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

Lung Transplant Recipients

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Descriptive question: In lung transplant recipients, what is the baseline risk of invasive aspergillosis in patients not receiving anti-*Aspergillus* prophylaxis and which factors increase this risk of invasive aspergillosis?

Methods

-Literature Search Strategy

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Methods

-PICO format

-Literature search strategy (same as Clinical Question A1)

-Eligibility criteria for selection of the studies

Tables and Figures

-PRISMA flow diagram of study identification and selection (same as Clinical Question A1)

Between anti-mold triazoles

Sub-question B1: In lung transplant recipients receiving anti-*Aspergillus* prophylaxis, should Isavuconazole be used rather than Voriconazole?

Tables and Figures

-Supplementary Table B1.1: GRADE evidence profile
-Supplementary Table B1.2: Characteristics of the included study
-Supplementary Table B1.3: Summary of the risk of bias of the included study
-Supplementary Figures B1.1: Forest plots for each patient-important outcome

-Other evidence comparing anti-mold triazoles

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-Stewardship considerations for prophylaxis with anti-mold triazoles

Between aerosolized amphotericin B formulations

Sub-question B2: In lung transplant recipients receiving anti-*Aspergillus* prophylaxis, should lipid formulation of aerosolized Amphotericin B or Amphotericin B Lipid Complex be used rather than aerosolized Amphotericin B deoxycholate?

Tables and Figures

-Supplementary Table B2.1: GRADE evidence profile
-Supplementary Table B2.2: Characteristics of the included studies
-Supplementary Tables B2.3: Summary of the risk of bias of the included studies
-Supplementary Figures B2.1: Forest plots for each patient-important outcome

-Other considerations for prophylaxis with aerosolized amphotericin B

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?

Population: Adult lung transplant recipients in the post-transplant period
Intervention: Universal anti-*Aspergillus* prophylaxis
= either echinocandins, triazoles, amphotericin B (IV or aerosolized) or itraconazole
Comparator: No anti-*Aspergillu*s prophylaxis
= either anti-yeast prophylaxis (fluconazole) or no prophylaxis
Outcomes (patient-important outcomes as per panel voting and reassess by subgroup)
Critical
-Reduction in Invasive Aspergillosis (IA)***
-Reduction in attributable mortality (only if defined *a priori*)
-Increase in serious adverse events (SAEs)
Important
-Reduction in mortality (all-cause)
-Increase in non-serious adverse events (AEs)
-Post-transplant colonization with *Aspergillus* (precursor of late IA)
-Breakthrough IA (especially when considering different duration of prophylaxis)
-Increase in Invasive Mold Infection
-Graft rejection
-Reduction in IA*** (rated as important rather than critical for choice of agents if benefits are similar and not influencing the decision-making process)
Removed outcome
-Need to change antifungal therapy (not a good surrogate outcome of neither clinical efficacy nor adverse events since consisting of a composite outcome that was defined very heterogeneously between studies)
Outcomes not reported:
-Length of hospital stay, readmission, quality of life
-Increase in long term adverse events (e.g. chronic lung allograft disease [CLAD] with aerosolized Amphotericin B or cutaneous squamous cell carcinoma [cSCC] with voriconazole)

Decision Thresholds for Critical Outcomes

Decision threshold (between trivial and small important effect): minimally important difference at which point we would decide on a different course of action (i.e. between no recommending and recommending prophylaxis).

In absence of literature to support a specific threshold, the whole panel voted for a 10% reduction in the incidence of IA between universal prophylaxis and no prophylaxis.

After assessing the impact on other outcomes (no effect on mortality), the impact on adverse events (no effect for some classes of antifungal), and the potential downstream consequences on IA in lung transplant (i.e. early attributable mortality), the subgroup proposed the following decision thresholds (between trivial and small or MID (minimal important difference)) for the critical outcomes:

-Incidence of IA: 40 events per 1000 patients (or 4%)
-Attributable mortality: 20 events per 1000 patients (or 2%)
-SAEs: 40 events per 1000 patients (or 4%)

All thresholds were voted and approved consensually by the entire panel.

Literature Search Strategy (last updated on April 4, 2025)

Ovid MEDLINE

#	Searches
1	exp Invasive Fungal Infections/
2	exp mycoses/
3	exp Fungi/
4	exp Lung Diseases, Fungal/
5	expAspergillosis/
6	exp Aspergillus/
7	exp Candida/
8	expCandidiasis/
9	expCryptococcosis/
10	expCryptococcus/
11	Coccidioides/
12	Coccidioidomycosis/
13	Fusariosis/
14	Fusarium/
15	exp Mitosporic Fungi/
16	exp Mucorales/
17	Mucormycosis/
18	Pseudallescheria/
19	Scedosporium/
20	Trichosporon/
21	Trichosporonosis/
22	exp Zygomycosis/
23	(Fungal adj2 disease*).mp.
24	(Fungal adj2 infection*).mp.
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30	(Mitosporic adj2 fungi*).mp.
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32	(Yeast? adj2 infection*).mp.
33	Antifungal.mp.
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47	Blastomycos*.mp.
48	C albicans.mp.
49	C glabrata.mp.
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51	C lusitaniae.mp.
52	C neoformans.mp.
53	C parapsilosis.mp.
54	C tropicalis.mp.
55	Candid?emia*.mp.
56	Candida.mp.
57	Candidamycos*.mp.
58	Candidias*.mp.
59	Candidos*.mp.
60	Coccidio?mycos*.mp.
61	Coccidiod*.mp.

62 Cryptococc*.mp.
63 Deuteromycete*.mp.
64 Deuteromycota*.mp.
65 Entomophthora.mp.
66 Entomophthoramycos?s.mp.
67 F solani.mp.
68 Fung?emia*.mp.
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83 Mycotic.mp.
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85 Petriellidium*.mp.
86 Phaeohyphomycos?s.mp.
87 Phycomycos?s.mp.
88 Pseudallescheria*.mp.
89 Rhizomucor.mp.
90 Rhizopus.mp.
91 Scedosporium*.mp.
92 Torula.mp.
93 Torulopsis utilis.mp.
94 Torulos?s.mp.
95 Trichosporon*.mp.
96 Zygomycet*.mp.
97 Zygomycos?s.mp.
98 or/1-97
99 exp Lung Transplantation/
100 (Lung? adj5 transplant*).tw,kf,kw.
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112 or/99-111
113 98 and 112
114 prophylaxis.mp.
115 prophylactic.mp.
116 pre-emptive*.mp.
117 preemptive*.mp.
118 prevent*.mp.
119 pc.fs.
120 exp Chemoprevention/
121 or/114-120
122 113 and 121
123 animals/ not (animals/ and humans/)
124 122 not 123
125 limit 124 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")
126 limit 124 to "all adult (19 plus years)"

127	124 not 125
128	126 or 127
129	remove duplicates from 128

Original search by Marinelli 2022 <1946 to September 23, 2020>
Updating the original search with limit: 2019-present
Search run on November 7th, 2023
Rerun on April 4th, 2025

Ovid MEDLINE Epub Ahead of Print and In-Process & Other Non-Indexed Citations

#	Searches
1	(Fungal adj2 disease*).mp.
2	(Fungal adj2 infection*).mp.
3	(Fungal adj2 pneumonia*).mp.
4	(Fungal adj2 sepsis).mp.
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23	B dermatitidis.mp.
24	Blastomyc?s.mp.
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43	Entomophthora.mp.
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45	F solani.mp.
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71 Torulopsis utilis.mp.
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73 Trichosporon*.mp.
74 Zygomycet*.mp.
75 Zygomycos?s.mp.
76 or/1-75
77 (Lung? adj5 transplant*).tw,kf,kw.
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89 or/77-88
90 76 and 89
91 prophylaxis.mp.
92 prophylactic.mp.
93 pre-emptive*.mp.
94 preemptive*.mp.
95 prevent*.mp.
96 or/91-95
97 90 and 96
98 remove duplicates from 97

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Embase

Searches
1 exp systemic mycosis/
2 exp mycosis/
3 exp fungus/
4 exp lung mycosis/
5 expaspergillosis/
6 exp Aspergillus/
7 exp Candida/
8 expcandidiasis/
9 expcryptococcosis/
10 expfilobasidiella/
11 expCoccidioides/
12 coccidioidomycosis/
13 fusariosis/
14 exp Fusarium/
15 expDeuteromycetes/

16 expZygomycetes/
17 exp zygomycosis/
18 pseudallescheria/
19 exp scedosporium/
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116 prophylactic.mp.
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119 prevent*.mp.
120 or/113-119
121 112 and 120
122 (exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/)
123 121 not 122
124 limit 123 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
125 limit 123 to (adult <18 to 64 years> or aged <65+ years>)
126 123 not 124
127 125 or 126
128 remove duplicates from 127

Original search by Marinelli 2022 <1974 to 2020 September 23>
Updating the original search with limit: 2019-present
Search run on November 7th, 2023
Rerun on April 4th, 2025

Cochrane Central Register of Controlled Trials

Searches
1 exp Invasive Fungal Infections/
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98	or/1-97
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115	prophylactic.mp.
116	pre-emptive*.mp.
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118	prevent*.mp.
119	pc.fs.
120	exp Chemoprevention/
121	or/114-120
122	113 and 121
123	remove duplicates from 122

Original search by Marinelli 2022 <2014 to Present>
Updating the original search with limit: 2019-present
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Cochrane Database of Systematic Reviews

#	Searches
1	(Fungal adj2 disease*).tw.
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Rerun on April 4th, 2025

Web of Science

# 1 TOPIC: (Fungal NEAR/2 disease* OR Fungal NEAR/2 infection* OR Fungal NEAR/2 pneumonia* OR Fungal NEAR/2 sepsis OR Fungi NEAR/4 blood OR Fungus NEAR/2 disease* OR Fungus NEAR/2 infection* OR Mitosporic NEAR/2 fungi* OR Mo$ld NEAR/2 infection* OR Yeast$ NEAR/2 infection* OR Antifungal OR Anti-fungal OR Antimycotic OR Anti-mycotic OR “A flavus” OR “A fumigatus” OR “A niger” OR “A terreus” OR Allescheria* OR Aspergilloma* OR Aspergillos* OR Aspergillus OR “B dermatitidis” OR Blastomyc$s OR Blastomycos* OR “C albicans” OR “C glabrata” OR “C krusei” OR “C lusitaniae” OR “C neoformans” OR “C parapsilosis” OR “C tropicalis” OR Candid$emia* OR Candida OR Candidamycos* OR Candidias* OR Candidos* OR Coccidio$mycos* OR Coccidiod* OR Cryptococc* OR Deuteromycete* OR Deuteromycota* OR Entomophthora OR Entomophthoramycos?s OR “F solani” OR Fung$emia* OR Fusarial OR Fusariomycos* OR Fusarios$s OR Fusarium* OR “Gilchrist* disease*” OR “H capsulatum” OR Histoplasmosi$ OR Hyphomycetes OR Monilia* OR Monosporium* OR Mucor OR Mucoral* OR Mucormycos* OR Mycos* OR Mycotic OR Neuroaspergillos* OR Petriellidium* OR Phaeohyphomycos$s OR Phycomycos$s OR Pseudallescheria* OR Rhizomucor OR Rhizopus OR Scedosporium* OR Torula OR “Torulopsis utilis” OR Torulos$s OR Trichosporon* OR Zygomycet* OR Zygomycos$s)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

# 2 TOPIC: (Lung$ NEAR/5 transplant* OR Lung$ NEAR/2 graft* OR Lung$ NEAR/2 allograft* OR Lung$ NEAR/2 allotransplant* OR Lung$ NEAR/2 homotransplant* OR Lung$ NEAR/2 homograft* OR Pulmonary NEAR/5 transplant* OR Pulmonary NEAR/2 graft* OR Pulmonary NEAR/2 allograft* OR Pulmonary NEAR/2 allotransplant* OR Pulmonary NEAR/2 homotransplant* OR Pulmonary NEAR/2 homograft*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

# 3 TOPIC: (prophylaxis OR prophylactic OR pre-emptive* OR preemptive* OR prevent*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

# 4 #3 AND #2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

Original search by Marinelli 2022 <2005 to Present>
Updating the original search with limit: 2019-present
Search run on November 7th, 2023
Rerun on April 4th, 2025

Eligibility criteria for selection of the studies

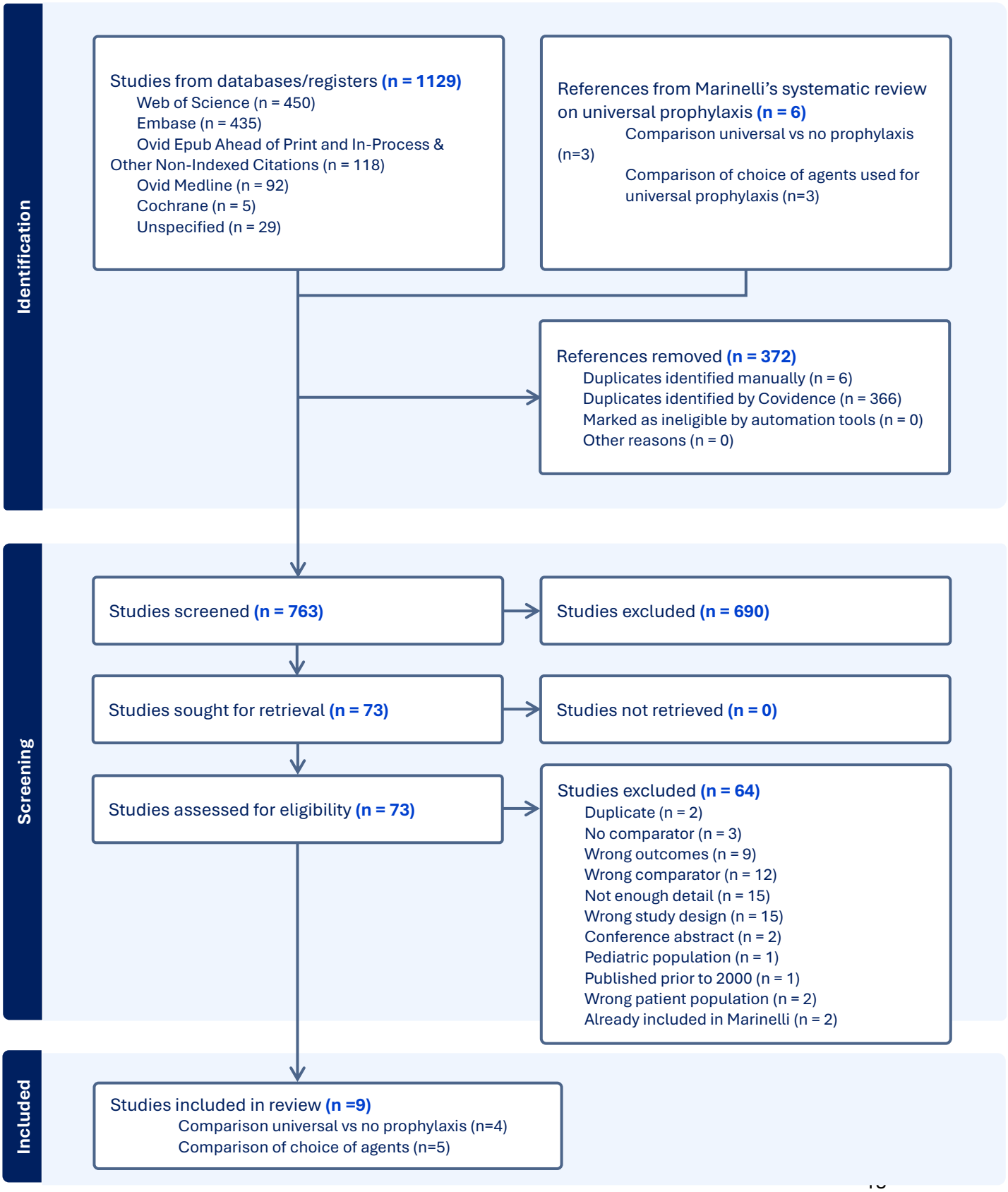
Inclusion criteria:

- Patient population: Adult lung transplant recipients in post-transplant period
- Anti-*Aspergillus* prophylaxis
  - Echinocandins such as caspofungin, micafungin or anidulafungin
  - Triazoles such as posaconazole, voriconazole or isavuconazole
  - Amphotericin B (IV or aerosolized AmB)
  - Itraconazole (any formulation)
- No anti-*Aspergillus* prophylaxis
  - Fluconazole (any formulation)
  - Absence of antifungal prophylaxis
- Strategies:
  - Universal prophylaxis: all lung transplant recipients
- Intervention / Comparison
  - Universal vs no prophylaxis
- Outcomes: Minimally including incidence of IA or adverse events associated with the use of anti-*Aspergillus* prophylaxis
- Study design: Randomized controlled trials (RCTs) and non-randomized comparative studies (i.e. observational studies)
- Year: published from 2000 up to present
- Language: English only

Exclusion criteria:

- Patient population:
  - Pediatric population
- Intervention / Comparator
  - Any comparison where the comparator group include a variety of different anti-*Aspergillus* and anti-yeast prophylaxis (without stratification by antifungal agent used)
- Study design
  - One-arm studies
  - Conference proceedings, abstracts, letters to the editor, comments

Supplementary Figure A1.1: PRISMA flow diagram of study identification and selection (last updated on April 4, 2025)



