cSCC development. Other contributing factors such as older age, prior history of skin cancer, and residence in high ultraviolet (UV) exposure regions further amplify this risk. Moreover, cSCCs associated with voriconazole may exhibit greater clinical aggressiveness, with higher rates of metastasis and mortality reported. Although less definitive, there is also some evidence suggesting a possible association with melanoma, though this link remains inconclusive.

Posaconazole
Posaconazole is available as an oral suspension, delayed-release tablets, powder for oral suspension, and intravenous (IV) solution. While the oral suspension has demonstrated efficacy comparable to voriconazole in preventing IFIs, its pharmacokinetics are highly variable during the perioperative period, resulting in inconsistent serum and alveolar drug concentrations [64, 65]. In contrast, newer formulations, delayed-release tablets, delayed-release suspensions, and IV preparations, offer improved pharmacokinetics and more consistent drug levels, enhancing reliability in clinical use [66, 67]. Despite achieving higher intrapulmonary concentrations than voriconazole, posaconazole has not yet shown superior clinical outcomes [56].

Posaconazole is generally better tolerated than voriconazole, with fewer adverse effects. Nevertheless, it can still cause gastrointestinal disturbances, hepatotoxicity, pseudohyperaldosteronism [68] and rarely QTc prolongation. Its clinical utility is somewhat constrained by variable absorption, particularly with the oral suspension, and by significant drug-drug interactions. Importantly, posaconazole is not associated with an increased risk of cSCC. However, some data suggest a potential link to basal cell carcinoma (adjusted HR 1.55; 95% CI: 1.00–2.41), though this finding lacks mechanistic support or data from prospective studies [69]. Given its favorable safety profile, posaconazole is considered a safer alternative for patients at elevated risk of skin cancer, especially those intolerant to voriconazole. Nevertheless, ongoing vigilance for adverse effects and drug interactions remains essential.

Isavuconazole
Isavuconazole is an extended spectrum triazole with broad activity against *Aspergillus spp.* and other molds, comparable to posaconazole. It has a favorable safety profile, with fewer AE than voriconazole, including a lower risk of hepatotoxicity and visual disturbances. Available in both oral and IV formulations, isavuconazole features convenient once-daily dosing and predictable pharmacokinetics, reducing the potential need for TDM. Additionally, unlike other triazoles, it is associated with QTc shortening rather than prolongation, making it safer for patients with cardiac risks. In a retrospective study of lung transplant recipients, isavuconazole showed comparable efficacy to voriconazole but with significantly fewer AE and lower rates of premature discontinuation, highlighting its potential as a preferred alternative in patients who are intolerant to voriconazole. Importantly, isavuconazole has not been associated with skin cancer and does not cause photosensitivity. While real-world clinical experience remains relatively limited due to its more recent introduction, current evidence suggests that isavuconazole carries the lowest risk of cutaneous malignancy among the other mold-active azoles currently used for prophylaxis.

Itraconazole
Itraconazole is a broad-spectrum triazole antifungal used for prophylaxis and treatment of fungal infections, with variable absorption and a modestly favorable safety profile compared to other mold-active azoles in lung transplant recipients. Retrospective and observational studies comparing itraconazole solution to voriconazole (often combined with aerosolized amphotericin B) showed similar effectiveness in preventing IFIs, with itraconazole associated with less hepatotoxicity [40, 57]. In general, itraconazole oral solution is not ideal for patients immediately post-lung transplant due to compromised gastrointestinal function caused by anesthesia, reduced motility, and concomitant use of proton pump inhibitors or H2-receptor antagonists for ulcer prophylaxis. A newer formulation, SUBA-itraconazole (Super BioAvailable), offers improved bioavailability compared to conventional itraconazole. A retrospective study of SUBA-itraconazole in lung transplant recipients found it well-tolerated, with few breakthrough IFIs and target prophylaxis levels (>0.5 µg/mL) achieved in 54% of patients using 100 mg twice daily [70]. While itraconazole has shown a potential association with increased risk of both basal cell carcinoma and cSCC, the causal relationship remains uncertain, and the absolute risk is lower than that observed with voriconazole. Nevertheless, itraconazole has notable limitations, including significant drug-drug interactions with calcineurin and mechanistic target of rapamycin (mTOR) inhibitors, potential hepatotoxicity, and highly variable absorption. Subtherapeutic drug levels have been reported in up to 55% of cases, even when TDM is employed, contributing to an increased risk of breakthrough fungal infections. These infections often lead to therapy modifications in more than 10% of patients [71]. Comparative studies suggest that posaconazole may result in fewer transitions to alternative therapies following fungal detection [57, 71]. As a result, itraconazole is generally considered a secondary option, although it is less costly than SUBA-itraconazole and the other mold-active azoles.

Summary

The choice of azole prophylaxis should be individualized based on patient-specific factors, cost considerations, and resource availability (See **Table 3**). Voriconazole is often positioned as a first-line option due to its lower cost; however, this requires close monitoring for adverse effects, routine dermatologic surveillance, and strict sun protection measures [59]. For patients who experience AE or are at high risk for cSCC, safer alternatives such as isavuconazole and posaconazole are preferred, though their higher costs may limit their accessibility. Itraconazole may serve as an alternative prophylactic option in lung transplant patients, particularly in resource-limited settings.