Supplementary Table A1.1: GRADE evidence profile

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

P: Adult In lung transplant recipients
I: Universal anti-*Aspergillus* prophylaxis
C: No anti-*Aspergillus* prophylaxis (i.e. no antifungal prophylaxis or Fluconazole)
Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Universal anti-*Aspergillus* prophylaxis	No anti-*Aspergillus* prophylaxis**	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (follow-up: range from a minimum of 14 months to 56 months)										**MID*:** at least 40 fewer per 1,000		
4[1-4]	non-randomized studies	very serious[a]	very serious[b]	not serious	very serious[c]	none	76/320 (23.8%)	81/317 (25.6%)	**RR 0.66** (0.31 to 1.45)	**87 fewer per 1,000** (from 176 fewer to 115 more)	⊕◯◯◯ Very low[a,b,c]	CRITICAL
								Baseline Risk of IA: 19.0%	**Critical concern about clinical and statistical heterogeneity makes these estimates unreliable**			
***Aspergillus* Colonization**												
2[1,4]	non-randomized studies	very serious[a]	not serious	serious[d]	very serious[c]	none	21/195 (10.8%)	35/218 (16.1%)	**RR 0.75** (0.46 to 1.22)	**40 fewer per 1,000** (from 87 fewer to 35 more)	⊕◯◯◯ Very low[a,c,d]	IMPORTANT
Mortality (all-cause) (follow-up at 12 months)										**MID*:** at least 20 fewer per 1,000		
2[1,4]	non-randomized studies	very serious[a,e]	very serious[b]	not serious	very serious[c]	none	25/195 (12.8%)	38/217 (17.5%)	**RR 0.62** (0.10 to 3.75)	**67 fewer per 1,000** (from 158 fewer to 482 more)	⊕◯◯◯ Very low[a,b,c,,e]	IMPORTANT
Serious Adverse Events										**MID*:** at least 40 fewer per 1,000		
1[3]	non-randomized studies	very serious[a]	not serious	not serious	very serious[c]	none	1/44 (2.3%)	0/11 (0.0%)	**RR 0.80** (0.03 to 18.42)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low[a,c]	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **RR:** risk ratio
***MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)**
****The comparator groups in all 3 included studies did not receive any antifungal prophylaxis.**

Explanations

a. All 4 studies were designed as pre/post-intervention studies, and they were all considered at critical risk of bias (ROBINS-I) mainly due to potential residual confounding and selection bias (potential unmeasured changes in enrolled participants and changes in standard of care overtime, missing information on patients' characteristics at baseline and adherence to prophylaxis, as well as asymmetric duration of follow-up (being longer in the No prophylaxis group) potentially overestimating the effect of prophylaxis (in Minari 2002 study).
b. Statistical significance noted in the meta-analysis (I^2 over 80%). The large heterogeneity between studies (e.g. variation in era, included population, surveillance protocols, standard of care, type of prophylaxis use (class of agents, dosage, route of administration, duration), or follow-up period) and lack of controlled studies, pertinent clinical characteristics of population and reasons for protocol deviation, intervention (adherence) and definitions of IA), which precluded the panel to come to any meaningful conclusion on the potential benefits of any type of antifungal prophylactic strategies.
c. The boundaries of the confidence interval cross the decision threshold (minimal important difference) for both important benefit and important harm, thus providing evidence of very serious imprecision.
d. *Aspergillus* colonization is known to be a precursor (intermediary step) of invasive aspergillosis.
e. Tofte 2012: When analyzing survival of only *Aspergillus*-positive patients (colonized or infected), no difference in mortality between groups (p = 0.386) and thus, Voriconazole prophylaxis did not influence mortality in patients colonized or infected with *Aspergillus*. The authors suspect that the measured effect of voriconazole on all-cause mortality is likely due to changes in standard of care with time.

References

1. Tofte N and al. Use of prophylactic voriconazole for three months after lung transplantation does not reduce infection with Aspergillus: a retrospective study of 147 patients. Scand J Infect Dis. 2012 Nov;44(11):835-41.
2. Minari A and al. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. Transpl Infect Dis. 2002 Dec;4(4):195-200.
3. Monforte V and al. Nebulized amphotericin B prophylaxis for Aspergillus infection in lung transplantation: study of risk factors. J Heart Lung Transplant. 2001 Dec;20(12):1274-81.
4. Gemert JPV, Fleurke GJ, Akkerman OW, Gan CT, Steenhuis WN, Kerstjens HAM, Verschuuren EAM, Postma DF. Aspergillus After Lung Transplantation: Prophylaxis, Risk Factors, and the Impact on Chronic Lung Allograft Dysfunction. Transpl Infect Dis. 2025 Jul-Aug;27(4):e70020.

Supplementary Table A1.2: Characteristics of the included studies

Study *(lead author, year of publication, location)*	**Population** *(type of patients, year of enrollment, n randomized, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(universal anti-Aspergillus prophylaxis, total duration)*	**Comparator** *(no anti-Aspergillus prophylaxis, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
van Gemert 2025** Groningen, the Netherlands Single Center	All lung transplant recipientss Before: 2013-2017 After: 2017-2022 N = 274 (254 bilateral lungs) Age (median): 56y Exclusion: NR	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA post-transplant A protocolized bronchoscopy was performed between 1 to 3 months after transplantation (culture, GM and PCR) and subsequent bronchoscopies were only performed on clinical indication.	Multivariate analysis to assess risk factors / clinical parameters associated with IA	**Baseline risk for IA: 32.5%** (median time to IA: 6 months) Baseline risk for mortality: 10.4% at 1-year	**Aerosolized AmB** (5mg bid) Duration: for the **duration of hospital stay**, depending on tolerance and/or toxicity (median duration received= 26 days (IQR 18-36) / adherence: good)	Nil	Standard definitions according to EORTC/MSG 2020 or ISHLT 2015 criteria Duration of follow-up: median 56 (IQR 32-88) months
Tofte 2012 Copenhagen, Denmark Single Center	All lung transplant recipients Before: 2002-2004 After: 2004-2006 N = 139 (92 single lung, 44 double lungs, 3 heart-lung) Age (median): 53y Inclusion: patients with at least 1 BAL performed post-transplant	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA (before or after 3 months post-transplant) Routine bronchoscopy (BAL and transbronchial biopsies with cultures) and chest X-ray at 2,4,6, and 12 weeks and 6,12,18 and 24 months (no BAL GM or PCR)	No stratification for risk of IA or IFI	**Baseline risk for IA: 17.1%** Baseline risk for mortality: 29.2% at 1-year	**Voriconazole** 200mg PO BID **TDM not systematically performed** Duration: **3 months** (median duration received= NR / non-adherence: NR but historical 5-10% due to adverse events)	Nil	Variation on ISHLT 2010 Duration of follow-up: 24 months
Minari 2002 Cleveland, USA Single Center	All SOT recipients including lung and lung-heart transplant recipients Before: 1990 – 1997 After: 1997- 1999 N = 188 (112 single lung, 5 lung-heart) Age (mean): 47y Exclusion: NR	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA (during follow-up, no specific timing) No routine BAL	No stratification for risk of IA of IFI	**Baseline risk for IA: 18.2%** Baseline risk for mortality: NR	**Aerosolized AmB** (5-10mg bid) post-transplant, with **Itraconazole** 200mg (capsules or solution) daily added when oral intake tolerated TDM: levels over 50mg/mL Duration: **for life** (median duration received and non-adherence = NR)	Nil	Standard definitions for IA in transplants (Paterson, Medicine 1999) Total duration of follow-up: between 2 and 9 years (reported in patient-year)
Monforte 2001 Barcelona, Spain Single Center	All lung transplant recipients Before: 1990 – 1993 After: 1993- 1998 N = 55 (25 single lung, 30 sequential double lung)	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA (during follow-up, no specific timing) No routine BAL	No stratification for risk of IA or IFI	**Baseline risk for IA: 72.7%** Baseline risk for mortality: NR	**Aerosolized AmB** (6mg TID) post-transplant x 4 months then 6mg die for life Duration: **for life** (median duration received = NR / non-adherence = 7/44 (3 stopped and 4 non-regular compliance),	Nil	Standard definitions as follows: *Aspergillus* tracheobronchitis diagnosed by clinical symptoms with purulent sputum production plus bronchoscopy findings with red edematous mucosa and mucus plugging; ulcerative tracheobronchitis diagnosed by bronchial biopsy and/or bronchoscopy findings with

	Age (mean): 43y Inclusion: patients who survived more than 7 days after transplantation				timing of non-adherence = NR)		necrotic ulcers in the anastomosis or in the tracheobronchial tree that disappeared after treatment; and invasive pulmonary aspergillosis diagnosed when *Aspergillus spp.* was found on lung histopathology or radiologic evidence of invasion was observed. Mean duration of follow-up: 14 months (range 0.3 -62 months)

Legend
AFT: antifungal therapy
AmB: amphotericin B
BAL: bronchoalveolar lavage
BID: twice a day
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
GM: Galactomannan
IA: invasive aspergillosis
IFI: invasive fungal infection,
ISHLT: The International Society of Heart and Lung Transplantation
IV: parenteral
NR: not reported
PO: oral
PCR: Polymerase chain reaction
SOT: solid organ transplantation
TID: three times a day
TDM: Therapeutic Drug Monitoring

High-Risk of IA (see our criteria for targeted anti-*Aspergillus* prophylaxis)
*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.
**Personal communication in addition to the published article

Supplementary Table A1.3: Summary of risk of bias of included studies

Study	Overall Risk of bias	Confounding	Selection of participants into the study	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result
Van Gemert 2025*	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention, or **individual factors such as pre-transplant *Aspergillus* colonization**) that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period).	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 9-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	After confirming with the authors, the intervention status and planned duration are clearly defined. However, the dosage used for prophylaxis was lower than commonly published in the literature.	After contacting the authors, the adherence to prophylaxis was judged to be "good" and the duration of prophylaxis was reported, but deviation from intervention (either due to adverse events or lack of tolerability) was not reported. The impact of prophylaxis on the outcome of interest remains unclear.	Most data comparing the before and after study was missing since the aim of the study was to assess factors associated with IA. After contacting the authors, baseline characteristics of the population (before and after) were available.	Diagnosis of IA was based on standard definitions, but surveillance BAL was only performed once between 1 and 3 months after transplant, while subsequent BAL were only performed on clinical indication. Nevertheless, no predetermined routine BAL was performed, and the timing of BAL was not reported. Time to IA diagnosis was late (median time of 6 months (IQR 1-18)) after lung transplant and in the context of a very short duration of prophylaxis (median 26 days (IQR 18-36)) and very long follow-up, this might have potentially underestimated the effect of the prophylaxis. Furthermore, the rate of colonization was very low due to the lack surveillance bronchoscopy.	The outcome measurement and analyses are consistent with the Methods.
Tofte 2012	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention, or **individual factors such as pre-transplant *Aspergillus* colonization**) that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 4-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care). The authors highly suspected that the change in mortality observed between prophylaxis group was rather due to fluctuations in mortality in the 2 different time periods (changes in routines or the inclusion of high-risk patients) rather than an effect of changes in prophylaxis	Intervention status and planned duration clearly defined	Adverse events and adherence to prophylaxis not mentioned, thus the potential benefits of the prophylaxis can't be fully estimated	All data presented in survival analysis curves, clearly presenting censored patients with time. Presentation of the characteristics of the population by prophylaxis group available but incomplete.	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported and similar in both groups.	The outcome measurement and analyses are consistent with the Methods.
Minari 2002	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention, or **individual factors such as pre-transplant *Aspergillus* colonization**) that could influence the outcomes (e.g. decreasing the incidence of IA in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 9-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration clearly defined	Adverse events and adherence to prophylaxis not mentioned, thus the potential benefits of the prophylaxis can't be fully estimated	Missing data (numbers reported in the tables and in the manuscript are discordant and all patients are clearly not accounted for and could impact the conclusion). No presentation of the characteristics of the population available.	Time to follow-up clearly asymmetrical and potentially overestimating the effect of the prophylaxis. No routine surveillance BAL. Diagnosis of IA was based on standard definitions and included non-specific findings, and diagnostic interventions were not reported.	The outcome measurement and analyses are consistent with the Methods.
Monforte 2001	**Critical**	Possible residual confounding is expected due to unmeasured and	Selection bias is suspected due to potential changes in	Intervention status and planned	Deviations from the interventions is mentioned (non-regular	No evidence of missing data, but no presentation of the	No routine surveillance BAL.	The outcome measurement and analyses are

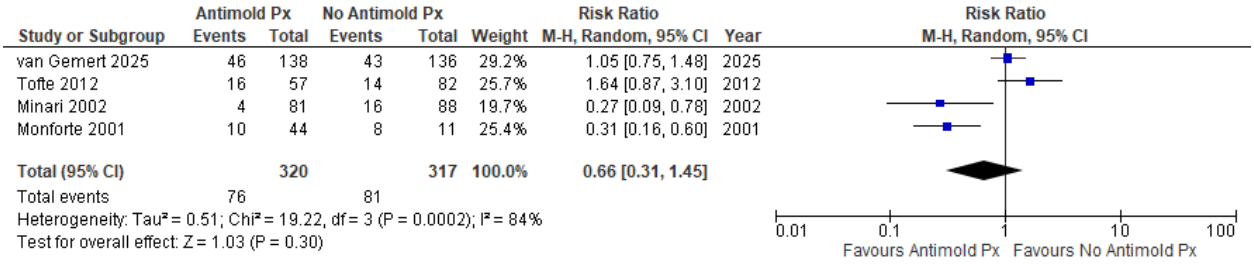
		uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention, or **individual factors such as pre-transplant *Aspergillus* colonization**) that could influence the outcomes (e.g. decreasing the incidence of IA in the post-intervention period)	enrolled participants over time (i.e. over a 7-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	duration clearly defined	compliance and cessation of prophylaxis), but their impact on the outcome of interest is not unclear.	characteristics of the population by prophylaxis group (before vs after) available.	Diagnosis of IA was based on standard definitions, but diagnostic interventions were not reported.	consistent with the Methods.
Legend BAL: bronchoalveolar lavage GM: galactomannan IA: invasive aspergillosis IQR: interquartile range PCR: polymerase chain reaction								
*Personal communication in addition to the published article.								

Risk of bias judgment

Low	
Moderate	
Serious	
Critical	
No information	

Supplementary Figures A1.2: Forest plots for each patient-important outcome

Figure A1.2.a: Invasive aspergillosis (follow-up: ranging from a minimum of 14 to 56 months)



Concerns about heterogeneity

Probable explanations of heterogeneity

-Different era (studied population in 1990 in 2 studies vs 2000 in one study vs 2010-2020 in a later study): evolving standard of care and immunosuppression strategies

-Different local surveillance protocols: bronchoscopy with new diagnostic tools enabling earlier IA detection and antifungal therapy

-Different comparisons of agents, route of administration and duration of universal prophylaxis between studies

-Different duration of follow-up.

Possible explanations for heterogeneity

-Unclear adherence (intermittent or cessation) / PK-PD (TDM, drug-drug interaction)

-Different geography (Minari: US; van Gemert, Tofte and Monforte: Europe)

-Different baseline risk of IA between studies

Due to the low number of studies, these potential sources of heterogeneity can't be explored and the panel judged that it remains unknown if universal prophylaxis provides benefits.

Concerns about generalizability

-No prophylaxis group: incidence of IA varied from 17.1-18.2%, to 32.5% and up to 72.7%

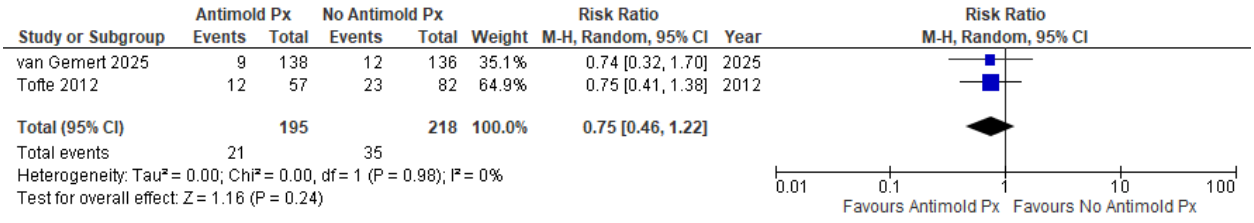
-Universal prophylaxis group: incidence of IA varied from 4.9%, to 22.7-28.1% and up to 33.3%

The very high incidence observed highlighted the potential lack of generalizability to the contemporary context (incidence IA without prophylaxis around 8-9%)

Breakthrough IA: NR

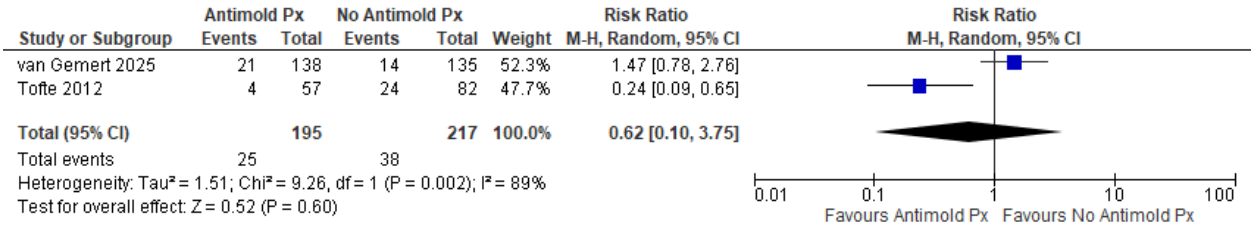
Invasive fungal infection: NR

Figure A1.2.b: Post-transplant *Aspergillus* colonization



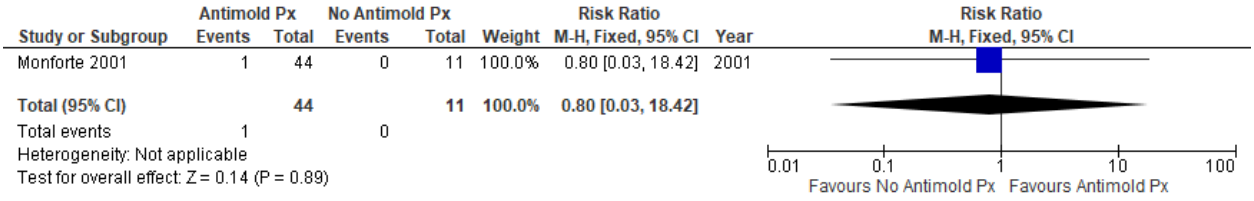
*Of note, Monforte 2001 reported colonization rate, however, they did not provide colonization data stratified by prophylaxis strategy.