Table 3. Comparison of characteristics, tolerability and cost of anti-mold triazoles

Category	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
Epidemiology/ Local Factors	Effective against *Aspergillus* but not *Mucorales;* suitable for regions with high *Aspergillus* prevalence	Effective against *Aspergillus* and *Mucorales;* suitable for regions with mixed fungal threats		Limited to regions with specific fungal burdens (e.g., endemic fungi) has an effect; against *Aspergillus* but not *Mucorales*
Clinical Evidence	Most studied azole in lung transplant population	Limited evidence; often used in high-risk or voriconazole-intolerant patients	Emerging evidence	Historical efficacy; limited use due to bioavailability and tolerability.
Adverse Events	Hepatoxicity (more common than other azoles); periostitis; squamous cell carcinoma with prolonged use	Better tolerated; gastrointestinal issues, reduced hepatotoxicity	Better tolerated; reduced hepatotoxicity; no QT prolongation	Reduced hepatoxicity; gastrointestinal intolerance
Drug-drug Interaction	Significant due to CYP450 metabolism	Moderate; interactions reduced with newer formulations	Fewer interactions compared to other azoles	Substantial due to CYP450 metabolism
Pharmacokinetic-dynamics	Variable. Requires TDM.	Consistent with delayed-release tablets and powder for oral suspension; good bioavailability	Predictable. TDM not required (may be considered in children <18 years old)	Poor and inconsistent bioavailability. Requires TDM.
Formulations	Oral and IV	Oral suspension, delayed-release tablet and IV	Oral and IV	Oral suspension and capsules
Cost	Lower than posaconazole and isavuconazole	Higher, especially with newer formulations	Higher	Lower than posaconazole and isavuconazole
Other Considerations	Avoid in patients with a history of cutaneous squamous cell carcinoma; higher side effect profile limits use in older or frail patients; avoid in areas with high sunlight exposure.	Suitable for patients intolerant to voriconazole with a history of cSCC		Inconsistent absorption and lower efficacy make it less favored for routine use in lung transplants. Overall, a less-preferred option. Alternative option, particularly in resource-limited settings.

Aerosolized Amphotericin B formulations

Summary of evidence: Amphotericin B Lipid Complex vs Amphotericin B deoxycholate

Our systematic review of the literature (spanning from 2000-2025) identified one randomized, controlled trial (RCT) comparing universal anti-*Aspergillus* prophylaxis with aerosolized ABLC to aerosolized Amphotericin B deoxycholate (d-AmB) [53].

Studied population and clinical setting:

A total of 100 adult lung and/or heart transplant recipients were enrolled between 1999 to 2002 in this single-center trial from North America. Among the 100 transplant recipients, 16 had single lung transplants, 81 had bilateral lung transplants, and one had heart-lung transplant (see Supplementary material, Table B2.2 Characteristics of the included study). Notable exclusions included: pregnant or lactating women, patients with hypersensitivity to amphotericin B or liposomal preparations, those unwilling or unable to comply with aerosolized drug administration, documented prior active IFIs (excluding colonization), mycetoma, or concomitant systemic antifungal therapy. Routine surveillance bronchoscopy was performed within 24hrs of transplant and at one month during the study. The reported rate of IA in the d-AmB group was 2.0% [53].

Studied comparison:

All patients received antifungal prophylaxis daily for 4 days, then once per week for 7 weeks (planned for a total of 11 doses), regardless of the agents received (ABLC 100mg or d-AmB 50mg). The total duration of received prophylaxis was generally shorter than planned as per RCT protocol (median of 35 days in the ABLC group vs 39 days in the d-AmB group) due to loss to follow-up (i.e. most patients returning to their local care providers) [53].

Studied outcomes:

The primary focus of the trial was on the tolerability of each agent, with outcomes including serious AE leading to discontinuation of prophylaxis and non-serious AE (such as dyspnea and cough). Rates of IA, breakthrough IA, IFI were also reported using Ascioglu 2002 definitions [48]. The total duration of follow-up was 2 months after initiation of study drug.

Study design, risk of bias, and other considerations:

This was a double-blind, randomized controlled trial, and the overall risk of bias was judged to be “low”. The main limitation of this trial was imprecision, driven by a small sample size and attrition due to frequent loss of follow-up after the first month post-transplant.

Benefits and harms

Based on the panel’s decision threshold (see Methods), the use of aerosolized ABLC as universal anti-*Aspergillus* prophylaxis in lung transplant recipients may result in comparable rates of IA, breakthrough IA, and IFI as those receiving aerosolized d-AmB (See Supplementary material, Table B1.1 GRADE Evidence Profile), but patients receiving aerosolized ABLC may experience AE less frequently: SAE (RD: -6.4%; 95% CI: -17.6% to 4.9%; low CoE), dyspnea (RD: -17.0%; 95% CI: -29.0% to -5.0%; moderate CoE), and cough (RD: -8.5%; 95% CI: -18.2% to 1.2%; low CoE).