Figure A1.2.c: All-cause mortality (at 12 months)



Attributable mortality: NR

Figure A1.2.d: Serious adverse events



Non-serious adverse events

Reported in Monforte 2001 by type of adverse events rather than per patients

Graft rejection: NR

Long term adverse events: NR

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

Population: Adult lung transplant recipients in the post-transplant period

Intervention: Targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy
= either echinocandins, triazoles, amphotericin B (IV or aerosolized) or itraconazole prophylaxis

Comparator: No anti-*Aspergillu*s prophylaxis
= either anti-yeast prophylaxis (fluconazole) or no prophylaxis

Outcomes (patient-important outcomes as per panel voting and reassess by subgroup)

Critical

-Reduction in Invasive Aspergillosis***

-Reduction in Attributable mortality

-Increase in Serious Adverse events

Important

-Reduction in mortality (all cause)

-Increase in non-serious AEs

-Post-transplant colonization with *Aspergillus* (precursor (intermediary step) of late IA)

-Breakthrough IA (especially when considering different duration of prophylaxis)

-Increase in Invasive Mold Infections

-Graft rejection

-Reduction in IA*** (rated as important rather than critical for choice of agents if benefits are similar and not influencing the decision-making process)

Removed outcome

-Need to change antifungal therapy (not a good surrogate outcome of neither clinical efficacy nor adverse events since consisting of a composite outcome that was defined very heterogeneously between studies)

Outcomes not reported:

-Length of hospital stay, readmission, quality of life

-Increase in long term adverse events (e.g. CLAD with aerosolized AmB or cSCC with voriconazole)

Literature Search Strategy (last updated on April 4, 2025)

Ovid Medline 1946 - current

1	exp Invasive Fungal Infections/
2	exp mycoses/
3	exp Fungi/
4	exp Lung Diseases, Fungal/
5	exp Aspergillosis/
6	exp Aspergillus/
7	exp Candida/
8	exp Candidiasis/
9	exp Cryptococcosis/
10	exp Cryptococcus/
11	Coccidioides/
12	Coccidioidomycosis/
13	Fusariosis/
14	Fusarium/
15	exp Mitosporic Fungi/
16	exp Mucorales/
17	Mucormycosis/
18	Pseudallescheria/
19	Scedosporium/
20	Trichosporon/
21	Trichosporonosis/
22	exp Zygomycosis/
23	(Fungal adj2 disease*).mp.
24	(Fungal adj2 infection*).mp.
25	(Fungal adj2 pneumonia*).mp.
26	(Fungal adj2 sepsis).mp.
27	(Fungi adj4 blood).mp.
28	(Fungus adj2 disease*).mp.
29	(Fungus adj2 infection*).mp.
30	(Mitosporic adj2 fungi*).mp.
31	(Mo?ld adj2 infection*).mp.
32	(Yeast? adj2 infection*).mp.
33	Antifungal.mp.
34	Anti-fungal.mp.
35	Antimycotic.mp.
36	Anti-mycotic.mp.
37	A flavus.mp.
38	A fumigatus.mp.
39	A niger.mp.
40	A terreus.mp.
41	Allescheria*.mp.
42	Aspergilloma*.mp.
43	Aspergillos*.mp.
44	Aspergillus.mp.
45	B dermatitidis.mp.
46	Blastomyc?s.mp.
47	Blastomycos*.mp.
48	C albicans.mp.
49	C glabrata.mp.
50	C krusei.mp.
51	C lusitaniae.mp.
52	C neoformans.mp.
53	C parapsilosis.mp.
54	C tropicalis.mp.
55	Candid?emia*.mp.
56	Candida.mp.
57	Candidamycos*.mp.
58	Candidias*.mp.
59	Candidos*.mp.
60	Coccidio?mycos*.mp.
61	Coccidiod*.mp.
62	Cryptococc*.mp.
63	Deuteromycete*.mp.
64	Deuteromycota*.mp.
65	Entomophthora.mp.

66 Entomophthoramycos?s.mp.
67 F solani.mp.
68 Fung?emia*.mp.
69 Fusarial.mp.
70 Fusariomycos*.mp.
71 Fusarios?s.mp.
72 Fusarium*.mp.
73 Gilchrist* disease*.mp.
74 H capsulatum.mp.
75 Histoplasmosi?.mp.
76 Hyphomycetes.mp.
77 Monilia*.mp.
78 Monosporium*.mp.
79 Mucor.mp.
80 Mucoral*.mp.
81 Mucormycos*.mp.
82 Mycos*.mp.
83 Mycotic.mp.
84 Neuroaspergillos*.mp.
85 Petriellidium*.mp.
86 Phaeohyphomycos?s.mp.
87 Phycomycos?s.mp.
88 Pseudallescheria*.mp.
89 Rhizomucor.mp.
90 Rhizopus.mp.
91 Scedosporium*.mp.
92 Torula.mp.
93 Torulopsis utilis.mp.
94 Torulos?s.mp.
95 Trichosporon*.mp.
96 Zygomycet*.mp.
97 Zygomycos?s.mp.
98 or/1-97
99 exp Lung Transplantation/
100 (Lung? adj5 transplant*).tw,kf,kw.
101 (Lung? adj2 graft*).tw,kf,kw.
102 (Lung? adj2 allograft*).tw,kf,kw.
103 (Lung? adj2 allotransplant*).tw,kf,kw.
104 (Lung? adj2 homotransplant*).tw,kf,kw.
105 (Lung? adj2 homograft*).tw,kf,kw.
106 (Pulmonary adj5 transplant*).tw,kf,kw.
107 (Pulmonary adj2 graft*).tw,kf,kw.
108 (Pulmonary adj2 allograft*).tw,kf,kw.
109 (Pulmonary adj2 allotransplant*).tw,kf,kw.
110 (Pulmonary adj2 homotransplant*).tw,kf,kw.
111 (Pulmonary adj2 homograft*).tw,kf,kw.
112 or/99-111
113 98 and 112
114 prophylaxis.mp.
115 prophylactic.mp.
116 pre-emptive*.mp.
117 preemptive*.mp.
118 prevent*.mp.
119 pc.fs.
120 exp Chemoprevention/
121 or/114-120
122 113 and 121
123 animals/ not (animals/ and humans/)
124 122 not 123
125 limit 124 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")
126 limit 124 to "all adult (19 plus years)"
127 124 not 125
128 126 or 127
129 remove duplicates from 128
130 preemptive.mp.
131 pre-emptive.mp.
132 targeted.mp.
133 culture*.mp.
134 coloni*.mp.
135 PCR.mp.

136 biomarker.mp.
137 high-risk.mp.
138 "high* risk".mp.
139 "increase* risk".mp.
140 universal.mp.
141 or/130-140
142 129 and 141
143 limit 142 to English language
Limit: 2000-present
Search run on February 22nd, 2024
Rerun on April 4th, 2025

Ovid Medline Epub Ahead of Print and In-process and other non-indexed citations

1 exp Invasive Fungal Infections/
2 exp mycoses/
3 exp Fungi/
4 exp Lung Diseases, Fungal/
5 exp Aspergillosis/
6 exp Aspergillus/
7 exp Candida/
8 exp Candidiasis/
9 exp Cryptococcosis/
10 exp Cryptococcus/
11 Coccidioides/
12 Coccidioidomycosis/
13 Fusariosis/
14 Fusarium/
15 exp Mitosporic Fungi/
16 exp Mucorales/
17 Mucormycosis/
18 Pseudallescheria/
19 Scedosporium/
20 Trichosporon/
21 Trichosporonosis/
22 exp Zygomycosis/
23 (Fungal adj2 disease*).mp.
24 (Fungal adj2 infection*).mp.
25 (Fungal adj2 pneumonia*).mp.
26 (Fungal adj2 sepsis).mp.
27 (Fungi adj4 blood).mp.
28 (Fungus adj2 disease*).mp.
29 (Fungus adj2 infection*).mp.
30 (Mitosporic adj2 fungi*).mp.
31 (Mo?ld adj2 infection*).mp.
32 (Yeast? adj2 infection*).mp.
33 Antifungal.mp.
34 Anti-fungal.mp.
35 Antimycotic.mp.
36 Anti-mycotic.mp.
37 A flavus.mp.
38 A fumigatus.mp.
39 A niger.mp.
40 A terreus.mp.
41 Allescheria*.mp.
42 Aspergilloma*.mp.
43 Aspergillos*.mp.
44 Aspergillus.mp.
45 B dermatitidis.mp.
46 Blastomyc?s.mp.
47 Blastomycos*.mp.
48 C albicans.mp.
49 C glabrata.mp.
50 C krusei.mp.
51 C lusitaniae.mp.
52 C neoformans.mp.
53 C parapsilosis.mp.
54 C tropicalis.mp.
55 Candid?emia*.mp.
56 Candida.mp.

57 Candidamycos*.mp.
58 Candidias*.mp.
59 Candidos*.mp.
60 Coccidio?mycos*.mp.
61 Coccidiod*.mp.
62 Cryptococc*.mp.
63 Deuteromycete*.mp.
64 Deuteromycota*.mp.
65 Entomophthora.mp.
66 Entomophthoramycos?s.mp.
67 F solani.mp.
68 Fung?emia*.mp.
69 Fusarial.mp.
70 Fusariomycos*.mp.
71 Fusarios?s.mp.
72 Fusarium*.mp.
73 Gilchrist* disease*.mp.
74 H capsulatum.mp.
75 Histoplasmosi?.mp.
76 Hyphomycetes.mp.
77 Monilia*.mp.
78 Monosporium*.mp.
79 Mucor.mp.
80 Mucoral*.mp.
81 Mucormycos*.mp.
82 Mycos*.mp.
83 Mycotic.mp.
84 Neuroaspergillos*.mp.
85 Petriellidium*.mp.
86 Phaeohyphomycos?s.mp.
87 Phycomycos?s.mp.
88 Pseudallescheria*.mp.
89 Rhizomucor.mp.
90 Rhizopus.mp.
91 Scedosporium*.mp.
92 Torula.mp.
93 Torulopsis utilis.mp.
94 Torulos?s.mp.
95 Trichosporon*.mp.
96 Zygomycet*.mp.
97 Zygomycos?s.mp.
98 or/1-97
99 exp Lung Transplantation/
100 (Lung? adj5 transplant*).tw,kf,kw.
101 (Lung? adj2 graft*).tw,kf,kw.
102 (Lung? adj2 allograft*).tw,kf,kw.
103 (Lung? adj2 allotransplant*).tw,kf,kw.
104 (Lung? adj2 homotransplant*).tw,kf,kw.
105 (Lung? adj2 homograft*).tw,kf,kw.
106 (Pulmonary adj5 transplant*).tw,kf,kw.
107 (Pulmonary adj2 graft*).tw,kf,kw.
108 (Pulmonary adj2 allograft*).tw,kf,kw.
109 (Pulmonary adj2 allotransplant*).tw,kf,kw.
110 (Pulmonary adj2 homotransplant*).tw,kf,kw.
111 (Pulmonary adj2 homograft*).tw,kf,kw.
112 or/99-111
113 98 and 112
114 prophylaxis.mp.
115 prophylactic.mp.
116 pre-emptive*.mp.
117 preemptive*.mp.
118 prevent*.mp.
119 pc.fs.
120 exp Chemoprevention/
121 or/114-120
122 113 and 121
123 animals/ not (animals/ and humans/)
124 122 not 123
125 limit 124 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")
126 limit 124 to "all adult (19 plus years)"

127 124 not 125
128 126 or 127
129 remove duplicates from 128
130 preemptive.mp.
131 pre-emptive.mp.
132 targeted.mp.
133 culture*.mp.
134 coloni*.mp.
135 PCR.mp.
136 biomarker.mp.
137 high-risk.mp.
138 "high* risk".mp.
139 "increase* risk".mp.
140 universal.mp.
141 or/130-140
142 129 and 141
143 limit 142 to English language
Limit: 2000-present
Search run on February 22nd, 2024
Rerun on April 4th, 2025

Embase
#1 'systemic mycosis'/exp
#2 'mycosis'/exp
#3 'fungus'/exp
#4 'lung mycosis'/exp
#5 'aspergillosis'/exp
#6 'aspergillus'/exp
#7 'candida'/exp
#8 'candidiasis'/exp
#9 'cryptococcosis'/exp
#10 'filobasidiella'/exp
#11 'coccidioides'/exp
#12 'coccidioidomycosis'
#13 fusariosis
#14 'fusarium'/exp
#15 'deuteromycetes'/exp
#16 'zygomycetes'/exp
#17 'zygomycosis'/exp
#18 'pseudallescheria'
#19 'scedosporium'/exp
#20 'trichosporon'/exp
#21 'trichosporon'/exp
#22 'trichosporonosis'/exp
#23 fungal NEAR/2 disease*
#24 fungal NEAR/2 infection*
#25 fungal NEAR/2 pneumonia*
#26 fungal NEAR/2 sepsis
#27 fungi NEAR/4 blood
#28 fungus NEAR/2 disease*
#29 fungus NEAR/2 infection*
#30 mitosporic NEAR/2 fungi*
#31 mo?ld NEAR/2 infection*
#32 yeast? NEAR/2 infection*
#33 antifungal
#34 'anti fungal'
#35 antimycotic
#36 'anti mycotic'
#37 'a flavus'
#38 'a fumigatus'
#39 'a niger'
#40 'a terreus'
#41 'allescheria*'
#42 'aspergilloma*'
#43 aspergillos*
#44 aspergillus
#45 'b dermatitidis'
#46 blastomyc?s
#47 blastomycos*
#48 'c albicans'

#49 'c glabrata'
#50 'c krusei'#49 'c glabrata'
#51 'c lusitaniae'
#52 'c neoformans'
#53 'c parapsilosis'
#54 'c tropicalis'
#55 candid?emia*
#56 candida
#57 candidamycos*
#58 candidias*
#59 candidos*
#60 coccidio?mycos*
#61 coccidiod*
#62 cryptococc*
#63 deuteromycete*
#64 deuteromycota*
#65 entomophthora
#66 entomophthoramycos?s
#67 'f solani'
#68 fung?emia*
#69 fusarial
#70 fusariomycos*
#71 fusarios?s
#72 fusarium*
#73 'gilchrist* disease*'
#74 'h capsulatum.'
#75 'histoplasmosi?'
#76 hyphomycetes
#77 monilia*
#78 monosporium*
#79 mucor*
#80 mucoral*
#81 mucormycos*
#82 mycos*
#83 mycotic
#84 neuroaspergillos*
#85 petriellidium*
#86 phaeohyphomycos?s
#87 phycomycos?s
#88 pseudallescheria*
#89 rhizomucor
#90 rhizopus
#91 scedosporium*
#92 torula
#93 'torulopsis utilis'
#94 torulos?s
#95 trichosporon*
#96 zygomycet*
#97 zygomycos?s
#98 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97
#99 'lung transplantation'/exp
#100 (lung? NEAR/5 transplant*):ti,kw
#101 (lung? NEAR/2 graft*):ti,kw
#102 (lung? NEAR/2 allograft*):ti,kw
#103 (lung? NEAR/2 allotransplant*):ti,kw
#104 (lung? NEAR/2 homotransplant*):ti,kw
#105 (lung? NEAR/2 homograft*):ti,kw
#106 (pulmonary NEAR/5 transplant*):ti,kw
#107 (pulmonary NEAR/2 graft*):ti,kw
#108 (pulmonary NEAR/2 allograft*):ti,kw
#109 (pulmonary NEAR/2 allotransplant*):ti,kw
#110 (pulmonary NEAR/2 homotransplant*):ti,kw
#111 (pulmonary NEAR/2 homograft*):ti,kw
#112 #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111

#113 #98 AND #112
#114 'prophylaxis'/exp
#115 prophylaxis
#116 prophylactic
#117 'pre emptive*'
#118 preemptive*
#119 prevent* OR 'chemoprevention'/exp
#120 #114 OR #115 OR #116 OR #117 OR #118 OR #119
#121 #113 AND #120
#122 #121 AND 'human'/de
#123 'pre emptive'
#124 preemptive
#125 targeted
#126 culture*
#127 coloni*
#128 galactomannan
#129 pcr
#130 biomarker
#131 'high risk'
#132 'high* risk'
#133 'increase* risk'
#134 universal
#135 #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134
#136 #122 AND #135
#137 'conference abstract':it
#138 #136 NOT #137
#139 #136 NOT #137 AND [english]/lim
Limit: 2000-present
Search run on February 22nd, 2024
Rerun on April 4th, 2025