Summary of evidence: Liposomal Amphotericin B vs Amphotericin B deoxycholate

Our systematic review of the literature (spanning from 2000-2025) identified three observational studies comparing universal anti-*Aspergillus* prophylaxis with aerosolized Liposomal Amphotericin B (L-AmB) to aerosolized Amphotericin B deoxycholate (d-AmB) [51, 52, 54].

Studied populations and clinical settings:

A total of 253 lung transplant recipients were included across three retrospective “before-and-after” cohort studies conducted during the early post-transplantation period. In these studies, the “before” periods corresponded to the comparator groups receiving universal anti-*Aspergillus* prophylaxis with aerosolized d-AmB, while the “after” periods corresponded to the intervention groups receiving aerosolized L-AmB. The transition from d-AmB to L-AmB was triggered by d-AmB shortage [51, 52, 54].

The enrollment timeframe spanned from 2002 to 2023. Studies were performed in North America (USA, from 2002 to 2004), Europe (Spain, from 2000 to 2005) and Asia (Japan, from 2021 to 2023). The two studies dating back more than two decades included most of the studied patients (n=191) [52, 54], while the more contemporary study only included 62 lung transplant recipients [51].

Among the 253 lung transplant recipients, 91 had single lung transplants, 158 had bilateral lung transplants, and four had heart-lung transplants (see Supplementary material, Table B2.2 Characteristics of the included studies). Surveillance bronchoscopy protocols were not reported. Rates of IA in the aerosolized d-AmB group ranged from 3.3% to 5.6%. One-year all-cause mortality was only reported in the Monforte cohort: 30.6% in the d-AmB group [52].

Studied comparisons:

The antifungal regimens and duration of prophylaxis varied considerably between these three studies. In the Lowry 2007 study, aerosolized L-AmB 20mg twice daily (for a median of 24 days) and d-AmB at 10mg twice daily (for a median of 20 days) were administered [54]. In Monforte 2010 study, lifelong prophylaxis was planned either with aerosolized L-AmB 25mg three times per week for 60 days, then 25mg once a week between 60 and 180 days, and 25mg once every 2 weeks, or with aerosolized d-AmB at 6mg three times per day for 120 days, followed by 6mg daily [52]. Lastly, Umemura 2024 study implemented a regimen of aerosolized amphotericin B in addition to oral itraconazole for the duration of post-transplantation hospitalization. Either aerosolized L-AmB 25mg three times per week (for a median 53 days) or aerosolized d-AmB 5g thrice per day (for a median 42 days) was received. The dose of oral itraconazole as well as the use of TDM were not reported in this study [51].

Studied outcomes:

All studies focused on different outcomes regarding efficacy and tolerability. For the incidence of IA and IFI during the post-transplant period, none of the three studies used the EORTC/MSG [19] or ISHLT [20] definitions. Monforte's study broadly categorizes tracheobronchitis, ulcerative tracheobronchitis, and IPA as "*Aspergillus* infection," potentially reducing specificity [52]. Lowry and Umemura studies did not clearly define IA or IFIs [51, 54]. Both Monforte and Umemura studies reported on rates of breakthrough IA.

Included studies reported SAE (generally defined as severe AE leading to discontinuation) and non-serious AE (dyspnea and cough). No study reported on *Aspergillus* colonization, mortality (all-cause or attributable), graft loss or rejection. The follow-up period to assess the outcomes ranged from 6 to 12 months (Umemura 2024 and Monforte 2010 respectively [51, 52]).

Study design, risk of bias, and other considerations:

The overall risk of bias of the identified evidence was judged to be “serious”, mainly due to the study design (i.e. single-center retrospective “before-and-after” cohort studies). The inclusion of patients from older studies may compromise validity of the conclusions, as evolving clinical practice, patient demographics, and healthcare standards could affect the findings’ generalizability to current clinical settings. Further, the addition of itraconazole in Umemura’s study might have influenced the incidence of IA and IFI, but possibly not impacting the tolerability profile between AmB formulations.

Benefits and harms

Based on the panel’s decision threshold (see Methods), the use of aerosolized L-AmB as universal anti-*Aspergillus* prophylaxis in lung transplant recipients may result in comparable rates of IA, breakthrough IA, and IFI as those receiving aerosolized d-AmB (See Supplementary material, Table B2.1 GRADE Evidence Profile). While the use of L-AmB may result in comparable rates of dyspnea or cough, patients may experience less serious AE (RD: -6.8%; 95% CI: -10.8% to 11.0%; very low CoE).

Other supporting evidence

Various formulations of AmB are available, each with unique properties that affect their suitability for aerosolized delivery. These formulations, outlined in Table 4, were originally developed for intravenous use and are not explicitly optimized for pulmonary administration, resulting in variations in alveolar deposition.

Despite the clear tolerability advantages of lipid-based formulations over d-AmB, there is limited clinical evidence directly comparing the efficacy of these three formulations for prophylaxis in lung transplant recipients. This highlights the need for further research to guide optimal selection.