Cochrane

#1 MeSH descriptor: [Invasive Fungal Infections] explode all trees
#2 MeSH descriptor: [Mycoses] explode all trees
#3 MeSH descriptor: [Fungi] explode all trees
#4 MeSH descriptor: [Lung Diseases, Fungal] explode all trees
#5 MeSH descriptor: [Aspergillosis] explode all trees
#6 MeSH descriptor: [Aspergillus] explode all trees
#7 MeSH descriptor: [Candida] explode all trees
#8 MeSH descriptor: [Candidiasis] explode all trees
#9 MeSH descriptor: [Cryptococcosis] explode all trees
#10 MeSH descriptor: [Cryptococcus] explode all trees
#11 Coccidioides
#12 Coccidioidomycosis
#13 Fusariosis
#14 Fusarium
#15 MeSH descriptor: [Mitosporic Fungi] explode all trees
#16 MeSH descriptor: [Mucorales] explode all trees
#17 Mucormycosis
#18 Pseudallescheria
#19 Scedosporium
#20 Trichosporon
#21 Trichosporonosis
#22 MeSH descriptor: [Zygomycosis] explode all trees
#23 Fungal NEAR/2 infection*
#24 Fungal NEAR/2 pneumonia*
#25 Fungal NEAR/2 sepsis*
#26 Fungi NEAR/4 blood
#27 Fungus NEAR/2 disease*
#28 Fungus NEAR/2 infection*
#29 mitosporic NEAR/2 fungi*
#30 Mo?ld NEAR/2 infection*
#31 Yeast? NEAR/2 infection*
#32 Yeast? NEAR/2 infection*
#33 Antifungal
#34 Anti-fungal
#35 Antimycotic
#36 Anti-mycotic
#37 "A flavus"
#38 "A fumigatus"

#39 "A niger"
#40 "A terreus"
#41 Allescheria*
#42 Aspergilloma*
#43 Aspergillos*
#44 Aspergillus
#45 "B dermatitidis"
#46 Blastomyc?s
#47 Blastomycos*
#48 "C albicans"
#49 "C glabrata"
#50 "C krusei"
#51 "C lusitaniae"
#52 "C neoformans"
#53 "C parapsilosis"
#54 "C tropicalis"
#55 Candid?emia*
#56 Candida
#57 Candidamycos*
#58 Candidias*
#59 Candidos*
#60 Coccidio?mycos*
#61 Coccidiod*
#62 Cryptococc*
#63 Deuteromycete*
#64 Deuteromycota*
#65 Entomophthora
#66 Entomophthoramycos?s
#67 "F solani"
#68 Fung?emia*
#69 Fusarial
#70 Fusariomycos*
#71 Fusarios?s
#72 Fusarium*
#73 Gilchrist* NEXT disease*
#74 "H capsulatum"
#75 Histoplasmosi?
#76 Hyphomycetes
#77 Monilia*
#78 Monosporium*
#79 Mucor
#80 Mucoral*
#81 Mucormycos*
#82 Mycos*
#83 Mycotic
#84 Neuroaspergillos*
#85 Petriellidium*
#86 Phaeohyphomycos?s
#87 Phycomycos?s
#88 Pseudallescheria*
#89 Rhizomucor
#90 Rhizopus
#91 Scedosporium*
#92 Torula
#93 "Torulopsis utilis"
#94 Torulos?s
#95 Trichosporon*
#96 Zygomycet*
#97 Zygomycos?s
#98 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR 79 OR 80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97
#99 MeSH descriptor: [Lung Transplantation] explode all trees
#100 (Lung? NEAR/5 transplant*):ti,ab,kw
#101 (Lung? NEAR/2 graft*):ti,ab,kw
#102 (Lung? NEAR/2 allograft*):ti,ab,kw

#103 (Lung? NEAR/2 allotransplant*):ti,ab,kw
#104 (Lung? NEAR/2 homotransplant*):ti,ab,kw
#105 (Lung? NEAR/2 homograft*):ti,ab,kw
#106 (Pulmonary NEAR/5 transplant*):ti,ab,kw
#107 (Pulmonary NEAR/2 graft*):ti,ab,kw
#108 (Pulmonary NEAR/2 allograft*):ti,ab,kw
#109 (Pulmonary NEAR/2 allotransplant*):ti,ab,kw
#110 (Pulmonary NEAR/2 homotransplant*):ti,ab,kw
#111 (Pulmonary NEAR/2 homograft*):ti,ab,kw
#112 #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111
#113 #98 AND #112
#114 prophylaxis
#115 prophylactic
#116 pre-emptive*
#117 preemptive*
#118 prevent*
#119 MeSH descriptor: [Chemoprevention] explode all trees
#120 #114 OR #115 OR #116 OR #117 OR #118 OR #119
#121 #113 AND #120
#122 pre-emptive
#123 preemptive
#124 targeted
#125 culture*
#126 coloni*
#127 galactomannan
#128 PCR
#129 biomarker
#130 high-risk
#131 high* NEAR/2 risk
#132 increase* NEAR/2 risk
#133 universal
#134 #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133
#135 #121 AND #134
Limit: 2000-present
Search run on February 22nd, 2024
Rerun on April 4th, 2025

Web of Science

# 1 TOPIC: (Fungal NEAR/2 disease* OR Fungal NEAR/2 infection* OR Fungal NEAR/2 pneumonia* OR Fungal NEAR/2 sepsis OR Fungi NEAR/4 blood OR Fungus NEAR/2 disease* OR Fungus NEAR/2 infection* OR Mitosporic NEAR/2 fungi* OR Mo$ld NEAR/2 infection* OR Yeast$ NEAR/2 infection* OR Antifungal OR Anti-fungal OR Antimycotic OR Anti-mycotic OR “A flavus” OR “A fumigatus” OR “A niger” OR “A terreus” OR Allescheria* OR Aspergilloma* OR Aspergillos* OR Aspergillus OR “B dermatitidis” OR Blastomyc$s OR Blastomycos* OR “C albicans” OR “C glabrata” OR “C krusei” OR “C lusitaniae” OR “C neoformans” OR “C parapsilosis” OR “C tropicalis” OR Candid$emia* OR Candida OR Candidamycos* OR Candidias* OR Candidos* OR Coccidio$mycos* OR Coccidiod* OR Cryptococc* OR Deuteromycete* OR Deuteromycota* OR Entomophthora OR Entomophthoramycos?s OR “F solani” OR Fung$emia* OR Fusarial OR Fusariomycos* OR Fusarios$s OR Fusarium* OR “Gilchrist* disease*” OR “H capsulatum” OR Histoplasmosi$ OR Hyphomycetes OR Monilia* OR Monosporium* OR Mucor OR Mucoral* OR Mucormycos* OR Mycos* OR Mycotic OR Neuroaspergillos* OR Petriellidium* OR Phaeohyphomycos$s OR Phycomycos$s OR Pseudallescheria* OR Rhizomucor OR Rhizopus OR Scedosporium* OR Torula OR “Torulopsis utilis” OR Torulos$s OR Trichosporon* OR Zygomycet* OR Zygomycos$s)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

# 2 TOPIC: (Lung$ NEAR/5 transplant* OR Lung$ NEAR/2 graft* OR Lung$ NEAR/2 allograft* OR Lung$ NEAR/2 allotransplant* OR Lung$ NEAR/2 homotransplant* OR Lung$ NEAR/2 homograft* OR Pulmonary NEAR/5 transplant* OR Pulmonary NEAR/2 graft* OR Pulmonary NEAR/2 allograft* OR Pulmonary NEAR/2 allotransplant* OR Pulmonary NEAR/2 homotransplant* OR Pulmonary NEAR/2 homograft*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

# 3 TOPIC: (prophylaxis OR prophylactic OR pre-emptive* OR preemptive* OR prevent*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

# 4 #3 AND #2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

#5 preemptive OR pre-emptive OR targeted OR culture* OR coloni* OR PCR OR biomarker OR high-risk OR "high* risk" OR "increase* risk" OR universal

#6 #4 AND #5

Limit: 2000-present
Search run on February 22nd, 2024
Rerun on April 4th, 2025

Eligibility criteria for selection of the studies

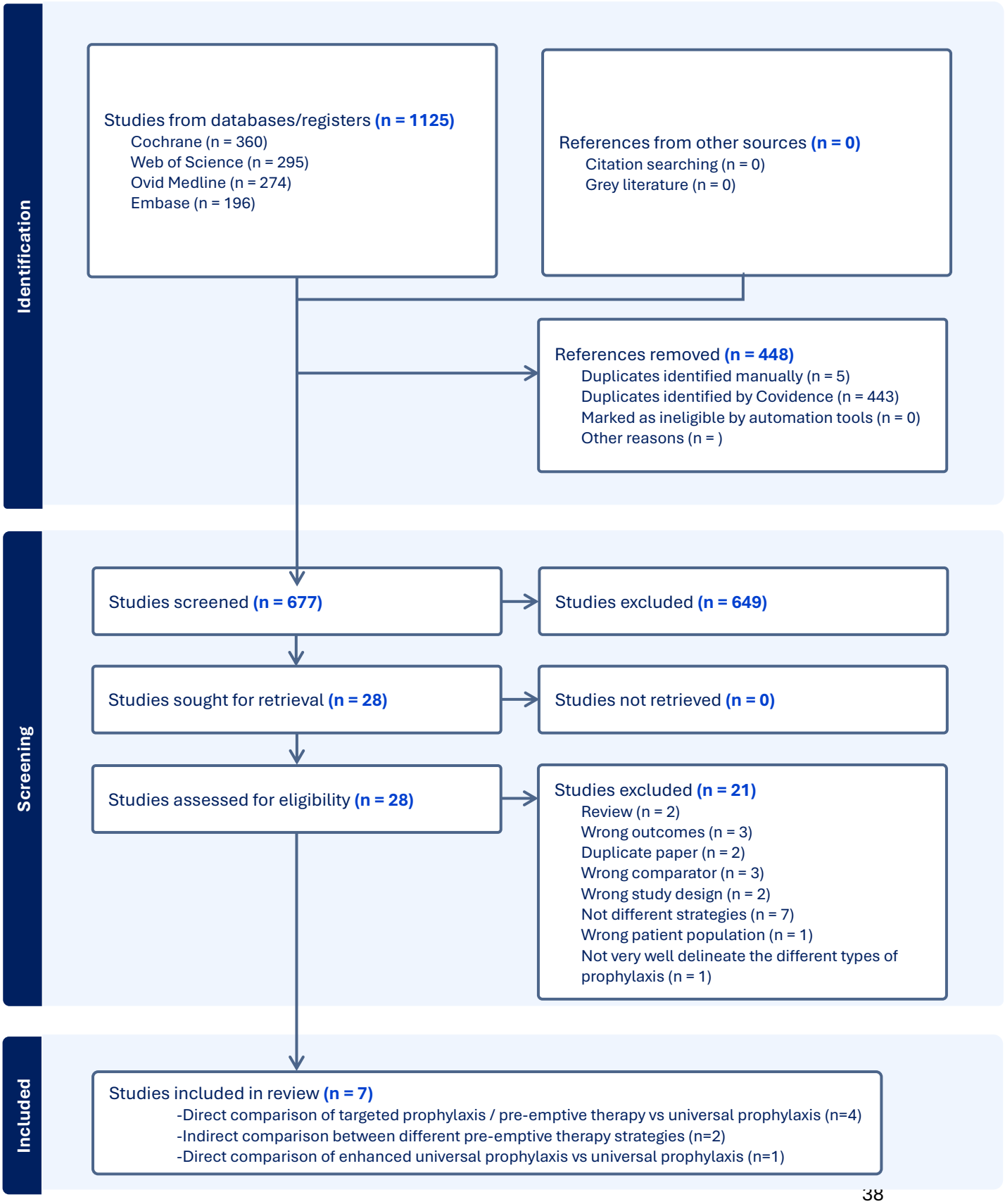
Inclusion criteria:

- Patient population: Adults lung transplant recipients in post-transplant period
- Anti-*Aspergillus* prophylaxis
  - Echinocandins such as caspofungin, micafungin or anidulafungin
  - Triazoles such as posaconazole, voriconazole or isavuconazole
  - Amphotericin B (IV or aerosolized AmB)
  - Itraconazole (any formulation)
- No anti-*Aspergillus* prophylaxis
  - Fluconazole (any formulation)
  - Absence of antifungal prophylaxis
- Strategies:
  - Targeted prophylaxis: lung transplant recipients at high-risk of IA (such as patients receiving ATG / OKT3, single lung transplant, …)
  - Pre-emptive therapy: lung transplant recipients with pre/post-transplant BAL with *Aspergillus* in culture and/or GM (index over 1) without associated disease
  - Enhanced universal prophylaxis: Addition of a targeted prophylaxis and/or pre-emptive therapy to a universal prophylaxis (for example, all lung transplant recipients receive aerosolized AmB and those with positive *Aspergillus* in culture also receive azoles)
- Intervention / Comparison
  - Universal vs Targeted prophylaxis / Pre-emptive therapy (culture +/- GM vs culture)
  - Universal vs Universal Enhanced prophylaxis
- Outcomes: Minimally including incidence of IA or adverse events associated with the use of anti-*Aspergillus* prophylaxis
- Study design: RCTs and non-randomized comparative studies (i.e. observational studies)
- Year: published from 2000 up to present
- Language: English only

Exclusion criteria:

- Patient population:
  - Pediatric population
- Intervention / Comparator
  - Any comparison where the comparator group include a variety of different anti-*Aspergillus* and anti-yeast prophylaxis (without stratification by antifungal agent used)
- Study design
  - One-arm studies
  - Conference proceedings, abstracts, letters to the editor, comments

Supplementary Figure A2.1: PRISMA flow diagram of study identification and selection (last updated on April 4, 2025)



Supplementary Table A2.1: GRADE evidence profile

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

P: Adult lung transplant recipients
I: Targeted anti-*Aspergillus* prophylaxis/ Pre-emptive therapy
C: Universal anti-*Aspergillus* prophylaxis
Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Targeted anti-*Aspergillus* prophylaxis / Pre-emptive therapy	Universal anti-*Aspergillus* prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (follow-up: range 12 to 18 months)										MID*: at least 40 fewer per 1,000		
3[1,3,4]	non-randomized studies	very serious[a]	very serious[b]	not serious	very serious[c]	none	31/178 (17.4%)	33/317 (10.4%)	**RR 2.38** (0.72 to 7.84)	**144 more per 1,000** (from 29 fewer to 712 more)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
									Critical concern about clinical and statistical heterogeneity makes these estimates unreliable			
Breakthrough IA (follow-up: range 12 months to 18 months)										MID*: at least 40 fewer per 1,000		
3[1,3,4]	non-randomized studies	very serious[a]	very serious[b]	not serious	very serious[c]	none	3/178 (1.7%)	8/317 (2.5%)	**RR 0.88** (0.11 to 6.81)	**3 fewer per 1,000** (from 22 fewer to 147 more)	⨁◯◯◯ Very low[a,b,c]	IMPORTANT
Post-transplant *Aspergillus* colonization (follow-up: range 12 months to 18 months)												
2[1,4]	non-randomized studies	very serious[a]	not serious	serious[d]	very serious[e]	none	18/132 (13.6%)	33/258 (12.8%)	**RR 1.06** (0.62 to 1.81)	**8 more per 1,000** (from 49 fewer to 104 more)	⨁◯◯◯ Very low[a,d,e]	IMPORTANT
Mortality (all-cause)										MID*: at least 20 fewer per 1,000		
2[3,4]	non-randomized studies	very serious[a]	not serious	not serious	very serious[e]	none	8/76 (10.5%)	10/124 (8.1%)	**RR 1.54** (0.14 to 16.48)	**44 more per 1,000** (from 69 fewer to 1,000 more)	⨁◯◯◯ Very low[a,e]	IMPORTANT
Serious Adverse Events										MID*: at least 40 fewer per 1,000		
2[2,4]	non-randomized studies	very serious[a]	not serious	not serious	very serious[e]	none	4/132 (3.0%)	123/258 (47.7%)	**RR 0.13** (0.01 to 2.22)	**415 fewer per 1,000** (from 472 fewer to 582 more)	⨁◯◯◯ Very low[a,e]	CRITICAL
Non-Serious Adverse Events												
1[4]	non-randomized studies	very serious[a]	not serious	not serious	very serious[e]	none	4/27 (14.8%)	29/65 (44.6%)	**RR 0.33** (0.13 to 0.85)	**299 fewer per 1,000** (from 388 fewer to 67 fewer)	⨁◯◯◯ Very low[a,e]	IMPORTANT
Graft Rejection												
1[2]	non-randomized studies	very serious[a]	not serious	not serious	very serious[e]	none	14/102 (13.7%)	78/193 (40.4%)	**RR 0.34** (0.20 to 0.57)	**267 fewer per 1,000** (from 323 fewer to 174 fewer)	⨁◯◯◯ Very low[a,e]	MPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **RR:** risk ratio
*MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)

Explanations

a. All 3 studies spanning four publications (Husain 2006, Linder 2021, Crone 2022, and Crone 2023) were designed as pre/post-intervention studies, and they were all considered at critical risk of bias (ROBINS-I) mainly due to potential residual confounding and selection bias (potential unmeasured changes in enrolled participants and changes in standard of care overtime. Further concerns were associated to missing information on patients' characteristics at baseline, significant deviation from the intended intervention due to non-adherence or interruption of prophylaxis, as well as suboptimal dosage, all potentially influencing the effect of prophylaxis.

b. Statistical significant noted in the meta-analysis (I2=87%, p-value=0.0004). The large heterogeneity between studies (e.g. variation in era, included population, surveillance protocols, standard of care, type of prophylaxis use (class of agents, dosage, route of administration, duration), or follow-up period) and lack of controlled studies, pertinent clinical characteristics of population and reasons for protocol deviation, intervention (adherence) and definitions of IA), which precluded the panel to come to any meaningful conclusion on the potential benefits of any type of antifungal prophylactic strategies.

c. The confidence interval includes both trivial benefits and large harms, thus providing evidence of very serious imprecision around the estimates of effect.

d. *Aspergillus* colonization is known to be a precursor (intermediary step) of invasive aspergillosis.

e. The boundaries of the confidence interval cross the decision threshold (minimal important difference) for both important benefit and important harm, thus providing evidence of very serious imprecision.