Table 4. Comparison of characteristics, tolerability and cost of three amphotericin B formulations adapted for aerosolized administration

Parameter	D-AmB	ABLC	L-AmB
Structure and effect on epithelial cells	AmB is bound to deoxycholate, which acts as detergent for solubility. Direct interaction with epithelial cell membrane can lead to membrane disruption, bronchial irritation and airway inflammation.	AmB is complexed with synthetic phospholipids forming ribbon-like sheets.	AmB is encapsulated in a unilamellar liposome -- reduces interaction with epithelial membrane.
Lung distribution	High airway irritation, non-specific deposition in upper airways.	Lower airway irritation than d-AmB, better lower airway deposition than d-AmB.	Lower airway irritation, superior deposition in alveoli and lower lung.
Patient tolerability	Associated with significant bronchospasm, cough, and irritation	Reduced bronchospasm compared to d-AmB	Minimal local irritation or bronchospasm
Retention in lungs	Hours	Several days	Several days
Dosing and frequency	Typically, one to three times daily	Weekly or bi-weekly due to prolonged lung retention	Weekly or bi-weekly due to prolonged lung retention
Storage stability	Stable at room temperature	Requires specific storage conditions	Stable under specific conditions
Ease of preparation	Simple reconstitution	Slightly more complex preparation	Slightly more complex preparation
Cost	Lowest among options	Moderate to high	Moderate to high
Ideal Use Case	Resource-limited settings or as a fallback option when liposomal formulations are unavailable. Availability may be limited due to past shortages.	Moderate- to high-resource settings with tolerability concerns. Discontinuation in the US market in August 2025.	Moderate- to high-resource settings with tolerability concerns.

Echinocandins

Use of Echinocandin agents for *Aspergillus* Prophylaxis in Lung Transplant Recipients

There are limited data supporting the primary use of echinocandins (anidulafungin, caspofungin, and micafungin) as single-agent prophylaxis of IA in lung transplant recipients [72]. In the early post-transplant period, when patients are hospitalized and intravenous therapy is more feasible than after hospital discharge, echinocandins have occasionally been used as bridging or alternate therapy when patients are temporarily unable to tolerate oral medications experiencing azoles hepatotoxicity post-transplant, however efficacy data are lacking [73]. Echinocandins has also been used in combination with azoles, in which cases their use has been directed more toward prevention of *Candid*a infections than *Aspergillus*-specific prophylaxis [74, 75]. Echinocandins are in general better tolerated than mold-

active azoles or polyenes, due to their favorable side effect profile [72]. Echinocandins do not have activity against *Cryptococcus* or the endemic fungi, so their use does not provide as broad coverage across the fungal spectrum as triazoles. In real-world practice, some centers that use nebulized amphotericin B for initial prophylaxis for lung transplant recipients may do so in combination with echinocandins [73].

In summary, while echinocandins have activity against *Aspergillus* spp. and might be useful in certain prophylaxis scenarios after lung transplantation, they are generally not the first-line choice for prophylaxis due to the limitations of their intravenous route of administration and the potential for breakthrough infections. Echinocandins require intravenous administration, which is a limiting factor for prolonged use compared to oral azoles.

Combination of agents

Use of Combined Antifungal Agents for *Aspergillus* Prophylaxis in Lung Transplant Recipients
This summary focuses specifically on prophylactic strategies that utilized concurrent administration of two or more antifungal agents during the early post-lung transplant period. Only regimens where agents overlapped in time, rather than sequential use, were included. Across the literature, a wide range of combinations has been reported, reflecting heterogeneity in institutional protocols and perceived risks.

Three major approaches to concurrent antifungal prophylaxis were observed across studies: (1) azole + aerosolized amphotericin B, (2) systemic amphotericin B + aerosolized amphotericin B (dual polyene), and (3) triple combinations involving an azole, echinocandin, and aerosolized amphotericin B. Among azole-based regimens, itraconazole [25, 43], voriconazole [40, 42], and isavuconazole [4] have all been paired with aerosolized formulations. The dual polyene strategy—systemic L-AmB plus aerosolized ABLC—was described by Boscolo et al. as part of a universal prophylaxis approach during hospitalization [76]. In the study by Koo et al., a “triple combination” strategy was employed, consisting of aerosolized amphotericin B for universal prophylaxis, short-course micafungin targeted to bilateral lung transplant recipients (who were considered at increased risk for candidiasis), and mold-active azoles initiated only if fungal growth was identified [32]; Ju et al. similarly used caspofungin and aerosolized amphotericin B during the early inpatient period, followed by azole maintenance [77].

An observation is that aerosolized amphotericin B appears consistently in nearly all combination regimens, regardless of the systemic agents used. This likely reflects efforts to compensate for limitations of systemic drug penetration, particularly to the bronchial anastomosis, which may have impaired vascular supply immediately post-transplant. The use of aerosolized therapy may help ensure local antifungal activity at this vulnerable interface. However, due to differences in study design, risk stratification, and lack of direct comparisons, it is not possible to draw firm conclusions about the superiority of one regimen over another.