References

1. Crone CG, and al. Invasive Aspergillosis among Lung Transplant Recipients during Time Periods with Universal and Targeted Antifungal Prophylaxis-A Nationwide Cohort Study. J Fungi (Basel). 2023 Nov 4;9(11):1079.
2. Crone CG and al. Adverse Events Associated with Universal versus Targeted Antifungal Prophylaxis among Lung Transplant Recipients-A Nationwide Cohort Study 2010-2019. Microorganisms. 2022 Dec 15;10(12):2478.
3. Linder KA and al. Evaluation of targeted versus universal prophylaxis for the prevention of invasive fungal infections following lung transplantation. Transpl Infect Dis. 2021 Feb;23(1):e13448.
4. Husain S and al. Voriconazole prophylaxis in lung transplant recipients. Am J Transplant. 2006 Dec;6(12):3008-16.

Supplementary Table A2.2: Characteristics of the included studies

Study *(lead author, year of publication, location)*	**Population** *(type of patients, Year of enrollment, n randomized, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(targeted anti-Aspergillus prophylaxis or pre-emptive therapy, total duration)*	**Comparator** *(universal anti-Aspergillus prophylaxis, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
Crone 2022 & Crone 2023** Copenhagen, Denmark Single Center	All lung transplant recipients Before: 2010-2016 (universal) After: 2016-2019 (targeted) N = 295 (of which, 30 were single lung) Age (median): 52y (universal prophylaxis) and 55y (targeted prophylaxis) Exclusion: NR	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA Routine bronchoscopy with biopsies with cultures at 2, 4, 6 and 12 weeks, then 6, 12, 18 and 24 months, and as clinically indicated (no BAL GM or PCR used for routine surveillance (i.e. only for the diagnosis of IA))	**High-risk for IA:** One or more of the following in 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	Baseline risk for IA: **Universal prophylaxis: 14.0%** Baseline risk for mortality: NR	**High-risk of IA:** Posaconazole 300mg daily + aerosolized ABLC TDM: not routinely performed Duration: 3 months (median duration received = 108 days (IQR 44-142) and 6% were started on prophylaxis)	Voriconazole 200mg BD TDM: not routinely performed Duration: 3 months (183/193 (95%) of patients were started on prophylaxis and 114/183 (62%) discontinued prematurely: median duration = 36 days (IQR 12-84) and a median time of discontinuation of 15 days (IQR 7-62). In 36 patients resuming prophylaxis, 23 (64%) completed the total expected duration)	ISHLT criteria Total duration of follow-up: 12 months
Linder 2021 Michigan, USA Single Center	All lung transplant recipients Before: 2014-2016 (universal) After: 2016-2017 (targeted) N = 105 (21 single lung, 84 double lung) Age (mean): 60y (universal prophylaxis) and 61y (targeted prophylaxis) Exclusion: -non-protocol-based strategy for ATF -insufficient data available to follow their post-transplant clinical course	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA Routine bronchoscopy with biopsies with cultures at 3 and 6 weeks, then 6 and 12 months, and as clinically indicated (no BAL GM or PCR used for routine surveillance (i.e. only for the diagnosis of IA))	**High-risk of IA:** If pre-transplant recipient colonised with *Aspergillus spp* or previous IPA, post-transplant surveillance BAL positive for *Aspergillus* with no features of IPA + serum GM -ve, or ATG therapy initiated	Baseline risk for IA: **Universal prophylaxis: 8.5%** Baseline risk for mortality: Universal prophylaxis: 14%	**High-risk of IA or *Aspergillus* colonization:** *Aspergillus spp*: Voriconazole 4mg/kg BD No TDM Duration: 3 months (median duration received and non-adherence = NR) & **High-risk of IC:** Fluconazole 400-800 mg PO daily or Micafungin 100mg x 14 days+ Nystatin x 6 weeks	Itraconazole (capsule) 200mg daily with/without aerosolized ABLC 12.5mg three times a week TDM: not routinely performed Duration: -Itraconazole: 6 months -aerosolized ABLC: 3 weeks or until surveillance bronchoscopy negative (median duration received and non-adherence = NR)	EORTC/MSG 2008 Duration of follow-up: 18 months
Husain 2006 Pittsburgh, USA Single Center	All lung transplant recipients Before: 2001-2002 (targeted) After: 2002-2004 (universal) N = 95 (46 single lung, 47 double lungs, 2 heart-lung) Age (median): 55y in targeted prophylaxis vs 51 in Universal prophylaxis	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA (at 12 months) Routine bronchoscopy (BAL and transbronchial biopsies with cultures) at 2 and 8 weeks, then every 3 months (targeted prophylaxis) vs at 2 weeks, and 2,4,6, 8, 10	**High-risk of IA:** Pre/post-transplant colonisation with *Aspergillus spp*	Baseline risk for IA: **Targeted prophylaxis: 23.3%** Baseline risk for mortality: Targeted prophylaxis: 17%	**Pre-transplant *Aspergillus* colonization**: Itraconazole (tablets) 200mg BD No TDM Duration: minimum of 3 months prior to transplant (median duration received and non-adherence = NR) &	Voriconazole 6mg x 2 loading dose BD followed by 200mg BD No TDM Duration: 4 months or longer if fungal colonization and Alemtuzumab for rejection (median duration received and non-adherence = NR)	EORTC/MSG 2002 Duration of follow-up: 12 months

	Exclusion: NR	and 12 months (universal prophylaxis), and as clinically indicated (no BAL GM or PCR)			**Post-transplant *Aspergillus* colonization:** Itraconazole (tablets) 200mg BD with or without aerosolized d-AmB No TDM Duration: 4-6 months post-transplant (median duration received = NR / non-adherence = 2 cases of *A.niger* did not receive prophylaxis and 1 case of *A. fumigatus* received aerosolized d-AmB without Itraconazole)		

Legend
AFT: antifungal therapy
BAL: bronchoalveolar lavage
BD: twice a day
CMV: cytomegalovirus
d-AmB: amphotericin B deoxycholate
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
GM: Galactomannan
IA: invasive aspergillosis
IFI: invasive fungal infection
ISHLT: The International Society of Heart and Lung Transplantation
IV: parenteral
NR: not reported
PCR: Polymerase chain reaction
PO: oral
TDM: Therapeutic Drug Monitoring
TDS: three times a day

ISHLT vs EORTC: ISHLT also has specific definitions for *Aspergillus* tracheobronchitis and anastomotic infection.
High-Risk of IA (see our criteria for targeted anti-*Aspergillus* prophylaxis)
*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.
**Crone 2022 and Crone 2023 publications report on the same cohort of patients but different outcomes (Crone 2022 reports on the incidence of IA while Crone 2023 reports on the adverse events) and are thus considered as a single study for the purpose of this analysis.

Supplementary Table A2.3: Summary of Risk of bias of included studies

Study	Overall Risk of bias	Confounding	Selection of participants into the study	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result
Crone 2022 & Crone 2023**	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 9-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration clearly defined	Critical non-adherence and interruption in the universal prophylaxis group impede any significant conclusion on potential benefits of prophylaxis (i.e. underestimation of the effect of universal prophylaxis).	All data presented in survival analysis curves, clearly presenting censored patients with time. Presentation of the characteristics of the population by prophylaxis group available but incomplete.	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported and similar in both groups.	The outcome measurement and analyses are consistent with the Methods.
Linder 2021	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. decreasing the incidence of IA in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 3-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration clearly defined	Adverse events and adherence to prophylaxis not mentioned. Critical concerns about the dosage of prophylaxis provided in the universal prophylaxis group impedes any significant conclusion on the potential benefits of prophylaxis. (i.e. underestimation of the effect of universal prophylaxis).	Missing data (numbers reported in the tables and in the manuscript are discordant and all patients are clearly not accounted for and could impact the conclusion. No presentation of the characteristics of the population available.	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported and similar in both groups.	The outcome measurement and analyses are consistent with the Methods.
Husain 2006	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. decreasing the incidence of IA in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 4-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration clearly defined	Adverse events and adherence to prophylaxis not mentioned. Critical deviation from the intended intervention in the targeted prophylaxis group (i.e. overestimation of the effect of universal prophylaxis.	No evidence of missing data, but no presentation of the characteristics of the population by prophylaxis group (before vs after) available.	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported and similar in both groups.	The outcome measurement and analyses are consistent with the Methods.

IA: invasive aspergillosis

**Crone 2022 and Crone 2023 publications report on the same cohort of patients but different outcomes (Crone 2022 reports on the incidence of IA while Crone 2023 reports on the adverse events) and are thus considered as a single study for the purpose of this analysis.

Risk of bias judgment

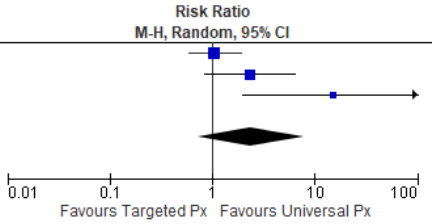
Low	
Moderate	
Serious	
Critical	
No information	

Supplementary Figures A2.2: Forest plots for each patient-important outcome

Figure A2.2.a: Invasive aspergillosis (follow up: 12 to 18 months)

Study or Subgroup	Targeted Px strategy Events	Total	Universal Px strategy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Crone 2023	15	102	27	193	43.9%	1.05 [0.59, 1.88]	2023
Linder 2021	9	46	5	59	36.1%	2.31 [0.83, 6.42]	2021
Husain 2006	7	30	1	65	20.0%	15.17 [1.95, 117.83]	2006
Total (95% CI)		**178**		**317**	**100.0%**	**2.38 [0.72, 7.84]**	
Total events	31		33				

Heterogeneity: Tau² = 0.75; Chi² = 7.23, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 1.43 (P = 0.15)



Concerns on heterogeneity

Probable explanations of heterogeneity

-Different eras (2000 vs 2020) with evolving standard of care

-Different local surveillance protocols: bronchoscopy with new diagnostic tools = earlier diagnosis and management / treatment of IA

-Difference in "before" and "after" study design: Husain 2006 transition from targeted to universal while the 2 other studies transition from universal prophylaxis to targeted prophylaxis / pre-emptive therapy

-Different types of targeted prophylaxis +/- pre-emptive therapy

-Different comparisons of agents, route of administration and duration of prophylaxis

-Between studies for the same prophylactic strategies

-Between studied prophylaxis groups within each study

Possible explanations for heterogeneity

-Non-adherence to intended intervention (from not started, intermittent or cessation) / PK-PD (no TDM and suboptimal dosing, drug-drug interaction)

-Different geography (Crone: Europe, Linder and Husain: USA)

-Different baseline risk between studies

Due to the low number of studies, these potential sources of heterogeneity can't be explored and the panel judged that it remains unknown if universal prophylaxis provides benefits.

Generalizability concerns:

-Targeted prophylaxis / Pre-emptive therapy group: incidence of IA varied from 14.7%, to 19.6%, and up to 23.3%

-Universal prophylaxis group: incidence of IA varied from1.5%, to 8.5%, and up to 14.0%

The very high incidence observed highlighted the potential lack of generalizability to the contemporary context

Figure A2.2.b: Breakthrough IA

Study or Subgroup	Targeted Px strategy Events	Total	Universal Px strategy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Crone 2023	1	102	2	193	35.3%	0.95 [0.09, 10.31]	2023
Linder 2021	0	46	5	59	29.1%	0.12 [0.01, 2.05]	2021
Husain 2006	2	30	1	65	35.7%	4.33 [0.41, 45.95]	2006
Total (95% CI)		**178**		**317**	**100.0%**	**0.88 [0.11, 6.81]**	
Total events	3		8				

Heterogeneity: Tau² = 1.59; Chi² = 3.91, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 0.12 (P = 0.91)

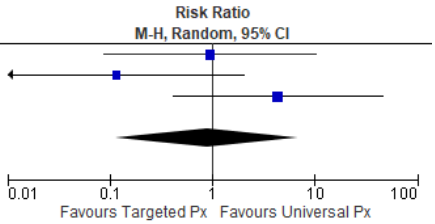


Figure A2.2.c: Invasive fungal infection (follow-up: 12 to 18 months)

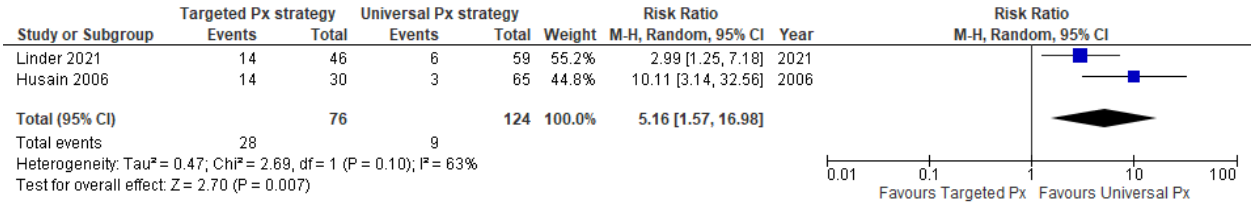
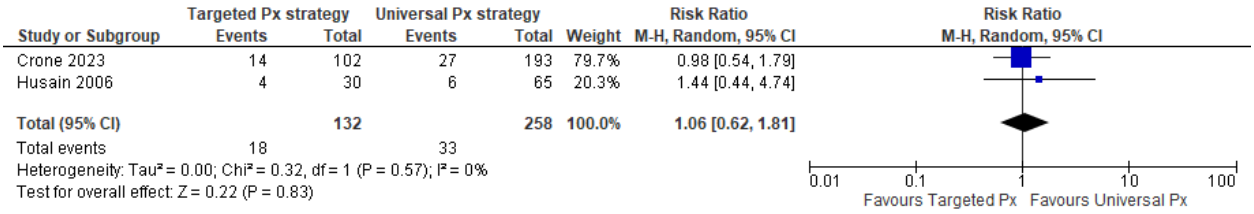


Figure A2.2.d: Post-transplant colonization (follow-up: 12 to 18 months)



Invasive non-*Aspergillus* mold infection (follow-up: 12 to 18 months): NR

Figure A2.2.e: Mortality (all-cause)

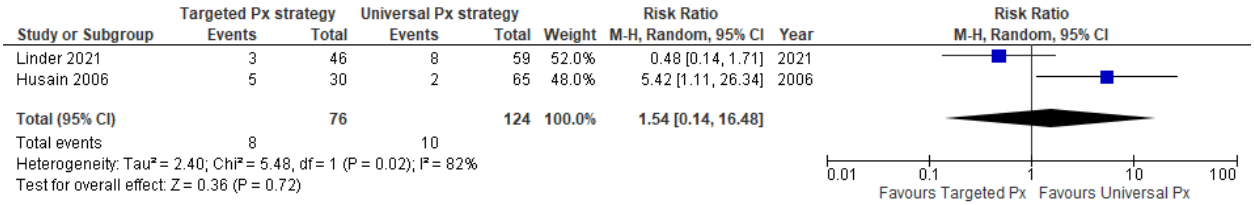


Figure A2.2.f: Attributable mortality

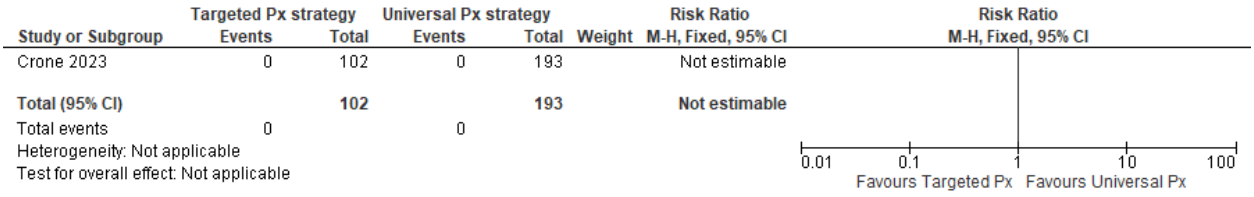


Figure A2.2.g: Serious adverse events

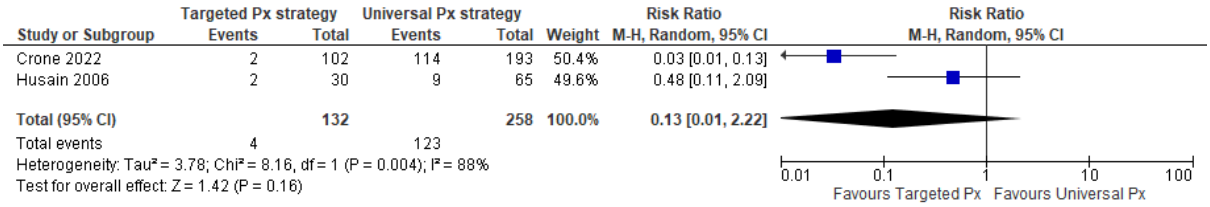


Figure A2.2.h: Non-serious adverse events

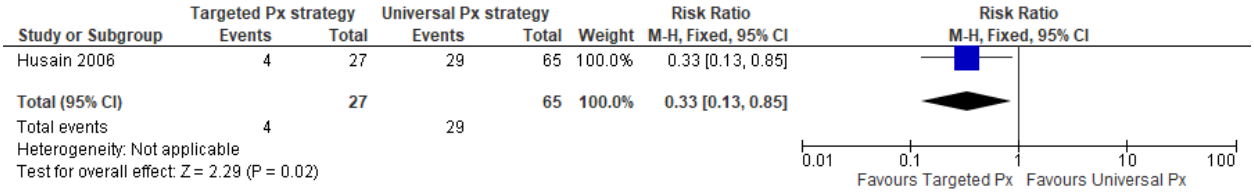


Figure A2.2.i: Graft rejection

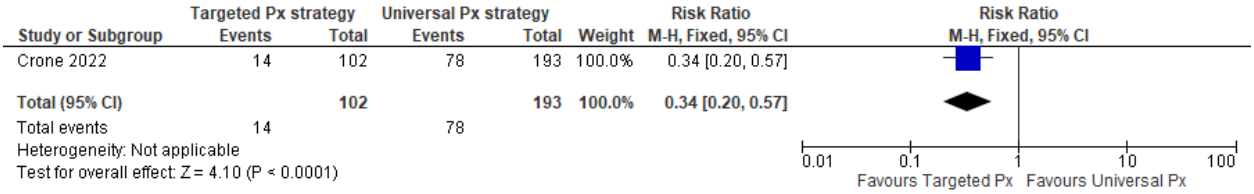
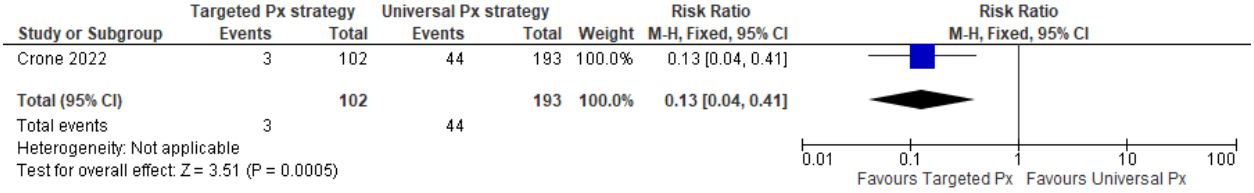


Figure A2.2.j: Graft rejection with low calcineurin inhibitor levels



Long term adverse events: NR

Sub-question A2: In lung transplant recipients, should pre-emptive anti-*Aspergillus* therapy based on *culture + galactomannan* be used rather than based on *culture only*?