Rationale for recommendation

In absence of direct comparisons between different classes of agents in the reviewed evidence, the panel judged that an individualized approach for selecting anti-*Aspergillus* prophylaxis or pre-emptive therapy (if considered) is preferable, as described above.

Conclusion

The guideline panel judges that clinicians should select anti-*Aspergillus* prophylaxis or pre-emptive therapy agents based on the following considerations: adverse events profile, drug-drug interactions, ease of administration and tolerability, associated costs and resources, availability, as well as local epidemiology.

Research gaps

Fungal infections, particularly IA, remain a major source of morbidity and mortality in lung transplant recipients. Yet, there is no consensus on who should receive antifungal prophylaxis, which agents to use, or the optimal duration, primarily due to a lack of high-quality, prospective data and harmonized definitions [78]. Improved understanding of IA risk factors is critical to inform prevention and treatment strategies. Key elements of risk stratification, such as surgical techniques, donor and recipient characteristics, immunologic status, and environmental exposures, must be better characterized. Newer tools, including fungal biomarkers, immune profiling, and genetic markers may offer opportunities for personalized prophylaxis. These insights, coupled with comparative effectiveness studies of both established and novel antifungal agents, are needed to evaluate clinical efficacy, resistance risk, drug-drug interactions, cost-effectiveness, and microbiologic impact.

Antifungal resistance is a growing concern, yet data on lung transplant-specific antifungal stewardship interventions and surveillance systems remain limited. Similarly, the long-term impact of fungal colonization and infection on graft outcomes, particularly the role of fungi in CLAD, is poorly understood. Longitudinal studies assessing fungal burden, immune response, and allograft health are needed to determine whether aggressive antifungal management improves outcomes.

Despite these knowledge gaps, existing data sources such as the ISHLT registry do not currently capture detailed information on risk factors, antifungal prophylaxis, diagnostic approaches, or fungal infection outcomes. In contrast, hematopoietic cell transplantation has benefited from dedicated clinical trials networks and data regarding infection in their registries. These have enabled prospective data collection and multicenter trials that have improved infection prevention and treatment strategies. A similar infrastructure is urgently needed in lung transplantation. Because lung transplantation volumes are relatively low, conventional randomized controlled trials (RCTs) are often underpowered, logistically challenging, and slow to complete. Alternative designs such as Desirability of Outcome Ranking (DOOR) and emulated target trials offer more efficient and clinically meaningful approaches to causal inference in this setting, particularly when integrated with comprehensive clinical, microbiologic, and diagnostic data streams. Such integration would further enable adaptive trial designs, strengthen resistance surveillance, and enhance antimicrobial stewardship efforts while generating robust evidence when traditional RCTs are not feasible. We propose the development of a dedicated lung transplant infection registry and clinical trials network within the existing ISHLT database infrastructure, with a near-term focus on IFIs. Such a registry would not only support standardized data collection on prophylaxis strategies and outcomes but also enable the identification of novel clinical and biologic risk factors. These data could directly inform the design of future clinical trials and risk-adapted prevention strategies. Integration of clinical, microbiologic, and diagnostic data would further support adaptive trial designs, resistance surveillance and stewardship efforts.

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Disclaimer: It is important to recognize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time

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(MSGERC). **S.P.H.** served in past advisory and consulting roles with Pfizer (advisory roles regarding infections associated with BCMA bispecific antibodies and myeloma therapies), Roche (advisory board regarding infectious complications of therapies for multiple myeloma), Treeline Biosciences (consulting regarding infectious complications of novel targets therapies for lymphoma) and Seres Therapeutics (consulting regarding infectious complications of leukemia therapy and use of live spore products in hematologic malignancy patients); received research funding from GlaxoSmithKline (GSK) for a study of sotrovimab prophylaxis against COVID-19 infection in immunocompromised individuals; serves in an advisory role (scientific) with Takeda (infection adjudication committee for a clinical trial). **S.A.K.** reported family relationships (spouse consulting roles or employment) with Boston Scientific, Janssen, Novartis, Myovant, Blue Earth Diagnostics, MDx Health, AIQ, Reversal Therapeutics, Stratagen Bio, and Nanocan; received research funding from GlaxoSmithKline (GSK); serves in an advisory role with Vertex Pharmaceuticals (member of a safety adjudication committee for a clinical trial; unrelated). **G.R.T.** served in advisory as a consultant for Cidara (clinical trial design). **M.G.S.** served as associate editor for Annals of Internal Medicine (American College of Physicians). **V.L.** received funding from Centre de Recherche du Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal (CIUSSS_NIM).

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Scynexis (Ibrexafungerp), and Sfunga (investigational antifungals); received research funding from the National Institutes of Health (including RECOVER, ACTT/ACTIV, U19 Coccidioidomycosis Research Center, STOMP, and preclinical infectious disease studies); received industry sponsorship from F2G (olorofim for resistant molds) and Cidara (Rezafungin). **G.R.T.** served in advisory roles for Astellas, Basilea, Elion, F2G, GSK, and Cidara related to antifungal agents (e.g., isavuconazole, olorofim, Fosmanogepix, Turletricin, Rezafungin, Ibrexafungerp); receives research funding from F2G (OASIS) and Astellas (Mycoses Study Group; Radiology Study). **C.O.M.** served in advisory roles for Gilead Sciences (liposomal amphotericin B), Merck Sharp & Dohme, Australia (caspofungin and posaconazole), Pfizer, Australia (voriconazole and anidulafungin) and Elio Therapeutics (SF001); received honoraria from Gilead Sciences (webinar chair, liposomal amphotericin B), Merck Sharp & Dohme, Australia (fungal diagnostics), and Pfizer, Australia (diagnostic stewardship); received research funding from F2G Ltd UK (F901318), Cidara Therapeutics Inc. (Rezafungin), Gilead Sciences (azole resistance studies), and Merck Sharp & Dohme, Australia (UPPRITE trial and posaconazole use in cystic fibrosis), all funding paid directly to institution. All other authors reported no conflicts of interest during the specified period.

Heart Transplant Recipients

Heart transplant recipients are susceptible to opportunistic infections, including IA. The primary risk of IA arises from post-transplant immunosuppression, which increases vulnerability to environmental fungal pathogens. Most IA cases occur within the first 90 days post-transplant, though late-onset infections have also been reported. Risk factors include prior cardiac surgeries, use of mechanical circulatory support devices, and concurrent cytomegalovirus (CMV) infection. The overall incidence of IA is uncertain, and it is unclear whether the risk in this population justifies the use of universal prophylaxis.

Incidence of IA in heart transplant recipients not receiving anti-*Aspergillus* prophylaxis

To understand the true burden of IA in heart transplant recipients, a mapping review of the literature published from 2000 to April 2025 was performed to estimate the incidence of IA among patients who did not receive anti-*Aspergillus* prophylaxis (See Supplemental material, Descriptive question for details). Across 16 observational studies that included 6,005 heart transplant recipients without routine mold-active prophylaxis [27, 79-93], 232 cases of proven or probable IA were identified. Definitions of IA were based on EORTC/MSG criteria, similar validated definitions, or clinical criteria excluding possible IA [19, 48, 55, 94]. The studies spanned multiple centers and countries, with transplant cohorts ranging from the early 1980s through 2020–2021. Across these cohorts, the pooled incidence of IA was approximately 3.8% (95% confidence interval 2.5 to 5.7%), with a median incidence of 3.9%.

The excess mortality directly attributable to IA could not be determined from the existing literature. Mortality appears particularly elevated among patients with multiple concurrent risk factors. These findings underscore that, although IA incidence is relatively low, affected patients face substantial mortality, emphasizing the importance of identifying and monitoring high-risk subgroups.

Risk factors for IA

Across the included studies, a range of patient-, procedure-, and environment-related factors were associated with the development of IA. The most consistently reported and reproducible risk factors were post-operative RRT, reoperation or redo thoracic surgery, CMV infection, and augmented immunosuppression for treatment of rejection [83, 89, 92].

Additional factors reported in individual cohorts included prolonged mechanical ventilation or intubation, extracorporeal membrane oxygenation, hypoalbuminemia, multiple pre-transplant hospitalizations, prior *Aspergillus* colonization, and environmental or programmatic exposures such as hospital construction, ventilation system failures, or clustering of cases. Although the strength of evidence varies for these additional contributors, the reproducibility of RRT, reoperation, CMV infection, and augmented immunosuppression across multiple studies supports their validity as key risk factors. The quality of evidence for risk factors is moderate as most data are derived from retrospective single-center cohorts with heterogeneous definitions and limited statistical power, leaving residual confounding as a concern

In heart-lung transplantation, the higher risk of IA-associated with lung transplantation should guide prophylaxis decisions, deferring to lung transplant prophylaxis guidelines where applicable.

Limitations

The majority of studies were retrospective and single-center, with variable follow-up durations, and inconsistent definitions of IA. The reliance on outbreak-driven report or environmental event investigation may have introduced publication bias, and the lack of randomized trials limits causal inference. Overall, the risk of bias is moderate: while data are reasonably consistent, the observational design and variable methodology reduce certainty and generalizability.

Conclusions

Given the relatively low pooled incidence of IA (3.8%), the use of universal anti-*Aspergillus* prophylaxis is likely to offer limited benefits and a less favorable balance of benefits and harms. The current evidence does not support routine universal prophylaxis against IA in heart transplant recipients.

Research gaps

The impact of extracorporeal membrane oxygenation, a newer medical procedure that impacts heart transplant candidates, has not been fully assessed in relation to IA risk. Future studies should systematically evaluate risk factors, including duration of intubation, redo thoracic operations, augmented immunosuppression, CMV infection, and RRT. Data on the safety and efficacy of targeted IA prophylaxis in the highest risk heart transplant recipients are needed, as is quantification of the IA-attributable mortality in this population.