Supplementary Table A2.4: GRADE evidence profile

P: Adult lung transplant recipients
I: Pre-emptive *anti-Aspergillus* therapy based on culture + galactomannan
C: Pre-emptive *anti-Aspergillus* therapy based on culture only
Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-emptive anti-*Aspergillus* therapy based on culture + GM	Pre-emptive anti-*Aspergillus* therapy based on culture only	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (follow-up: median 12 months)										**MID*:** at least 40 fewer per 1,000		
2	non-randomized studies	serious[a]	not serious	serious[b]	very serious[c]	none	54/519 (10.4%)	29/328 (8.8%)	**RR 1.18** (0.77 to 1.81)	**16 more per 1,000** (from 20 fewer to 72 more)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Invasive Fungal Infection (follow-up: median 12 months)												
2	non-randomized studies	serious[a]	not serious	serious[b]	very serious[d]	none	75/519 (14.5%)	71/328 (21.6%)	**RR 0.67** (0.50 to 0.90)	**71 fewer per 1,000** (from 108 fewer to 22 fewer)	⨁◯◯◯ Very low[a,b,d]	IMPORTANT
Mortality (all-cause) (follow-up: median 12 months)										**MID*:** at least 20 fewer per 1,000		
2	non-randomized studies	serious[a]	not serious	serious[b]	very serious[e]	none	66/519 (12.7%)	45/328 (13.7%)	**RR 0.93** (0.65 to 1.32)	**10 fewer per 1,000** (from 48 fewer to 44 more)	⨁◯◯◯ Very low[a,b,e]	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **RR:** risk ratio
***MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)**

Explanations

a. The two included publications were conducted at the same center but at different times, and thus were conceptually considered as one "before" (Hosseini-Moghaddam 2015) and "after" (Husain 2018) intervention study, which was considered at critical risk of bias (ROBINS-I) mainly due to potential residual confounding and selection bias (potential unmeasured changes in enrolled participants and changes in standard of care overtime). Further concerns were associated significant deviation from the intended intervention due to non-adherence or interruption of prophylaxis.
b. Indirect comparison from two published studies, which is equivalent to a "before and after" study since derived from the same single center.
c. The confidence interval includes both trivial benefits and large harms, thus providing evidence of very serious imprecision around the estimates of effect.
d. The confidence interval includes both large benefits and trivial harms, thus providing evidence of very serious imprecision around the estimates of effect.
e. The boundaries of the confidence interval cross the decision threshold (minimal important difference) for both important benefit and important harm, thus providing evidence of very serious imprecision.

References

1. Hosseini-Moghaddam SM and al.. The Effectiveness of Culture-Directed Preemptive Anti-Aspergillus Treatment in Lung Transplant Recipients at One Year After Transplant. Transplantation. 2015 Nov;99(11):2387-93
2. Husain S and al. A strategy for prevention of fungal infections in lung transplantation: Role of bronchoalveolar lavage fluid galactomannan and fungal culture. J Heart Lung Transplant. 2018 Jul;37(7):886-894.

Supplementary Table A2.5: Characteristics of the included studies (indirect comparison from the same population)

Study *(lead author, year of publication, location)*	**Population** *(type of patients, year of enrollment, n randomized, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(pre-emptive anti-Aspergillus therapy based on **culture+GM**, total duration)*	**Comparator** *(pre-emptive anti-Aspergillus therapy based on **culture only**, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
Hosseini-Moghaddam 2015** Ontario, Canada Single-arm study	All lung transplant recipients Before:2006-2009 N = 328 (47 single lung, 272 double lungs, 9 heart/lung) Age (median): 54y	Single-arm retrospective study Primary outcomes: Incidence of proven or probable IA Routine bronchoscopy with biopsies with cultures at 3 and 6 weeks, then 6 and 12 months, and as clinically indicated	**High-risk of IA:** both pre- and post-transplant colonisation	NA	NA	Voriconazole 200mg BD for 3 months +/- aerosolized AmB deoxycholate (20 mg BD) for at least 7 days **Deviation from the intervention**: -of a total of 113 patients with pre/post-transplantation colonization, only 76 received it and 36 completed the full-3 month (31.9%), while 40 patients received a mean of 38.9 +/- 3.9 days (35.4%)	ISHLT 2011 Duration of follow-up: 12 months
Husain 2018** Ontario, Canada Single-arm study	All lung transplant recipients After: 2010-2014 N=519 (85 single lung, 431 double lungs, 3 heart/lung) Age (median): 57y	Single-arm prospective study Primary outcomes: Incidence of proven or probable IA Routine bronchoscopy with biopsies with cultures at 3 and 6 weeks, then 6 and 12 months, and as clinically indicated	**High-risk of IA:** history of IA within 6 months of transplant or pre-transplant colonization & post-transplant colonization or GM (index value more or equal to 1)	NA	Voriconazole (if intolerance or adverse events, switched to aerosolized AmB (20mg BD) or an echinocandin) & voriconazole (unless judged as a false positive) X a minimum of 42 days **Median duration** received = 101 (IQR 89 to 167) days **Deviation from the intervention**: -of pre-transplant colonization 30/65 received prophylaxis -of 164 with post-transplant colonization or GM: 25 received therapy and 53 pre-emptive therapy and 86 none -of NO colonization or GM 31/290 received prophylaxis	NA	ISHLT 2011 Duration of follow-up: 12 months

Legend
AmB: amphotericin B
AFT: antifungal therapy
BAL: bronchoalveolar lavage
BD: twice a day
GM: Galactomannan
IA: invasive aspergillosis
IFI: invasive fungal infection
ISHLT: International Society of Heart and Lung Transplantation
IV: parenteral
NR: not reported
PCR: Polymerase chain reaction,
PO: oral
TDM: Therapeutic Drug Monitoring
TDS: three times a day

ISHLT vs EORTC: ISHLT also has specific definitions for *Aspergillus* tracheobronchitis and anastomotic infection.
High-Risk of IA (see our criteria for targeted anti-A*spergillus* prophylaxis)
*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.
**The two included publications were conducted at the same center but at different times, and thus were conceptually considered as one "before" (Hosseini-Moghaddam 2015) and "after" (Husain 2018) intervention study

Supplementary Figures A2.3: Forest plots for each patient-important outcome

Figure A2.3.a: Invasive aspergillosis (12 months)

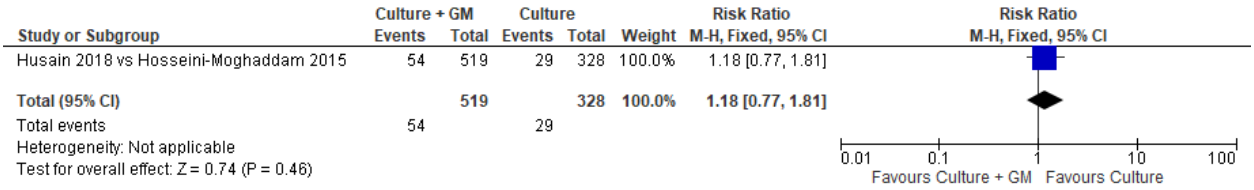


Figure A2.3.b: Invasive fungal infection (12 months)

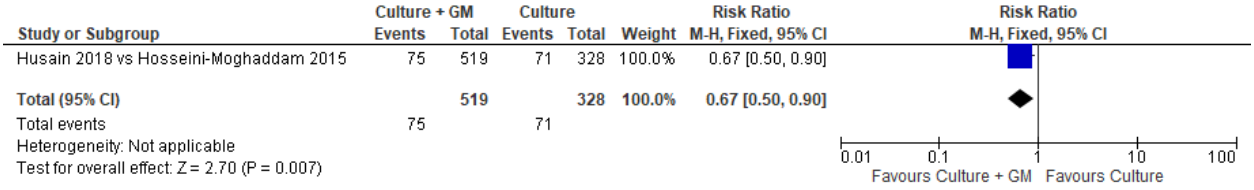
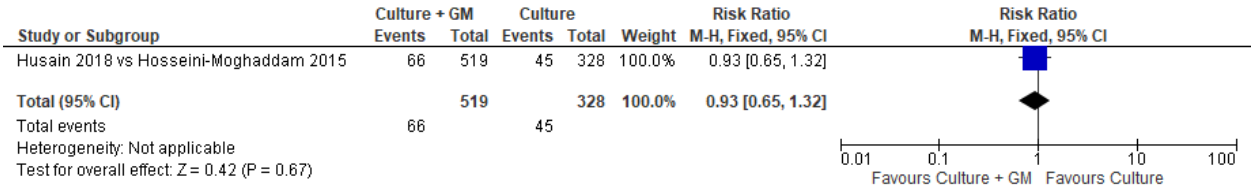


Figure A2.3.c: Mortality (all-cause) (12 months)



Graft rejection (12 months): <u>not comparable</u> (Husain2018: biopsy vs Hosseini-Moghaddam 2015: biopsy + clinical)

Adverse events: NR

Clinical question A3: In lung transplant recipients, should enhanced universal anti-*Aspergillus* prophylaxis be used rather than universal anti-*Aspergillus* prophylaxis?

Supplementary Table A3.1: GRADE evidence profile

Clinical question A3: In lung transplant recipients, should **enhanced universal anti-*Aspergillus* prophylaxis** be used rather than **universal anti-*Aspergillus* prophylaxis**?

P: Adult lung transplant recipients
I: Enhanced universal anti-*Aspergillus* prophylaxis
C: Universal anti-*Aspergillus* prophylaxis
Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced universal anti-*Aspergillus* prophylaxis	Universal anti-*Aspergillus* prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (follow-up: 12 months)										**MID*:** at least 40 fewer per 1,000		
1	non-randomized studies	very serious[a]	not serious	not serious	very serious[b]	none	3/83 (3.6%)	8/82 (9.8%)	**RR 0.37** (0.10 to 1.35)	**61 fewer per 1,000** (from 88 fewer to 34 more)	⨁◯◯◯ Very low[a,b]	CRITICAL
Invasive Fungal Infection (follow-up: 12 months)												
1	non-randomized studies	very serious[a]	not serious	not serious	very serious[c]	none	10/83 (12.0%)	29/82 (35.4%)	**RR 0.34** (0.18 to 0.65)	**233 fewer per 1,000** (from 290 fewer to 124 fewer)	⨁◯◯◯ Very low[a,c]	IMPORTANT
Mortality (all-cause)										**MID*:** at least 20 fewer per 1,000		
1	non-randomized studies	very serious[a]	not serious	not serious	very serious[c]	none	9/83 (10.8%)	13/82 (15.9%)	**RR 0.68** (0.31 to 1.51)	**51 fewer per 1,000** (from 109 fewer to 81 more)	⨁◯◯◯ Very low[a,c]	IMPORTANT
Attributable Mortality										**MID*:** at least 20 fewer per 1,000		
1	non-randomized studies	very serious[a]	not serious	not serious	very serious[c]	none	0/83 (0.0%)	3/82 (3.7%)	**RR 0.14** (0.01 to 2.69)	**31 fewer per 1,000** (from 36 fewer to 62 more)	⨁◯◯◯ Very low[a,c]	CRITICAL
Serious Adverse Events										**MID*:** at least 40 fewer per 1,000		
1	non-randomized studies	very serious[a]	not serious	not serious	very serious[d]	none	0/83 (0.0%)	0/82 (0.0%)	not estimable	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ Very low[a,d]	CRITICAL
Non-Serious Adverse Events												
1	non-randomized studies	very serious[a]	not serious	not serious	very serious[d]	none	0/83 (0.0%)	0/82 (0.0%)	not estimable	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ Very low[a,d]	IMPORTANT
Graft Rejection												
1	non-randomized studies	serious[a]	not serious	not serious	very serious[c]	none	30/83 (36.1%)	39/82 (47.6%)	**RR 0.76** (0.53 to 1.10)	**114 fewer per 1,000** (from 224 fewer to 48 more)	⨁◯◯◯ Very low[a,c]	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced universal anti-*Aspergillus* prophylaxis	Universal anti-*Aspergillus* prophylaxis	Relative (95% CI)	Absolute (95% CI)		

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **RR:** risk ratio
***MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)**

Explanations

a. The included study was designed as pre/post-intervention studies, and is considered at serious risk of bias (ROBINS-I) mainly due to potential residual confounding and selection bias (potential unmeasured changes in enrolled participants and changes in standard of care over time as well use of echinocandins as part of the enhanced universal prophylaxis which likely results in overestimating the potential benefit the enhanced universal prophylactic strategy.
b. The confidence interval includes both large benefits and trivial harms, thus providing evidence of very serious imprecision around the estimates of effect.
c. The boundaries of the confidence interval cross the decision threshold (minimal important difference) for both important benefit and important harm, thus providing evidence of very serious imprecision.
d. No events reported in both groups, thus providing evidence of very serious imprecision.

References

1. Koo S and al. A targeted peritransplant antifungal strategy for the prevention of invasive fungal disease after lung transplantation: a sequential cohort analysis. Transplantation. 2012 Aug 15;94(3):281-6.

Supplementary Table A3.2: Characteristics of the included study

Study *(lead author, year of publication, location)*	**Population** *(type of patients, year of enrollment, n randomized, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(Enhanced universal anti-Aspergillus prophylaxis, total duration)*	**Comparator** *(Universal anti-Aspergillus prophylaxis, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
Koo 2012 Massachusetts, USA Single Center	All lung transplant recipients Before: 2003-2007 (universal) After: 2007-2010 (enhanced universal) N = 165 (of which, 84 were single lung) Age (median): 55y (universal prophylaxis) and 54y (enhanced universal prophylaxis) Exclusion: none (consecutive patients)	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA Routine bronchoscopy with biopsies with cultures at 1, 3, 6 and 12 months (no BAL GM or PCR)	**High-risk IA:** -bilateral lung transplant -peri-transplant cultures	Baseline risk for IA: **Universal prophylaxis: 9.8%** Baseline risk for mortality: Universal prophylaxis: 15.9%	Aerosolized AmB in all patients during the initial lung transplant hospitalization & Micafungin 100 mg IV daily from anesthesia to 7 to 10 days after lung transplant in all bilateral lung transplant recipients & If growth of **yeast or mold in peri-transplant lung cultures (donor and recipient)** or **evidence of active IFD in their explants**: further oral antifungal therapy tailored to individual fungal species, for 3to 6 months after LT. Deviation from the intervention: -48 out of 49 bilateral lung transplant received micafungin 7-10 days -1 received secondary prophylaxis with Voriconazole -6 received pre-emptive therapy (median duration: 277 days (range 6-365)	Aerosolized d-AmB 25 mg BD or L-AmB 20 mg twice daily during the initial lung transplant hospitalization *The necessity of further oral antifungal therapy was determined at the discretion of the inpatient clinical team Derivation from the intervention: -1 without positive culture for *Aspergillus* received voriconazole -1 with positive culture *Aspergillus* received voriconazole -6 with positive culture for *Aspergillus* did not receive pre-emptive therapy	EORTC/MSG 2008 Duration of follow-up: 12 months

Legend
AFT: antifungal therapy
BAL: bronchoalveolar lavage
BD: twice a day
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group; d-AmB: amphotericin deoxycholate; L-AmB: liposomal amphotericin
GM: Galactomannan
IA: Invasive Aspergillosis
IFI: Invasive Fungal Infection
IV: parenteral
NR: not reported
PCR: Polymerase chain reaction
PO: oral
TDM: Therapeutic Drug Monitoring
TDS: three times a day

High-Risk of IA (see our criteria for targeted anti-*Aspergillus* prophylaxis)
*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.