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topics; served in editorial roles with the *Journal of Heart and Lung Transplantation and Transplant Infectious Diseases*. **N.P.** served in past advisory/consulting roles with ClearView and Alcimed (unrelated); held editorial roles with *Medical Mycology* and the *Journal of Heart and Lung Transplantation Open*. **M.H.N.** received research grants from bioMérieux (target NGS for fungal diagnosis direct from samples) and Melinta (Rezafungin clinical trial). **J.H.Y.** received research funding for subject enrollment on clinical trials from AlloVir (adoptive T cells) and Ansun (DAS-181 for viral infections); served as Editor-in-Chief for *Clinical Microbiology Reviews*; serves as an Associate Editor for *Transplantation and Cellular Therapy;* receives research funding for subject enrollment on clinical trials from AiCuris (HSV infection), GSK (RSV vaccination), Lumen (C diff infection), Pulmotect (respiratory viral infections), SNIPR (phage therapy), Shire/Takeda (CMV infection), and Vedanta (C diff infection). **M.M.S.** received funding from the Public Health Agency of Canada for initiatives related to antimicrobial stewardship. **D.R.A.** served in advisory roles for Roche, Basilea, Cidara, Astellas, Mundipharma, F2G, Amplyx, and Elion; owned stock in Symbiotica; served on the editorial board for *Clinical Infectious Diseases*/*Journal of Infectious Diseases* (CID/JID) as editor for *Antimicrobial Agents and Chemotherapy* (AAC), *Journal of Infectious Diseases*, mBio, and PLoS Pathogens; served as a member for the Clinical and Laboratory Standards Institute (CLSI). **M.I.A.** served as a consultant for Karius (application of Karius for fungal diagnostics in immunocompromised children); Miravista (evaluating fungal diagnostics in children with research support paid to institution); received travel reimbursement from St. Jude Children's Research Hospital (participation in infectious disease research conferences); serves as an editorial board member for *Transplant Infectious Disease* and the *Journal of the Pediatric Infectious Diseases Society*; serves on the American Academy of Pediatrics (AAP) Committee on Infectious Diseases). **E.J.B.** served in advisory roles for Avir Pharma and GSK; participates as a guidelines panel member for the American Society of Clinical Oncology and Infectious Diseases Society of America (neutropenic fevers); received honoraria as Section Editor, Up-to-Date. **P.H.C.** participated in a speakers bureau for Astellas (isavuconazole); received research funding from Aicuris (recruited patients for HSV Pritelevir study); received other remuneration from Pfizer (data review on Aztreonam-Avibactam study); served as president at Michigan State Infectious Diseases Society; serves as editor at the *British Journal of Antimicrobial Agents and Chemotherapy*. **S.C-A.C.** received organizational benefits from MSD Australia (untied educational grants); served as Pathology editor for the *Journal of Clinical Microbiology*, editor for *Microbiology*, editor-in-chief for *Medical Mycology*, and as a board member for the Mycoses Study Group Education and Research Consortium (MSGERC). **S.P.H.** served in past advisory and consulting roles with Pfizer (advisory roles regarding infections associated with BCMA bispecific antibodies and myeloma therapies), Roche (advisory board regarding infectious complications of therapies for multiple myeloma), Treeline Biosciences (consulting regarding infectious complications of novel targets therapies for lymphoma) and Seres Therapeutics (consulting regarding infectious complications of leukemia therapy and use of live spore products in hematologic malignancy patients); received research funding from GlaxoSmithKline (GSK) for a study of sotrovimab prophylaxis against COVID-19 infection in immunocompromised individuals; serves in an advisory role (scientific) with Takeda (infection adjudication committee for a clinical trial). **S.A.K.** reported family relationships (spouse consulting roles or employment) with Boston Scientific, Janssen, Novartis, Myovant, Blue Earth Diagnostics, MDx Health, AIQ, Reversal Therapeutics, Stratagen Bio, and Nanocan; received research funding from GlaxoSmithKline (GSK); serves in an advisory role with Vertex Pharmaceuticals (member of a safety adjudication committee for a clinical trial; unrelated). **G.R.T.** served in advisory as a consultant for Cidara (clinical trial design). **M.G.S.** served as associate editor for Annals of Internal Medicine (American College of Physicians). **V.L.** received funding from Centre de Recherche du Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal (CIUSSS_NIM).