Supplementary Table A3.3: Summary of risk of bias of included study

Study	Overall Risk of bias	Confounding	Selection of participants into the study	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result
Koo 2012	**Critical**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 7-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration clearly defined, but pre-emptive therapy included treatment of IA and secondary prophylaxis.	Administration of echinocandins as part of the enhanced universal prophylaxis creates a deviation from intended intervention that likely results in overestimating the potential benefit of this prophylaxis strategy.	Some missing data (e.g. number of patients with *Aspergillus* positive culture intra-transplant in cohort 1)	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported and similar in both groups.	The outcome measurement and analyses are consistent with the Methods.

Legend
IA: invasive aspergillosis

Risk of bias judgment

Low	
Moderate	
Serious	
Critical	
No information	

Supplementary Figures A3.1: Forest plots for each patient-important outcome

Figure A3.1.a: Invasive aspergillosis (follow-up: 12 months)

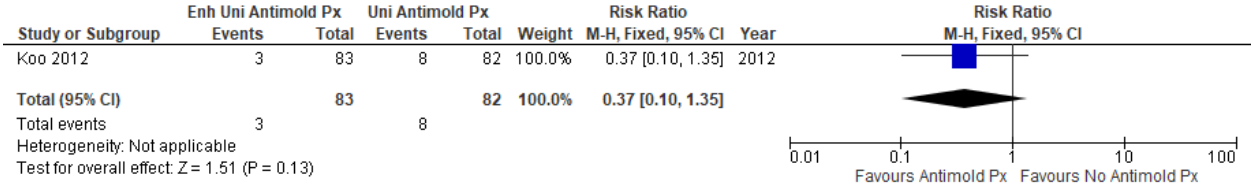


Figure A3.1.b: Invasive fungal infection (follow-up: 12 months)

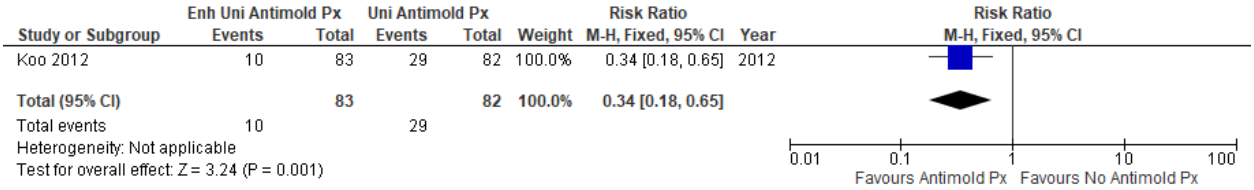


Figure A3.1.c: Mortality (all-cause)

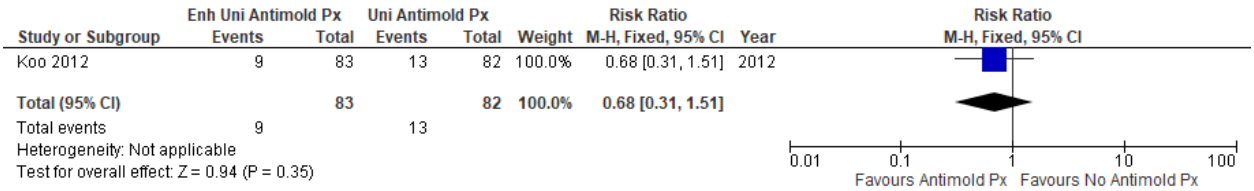


Figure A3.1.d: Attributable mortality

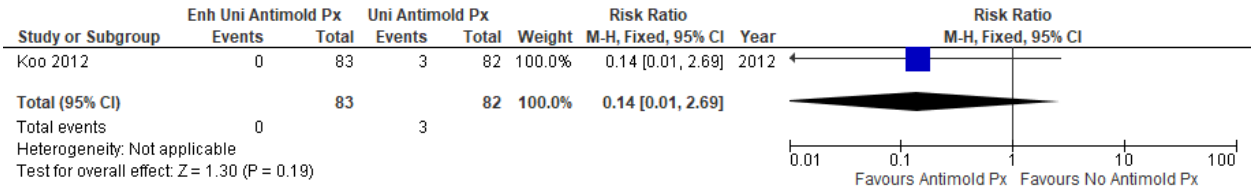


Figure A3.1.e: Serious adverse events

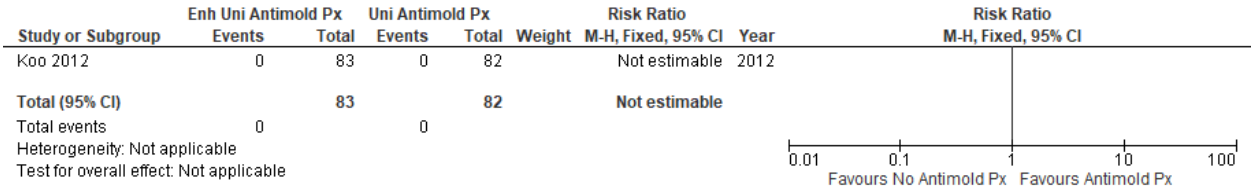


Figure A3.1.f: Non-serious adverse events

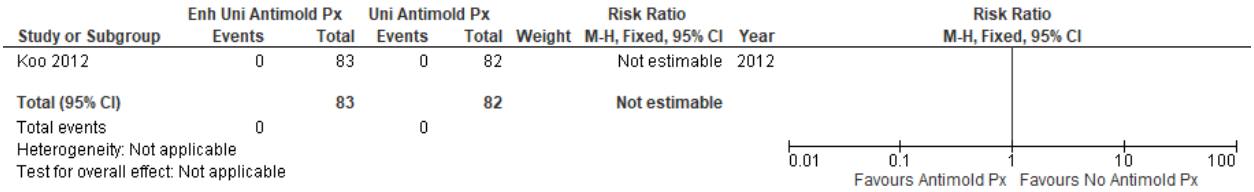
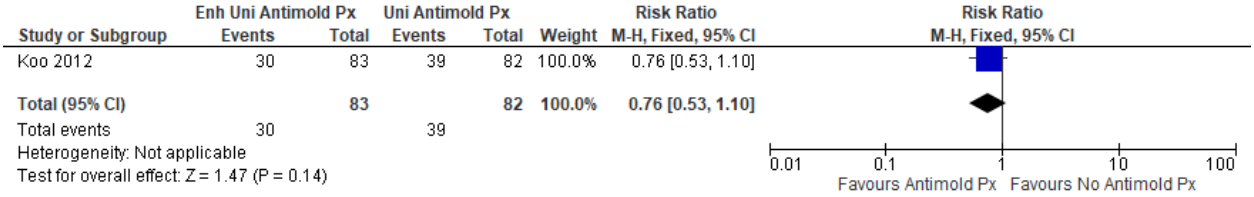


Figure A3.1.g: Graft rejection



Descriptive question: In lung transplant recipients, what is the baseline risk of invasive aspergillosis in patients not receiving anti-*Aspergillus* prophylaxis and which factors increase this risk?

Literature Search Strategy (last updated on April 1st, 2025)

PUBMED

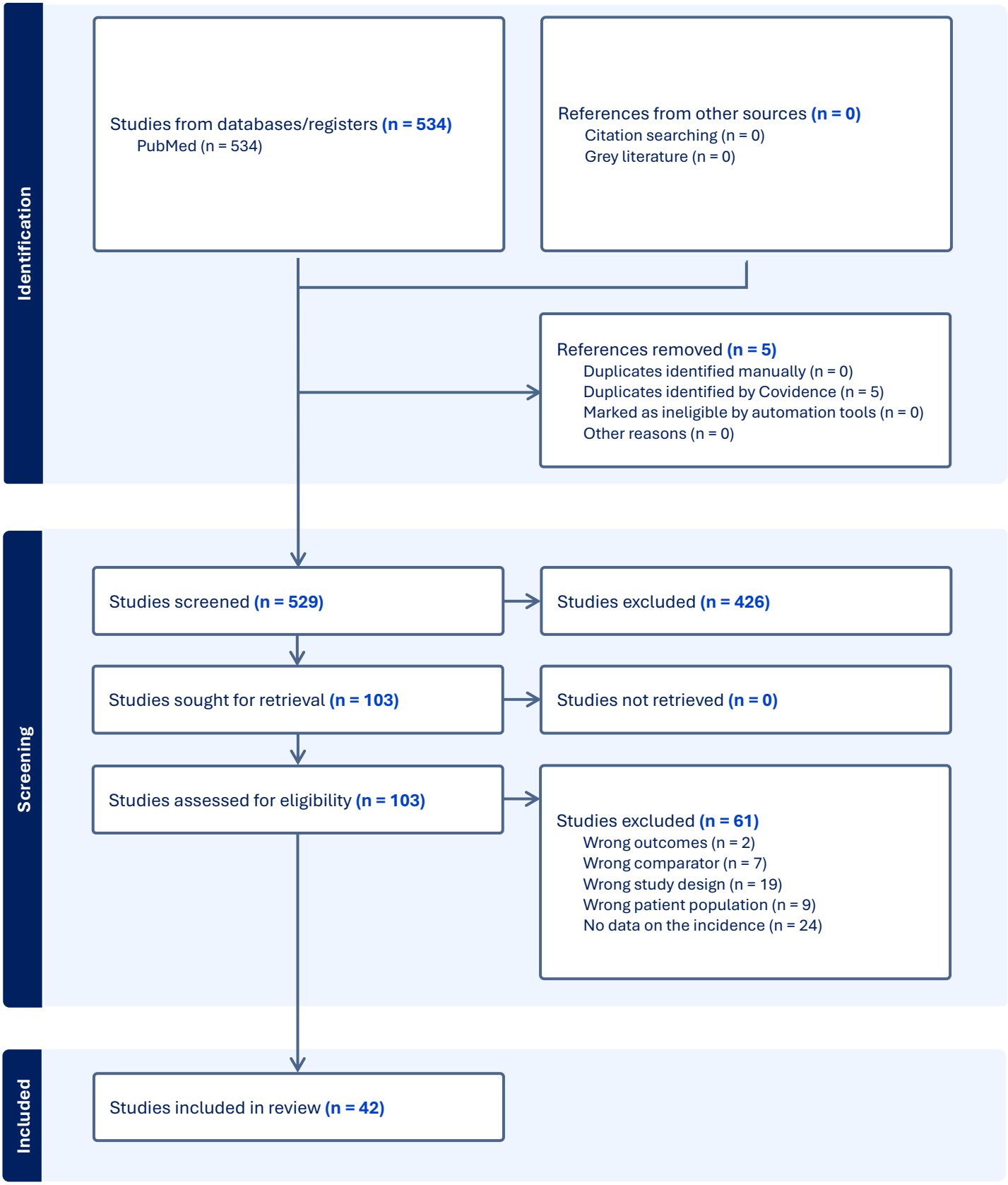
((((("invasive mold*") OR ("invasive mould*") OR ("invasive fung*") OR (aspergill*) OR (aspergillus) OR (aspergillosis)) OR (("anti-fungal*" OR "antifungal*" OR antimold* OR anti-mold* OR anti-mould* OR antimould* OR antiaspergill* OR anti-aspergill* OR Voriconazole OR Posaconazole OR Isavuconazole OR Amphotericin OR Echinocandin OR Caspofungin OR Micafungin OR Anidulafungin OR Itraconazole OR triazole OR azole) AND (prophyla*))

AND
("Lung Transplantation"[Mesh] OR "lung transplant*"))

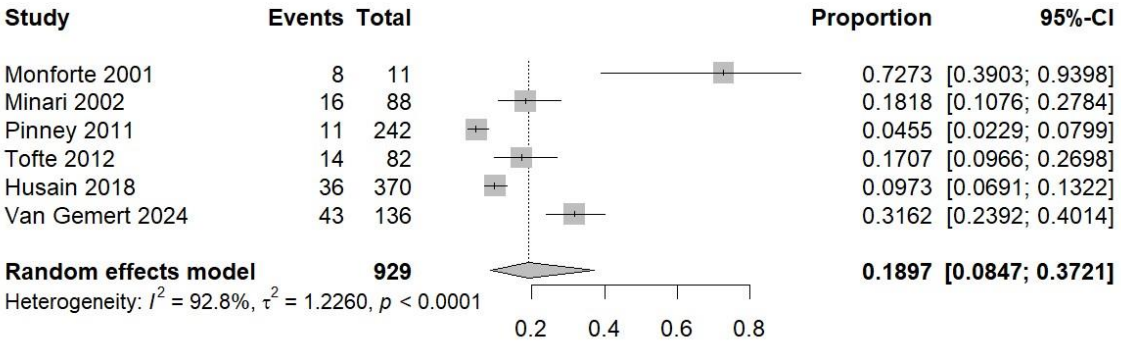
NOT
"Case Reports" [Publication Type] OR "Editorial" [Publication Type] OR "Comment" [Publication Type]

Limits: English; 2000-present
Search run on August 28th, 2023
Rerun on April 1st, 2025

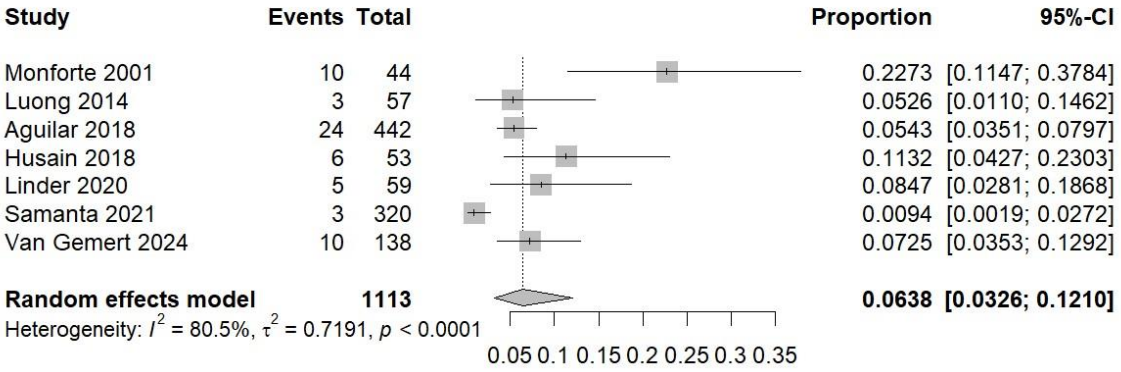
Supplementary Figure A4.1: PRISMA Flow diagram of study identification and selection (last updated on 1st April 2025)



Supplementary Figure A4.2: Forest plot of incidence of invasive aspergillosis in lung transplant recipients not receiving anti-*Aspergillus* prophylaxis

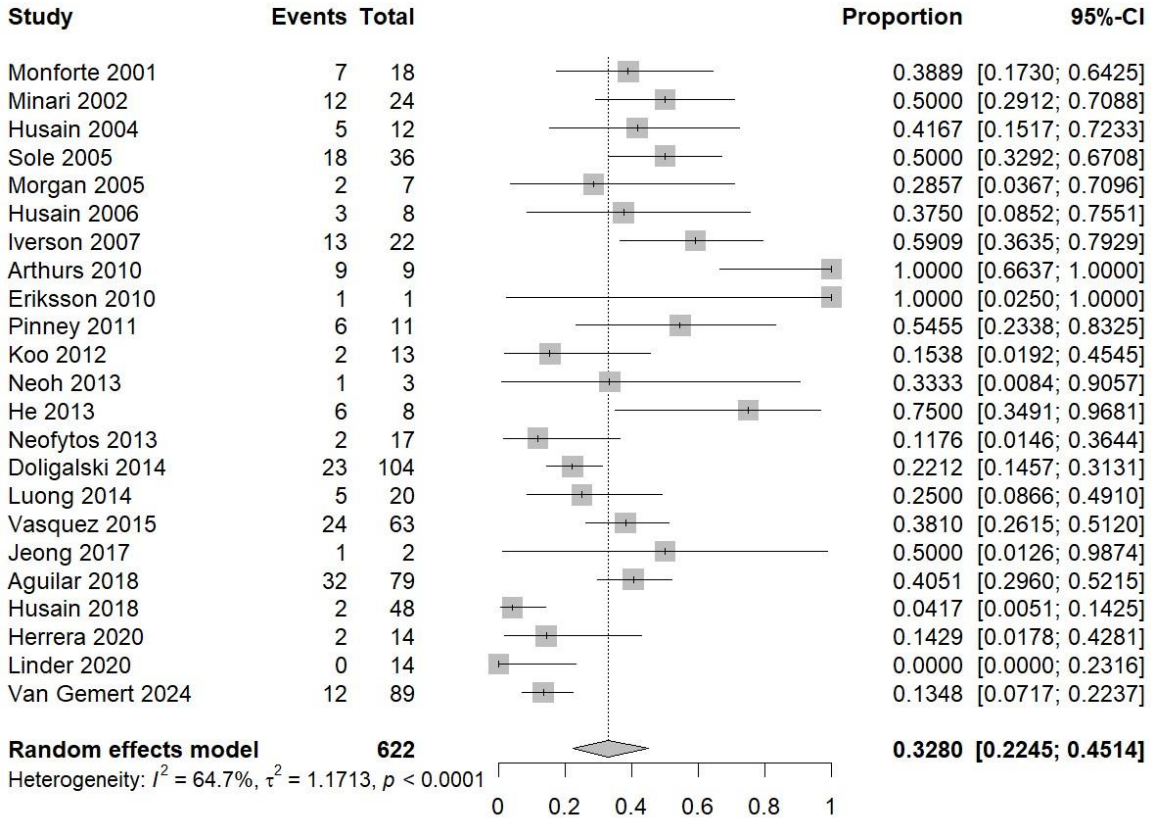


Supplementary Figure A4.3: Forest plot of incidence of breakthrough invasive aspergillosis in lung transplant recipients receiving anti-*Aspergillus* prophylaxis



Monteforte (2001) [1] documented a high breakthrough infection rate of 23% with aerosolized amphotericin B (AmB), although the baseline IA rate at that center was markedly elevated (73%). In contrast, Aguilar (2018) [2] reported an overall rate of 5.4%, though prophylactic regimens were heterogeneous, including itraconazole, voriconazole and aerosolized AmB. Notably, 88% (21/24) of breakthrough cases in Aguilar's study occurred with itraconazole or aerosolized AmB, whereas voriconazole use was associated with a much lower breakthrough incidence (0.9%). Linder (2020) [3] found an 8.5% breakthrough rate with low dose itraconazole (without therapeutic drug monitoring [TDM]). In contrast, Samanta (2021) [4] observed very low breakthrough rates with isavuconazole combined with inhaled AmB (0.7%), or voriconazole (1.3%), although TDM was not performed. Only one study met criteria for pre-emptive therapy: Husain (2018) [5] reported a breakthrough rate of 11.3% (6/53) using a culture- or GM-guided pre-emptive approach with voriconazole.