The following panelists have reported relationships **related** to the topic of fungal infections/antifungal therapies since 2021–2025, when the guideline work began, with the indicated companies. **S.M.H.** received educational grants from Merck (posaconazole), Astellas , Avir Pharma, Sanofi, and GlaxoSmithKline (GSK); served in advisory roles with TFF Pharmaceuticals (inhaled voriconazole), Takeda (Maribavir), ITB Med (siplizumab), and TFF Pharmaceuticals; received research funding from the National Institutes of Health, University Health Network, Princess Margaret Hospital Foundation, PSI Foundation (PC945 studies), Scynexis (Ibrexafungerp studies), Pulmocide (opelconazole studies), F2G (olorofim studies), Baselia (Fosmanogepix) and Gilead (immunomodulatory effects of antifungals) (all paid to institution); served in an editorial role as section editor for the *Journal of Heart and Lung Transplantation and Transplant Infectious Diseases.* **N.P.** served in advisory roles for Pulmocide (opelconazole) and Basilea (Fosmanogepix); received research funding from Scynexis (candidemia/invasive candidiasis studies), Merck (long-term outcomes of SARS-CoV-2 infections and COVID-19 vaccine breakthrough risk in kidney transplant recipients –

clinical burden of RSV and other respiratory viral infections in immunocompromised hosts), CareDx, Inc. (kidney allograft outcomes, Allosure registry), Pulmocide Ltd (opelconazole clinical trials), IMMY Diagnostics (Aspergillus galactomannan assay evaluation), Pearl Diagnostics (urine MycoMEIA), Applied BioCode (ABC assay), Fujifilm (Beta-d-glucan), Zepto Life Technology (cfDNA) and the Cystic Fibrosis Foundation, National Institutes of Health, Health Systems Research Institute, and Chulalongkorn University (various studies on fungal infections, transplant outcomes, and infectious disease diagnostics). **M.H.N.** received research funding from NIH/NIAID and CDC/Mycoses Study Group, investigator-initiated research grants from bioMérieux (target NGS for fungal diagnosis direct from samples) and Melinta (Rezafungin clinical trial), clinical trial funding from F2G Ltd UK (olorofim) and Pulmocide (opelconazole); all funds were paid directly to the University of Pittsburgh; serves on the advisory board for Basilea Pharmaceutica International Ltd (Fosmanogepix) and Pulmocide (opelconazole). **J.H.Y.** received research funding for subject enrollment on clinical trials from Basilea (Fosmanogepix), Cidara/Mundipharma (Rezafungin), F2G (olorofim), and Scynexis (Ibrexafungerp); received industry support from the NIH for studies related to antifungal and infectious disease therapeutics; receives research funding for subject enrollment on clinical trials from Pulmocide (opelconazole) and Zepto (fungal diagnostics); serves on the Aspergillus Guidelines panel with the European Confederation of Medical Mycology. **M.I.A.** received research funding and remuneration related to antifungal/viral therapeutics from Merck (letermovir), Shire (maribavir), and Miravista (Histoplasma diagnostics); received research funding from NIH (comparison of high dose vs standard dose influenza vaccine in HCT recipients – multicenter prospective study of human adenovirus infection and disease in pediatric HCT recipients and non-invasive diagnosis of pediatric pulmonary invasive mold infection); served as a consultant for Karius (diagnostics). **A.C.A.** received extensive research funding from Merck, Astellas, Nabriva, Paratek, and Summit Therapeutics for clinical trials involving antifungal and antibacterial agents; received honoraria from Astellas related to isavuconazole and micafungin. **S.C-A.C.** received research funding from F2G, Pfizer Australia for studies involving fungal infections, and prior funding from PRSP for infectious disease surveillance including mycology. **S.P.H.** served in advisory roles for F2G (olorofim) and Melinta (Rezafungin); received research funding from F2G, Scynexis, Mundipharma, Cidara, and Elion related to antifungal therapeutics (all paid to institution). **S.A.K.** received research funding from Scynexis and GSK related to antifungal and infectious disease therapeutics; received research funding from the NIH for work related to pneumonia diagnostics. **T.F.P.** served in advisory and consulting roles for F2G (olorofim and other investigational antifungals), Basilea (isavuconazole and Fosmanogepix), Gilead (amBisome), Pfizer (voriconazole), Scynexis (Ibrexafungerp), and Sfunga (investigational antifungals); received research funding from the National Institutes of Health (including RECOVER, ACTT/ACTIV, U19 Coccidioidomycosis Research Center, STOMP, and preclinical infectious disease studies); received industry sponsorship from F2G (olorofim for resistant molds) and Cidara (Rezafungin). **G.R.T.** served in advisory roles for Astellas, Basilea, Elion, F2G, GSK, and Cidara related to antifungal agents (e.g., isavuconazole, olorofim, Fosmanogepix, Turletricin, Rezafungin, Ibrexafungerp); receives research funding from F2G (OASIS) and Astellas (Mycoses Study Group; Radiology Study). **C.O.M.** served in advisory roles for Gilead Sciences (liposomal amphotericin B), Merck Sharp & Dohme, Australia (caspofungin and posaconazole), Pfizer, Australia (voriconazole and anidulafungin) and Elio Therapeutics (SF001); received honoraria from Gilead Sciences (webinar chair, liposomal amphotericin B), Merck Sharp & Dohme, Australia (fungal diagnostics), and Pfizer, Australia (diagnostic stewardship); received research funding from F2G Ltd UK (F901318), Cidara Therapeutics Inc. (Rezafungin), Gilead Sciences (azole resistance studies), and Merck Sharp & Dohme, Australia (UPPRITE trial and posaconazole use in cystic fibrosis), all funding paid directly to institution. All other authors reported no conflicts of interest during the specified period.

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