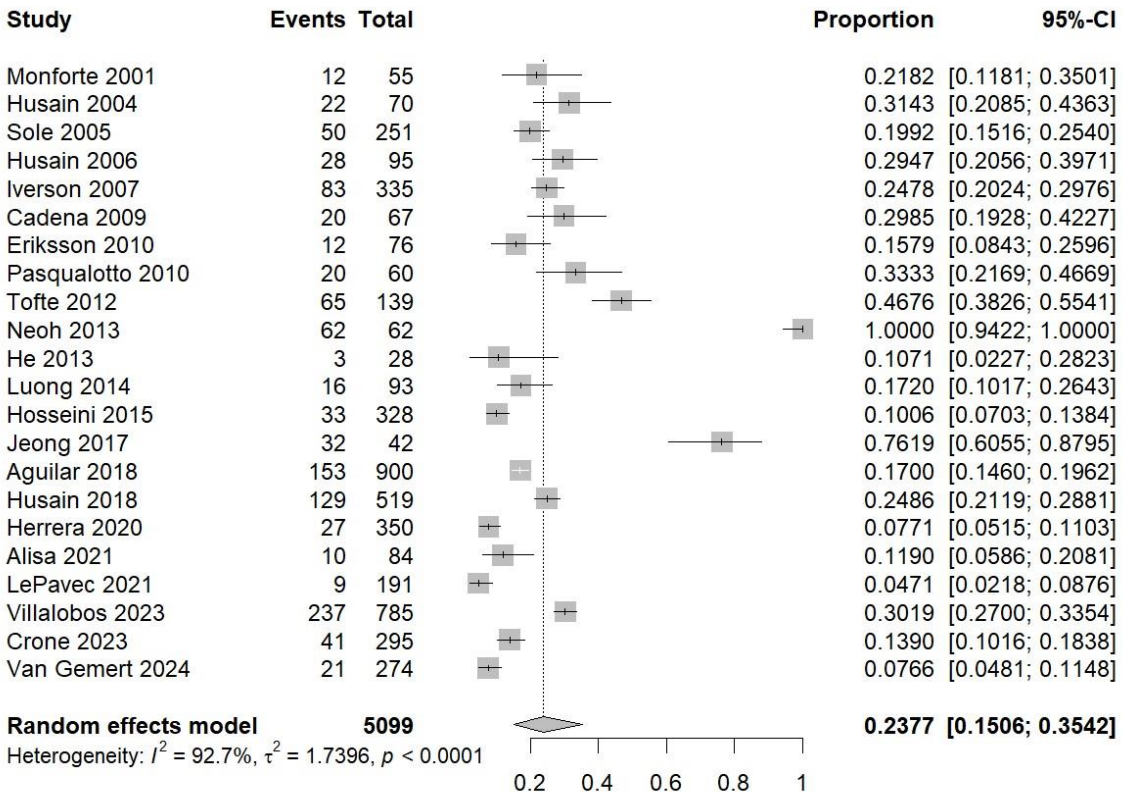
Supplementary Figure A4.4: Forest plot of mortality rate in lung transplant recipients with proven or probable invasive aspergillosis



The all-cause mortality rate among lung transplant recipients who developed IA was 33% (95% CI 0.22-0.45). Mortality outcomes among lung transplant recipients with proven or probable IA exhibit considerable variability across studies, influenced by differences in study design, follow-up duration, and antifungal strategies. Aguilar et al. (Canada, 2018) [2] reported the highest absolute mortality, with 32 deaths among 79 (40.5%) IA cases over four years of follow-up. Arthur et al. (USA, 2010) [6] documented 100% mortality (9/9) over five years, underscoring the potential lethality of IA in certain cohorts. Doligalski (USA, 2014) [7], Vasquez (USA, 2015) [8]and van Gemert (2025) [9] reported one-year mortality rates of 22% (23/104), 38% (24/63), and 13% (12/89), respectively. Conversely, studies such as Husain (Canada, 2018) [2] and Linder (USA, 2020) [3] reported significantly lower mortality rates (4.2% [2/48] and 0% [0/14], respectively), potentially reflecting improvements in patient selection, early diagnosis, and treatment practices.

Additional studies report varied mortality outcomes, often limited by unclear or inconsistent definitions of mortality timelines. For example, Eriksson (Finland, 2010) [10] and Neoh (Australia, 2013) [11] reported minimal events over a one-year follow-up, while Monteforte (Spain, 2001) [1] observed seven deaths among 18 IA cases, with a mean follow-up of 14 months. Iversen (Denmark, 2007) [12] notably reported a high mortality rate (13 deaths among 22 IA cases) in lung transplant patients treated with lipid formulation amphotericin followed by itraconazole in the 1990's and early 2000's, emphasizing the poor prognosis in this population historically. Other studies (e.g., Sole, Minari, and Pinney) [9, 13-15] lacked clearly defined mortality follow-up periods, limiting interpretability.

Supplementary Figure A4.5: Forest plot of the rate of *Aspergillus* colonization in lung transplant recipients



Risk factors for invasive mold infections

Additionally, two cohort studies by Baker et al. (2020) [16] and Huggins et al. (2023) [17] emphasized further clinical risk factors for IMI, including IA. Baker et al. found significant associations between IMI and prolonged post-operative mechanical ventilation, renal replacement therapy (RRT) during transplant hospitalization, post-operative extracorporeal membrane oxygenation (ECMO), female donor gender, diabetes mellitus, and primary graft failure from previous transplantation[16]. Similarly, Huggins et al. identified post-transplant RRT as a strong risk factor for early IMI (≤90 days post-transplant) and demonstrated that mold-active antifungal prophylaxis effectively reduced this risk. For late-onset IMI (91–365 days post-transplant), recent acute cellular rejection and post-transplant RRT remained significant risk factors, while female donor gender emerged as protective [17]. This discrepancy regarding the influence of donor gender between these studies highlights a complex and potentially multifactorial relationship requiring further clarification.

Supplementary Table A4.1: Evidence to decision framework

Desirable effects

How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ **Don't know**	Due to critical concerns regarding the risk of bias of the entire included evidence, unexplorable multiple causes of heterogeneity and lack of generalizability to current clinical practice, the panel concluded that the potential benefits of the different prophylactic strategies remain unknown.	

Undesirable effects

How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ **Varies** ○ Don't know	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 therapeutic drug monitoring (TDM), and 5) total duration of prophylaxis (duration of post-transplantation to life).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ **Don't know**		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	See Evidence Profile table	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ **Probably no important uncertainty or variability**	No studies identified. No patient representatives were identified for this section of the guideline.	The panel assumes that patients enrolled for lung transplant recipients would generally support interventions that would provide a favorable balance of benefits and harms.

○ No important uncertainty or variability		

Resources required

How large are the resource requirements (costs)?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Considering the unfavorable balance of effects, using universal anti-A*spergillus* prophylaxis would only add more direct costs. Daily costs (US$ per day) of anti-*Aspergillus* agents (average wholesale prices (AWP) versus acquisition costs (AC) in a single center, US November 2024):

New triazoles	Daily dose	Cost per day (US$)	
		AWP	AC
Voriconazole	200 mg (PO / IV)	$24 to 113 / 28 to 153	$2 / 83
Posaconazole	300 mg (PO / IV)	$22 to 234 / 19 to 38	$174 / 330
Isavuconazole	372 mg (PO / IV)	$270 / 459	$145 / 247

Old triazole	Daily dose	Cost per day (US$)	
		AWP	AC
Itraconazole	200 mg (PO solution / capsule)	$ 92 to 110 / 17 to 68	$20/ 8

Cost of antifungal drug (AmB) for aerosolized treatment

Aerosolized Amphotericin B	Typical doses	AWP product cost	Estimated cost (US$)		
			Per dose during intubation	Daily	For the first 3 months
Liposomal Amphotericin B	25 mg tiw	$188 per 50 mg vial		(given three times weekly)	$4,512
Amphotericin B lipid complex (ABLC)	50 mg weekly. Some study includes 100 mg X4 given during intubation	$135 per 50 mg (10 ml vial) $230 per 100 mg (20 ml vial)	$920	(given once weekly)	$2,540
Amphotericin B deoxycholate	20 mg three times daily. Some study includes 50 mg X4 given during intubation	$12 per 50 mg (10 ml vial)	$48	$36	$1,344

All AWP pricing data were extracted from the 2006 Drug Topics Redbook (Published by Medical Economics, Inc. (E):http://www.medec.com).

The prices presented are AWP for daily dose for generic brand of antifungal except for isavuconazole which generic formulations is not yet available. The AWP is used because it provides a standardized, readily available benchmark for drug pricing. However, AWP does not account for the various discounts and rebates pharmacies typically received from whole salters, thus likely represents an overestimation of drug costs. To give an example of drug cost from payer perspective, we display acquisition prices at a large academic

		center which have been adjusted for all rebates and/or price concessions. Note that costs are subject to change based on institutional contracts, local pricing, and drug availability, and the availability of generic formulation. Of note, ABLC was discontinued from manufacturing in August 2025, and pricing might no longer apply depending on market availability These direct costs are not including the costs associated with specific TDM nor other associated costs related to routine follow-up or administration of the prophylaxis. Costs associated with an episode of IA (either related to diagnosis, management or treatment): no recent data available. These direct costs are not including the costs associated with equipment (nebulizer purchase, cleaning), consumables (nebulizer cups, mouthpiece or masks, tubing), and supplies (sterile diluents or water, syringes, etc). Costs associated with an episode of IA (either related to diagnosis, management or treatment): no recent data available.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not applicable	

Cost-effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ **No included studies**		Considering the unknown balance of effects, the cost-effectiveness can't be assessed.

Summary of Judgments

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

Type of Recommendation				
Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

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)?

Population: Adult lung transplant recipients post-transplant period

Intervention

= Universal anti-*Aspergillus* prophylaxis with either echinocandins, triazoles, amphotericin B (IV or aerosolized) or itraconazole

Comparator:

= Universal anti-*Aspergillus* prophylaxis with either echinocandins, triazoles, amphotericin B (IV or aerosolized) or itraconazole

Outcomes (patient-important outcomes as per panel voting and reassess by subgroup)

Critical

-Increase in SAEs

Important

-Reduction in IA*** (rated as important rather than critical for choice of agents if benefits are similar and not influencing the decision-making process)

-Reduction in attributable mortality

-Reduction in mortality (all-cause)

-Increase in non-serious AEs

-Post-transplant colonization with *Aspergillus* (precursor (intermediary step) of late IA)

-Breakthrough IA (especially when considering different duration of prophylaxis)

-Increase in Invasive Mold Infection

-Graft rejection

Removed outcome

-Need to change antifungal therapy (not a good surrogate outcome of neither clinical efficacy nor adverse events since consisting of a composite outcome that was defined very heterogeneously between studies)

Outcomes not reported:

-Length of hospital stay, readmission, quality of life

-Increase in long term adverse events (e.g. CLAD with aerosolized AmB or cSCC with voriconazole)

Eligibility criteria for selection of the studies

Inclusion criteria:

- Patient population: Adults lung transplant recipients in post-transplant period
- Anti-*Aspergillus* prophylaxis
  - Echinocandins such as caspofungin, micafungin or anidulafungin
  - Triazoles such as posaconazole, voriconazole or isavuconazole
  - Amphotericin B (IV or aerosolized AmB)
  - Itraconazole (any formulation)
- Strategies:
  - Universal prophylaxis: all lung transplant recipients
- Intervention / Comparison
  - Universal vs Universal prophylaxis with different anti-*Aspergillus* agents
- Outcomes: Incidence of serious adverse events associated with the use of anti-*Aspergillus* prophylaxis
- Study design: RCTs and non-randomized comparative studies (i.e. observational studies)
- Year: published from 2000 up to present
- Language: English only

Exclusion criteria:

- Patient population:
  - Pediatric population
- Intervention / Comparator
  - Any comparison where the comparator group include a variety of different anti-*Aspergillus* and anti-yeast prophylaxis (without stratification by antifungal agent used)
- Study design
  - One-arm studies
  - Conference proceedings, abstracts, letters to the editor, comments

Between anti-mold triazoles

Supplementary Table B1.1: GRADE evidence profile

Sub-Question B1: In lung transplant recipients receiving anti-*Aspergillus* prophylaxis, should **Isavuconazole** be used rather than **Voriconazole**?

P: Adult lung transplant recipients
I: Isavuconazole (universal prophylaxis)
C: Voriconazole (universal prophylaxis)
Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isavuconazole prophylaxis	Voriconazole prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Invasive *Aspergillus* Infection (follow-up: 12 months)										MID*: at least 40 fewer per 1,000		
1	non-randomized studies	serious[a]	not serious	not serious	very serious[b]	none	4/144 (2.8%)	7/156 (4.5%)	**RR 0.62** (0.19 to 2.07)	**17 fewer per 1,000** (from 59 fewer to 25 more)	⨁◯◯◯ Very low	IMPORTANT
Breakthrough IA												
1	non-randomized studies	serious[a]	not serious	not serious	not serious	none	2/144 (1.4%)	2/156 (1.3%)	**RR 1.08** (0.15 to 7.59)	**1 more per 1,000** (from 25 fewer to 27 more)	⨁◯◯◯ Very low	IMPORTANT
Invasive Fungal Infection (follow-up: 12 months)												
1	non-randomized studies	serious[a]	not serious	not serious	very serious[b]	none	10/144 (6.9%)	7/156 (8.3%)	**RR 0.83** (0.38 to 1.84)	**14 fewer per 1,000** (from 74 fewer to 46 more)	⨁◯◯◯ Very low	IMPORTANT
Mortality (all-cause)										MID*: at least 20 fewer per 1,000		
1	non-randomized studies	serious[a]	not serious	not serious	very serious[c]	none	14/144 (9.7%)	18/156 (11.5%)	**RR 0.84** (0.44 to 1.63)	**18 fewer per 1,000** (from 88 fewer to 52 more)	⨁◯◯◯ Very low	IMPORTANT
Serious Adverse Events										MID*: at least 40 fewer per 1,000		
1	non-randomized studies	serious[a]	not serious	not serious	not serious	none	15/138 (10.9%)	54/152 (35.5%)	**RR 0.31** (0.18 to 0.52)	**247 fewer per 1,000** (from 339 fewer to 154 fewer)	⨁◯◯◯ Very low	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **RR:** risk ratio
*MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)

Explanations

a. The included study was designed as pre/post-intervention studies, and is considered at serious risk of bias (ROBINS-I) mainly due to potential residual confounding and selection bias (potential unmeasured changes in enrolled participants and changes in standard of care over time as well different use of aerosolized AmB between the 2 groups (40% in the "before" group vs 100% in the "after" group) which likely results in overestimating the potential benefit of prophylaxis with isavuconazole.
b. The confidence interval includes both moderate benefits and trivial harms, thus providing evidence of very serious imprecision around the estimates of effect.
c. The confidence interval includes both large benefits and trivial harms, thus providing evidence of very serious imprecision around the estimates of effect.

References

1. Samanta P and al. Isavuconazole Is as Effective as and Better Tolerated Than Voriconazole for Antifungal Prophylaxis in Lung Transplant Recipients. Clin Infect Dis. 2021 Aug 2;73(3):416-426.

Supplementary Table B1.2: Characteristics of the included study

Study *(lead author, year of publication, location)*	**Population** *(type of patients, year of enrollment, n randomized, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(Newer triazoles anti-Aspergillus prophylaxis, total duration)*	**Comparator** *(Voriconazole anti-Aspergillus prophylaxis, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
Samanta 2020 Pennsylvania, USA Single Center	All lung transplant recipients receiving at least 5 days of prophylaxis Before: 2013-2015 After: 2015-2018 N = 300 (of which, 164 were double lung) Age (median): 58y in Isavuconazole group vs 60y in Voriconazole group Exclusion: patients receiving other prophylaxis, <5 days of prophylaxis, death within 1 month and active IPA in donor lung	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IFI Routine bronchoscopy with biopsies with cultures:14 days after transplant, then every 2 months during the first year.	The entire cohort was considered at high-risk of invasive Mucorales infection	Baseline risk for IA: **Voriconazole prophylaxis: 4.5%** Baseline risk for mortality: **Voriconazole prophylaxis:** 11.5%	Isavuconazole 372 mg IV/PO q8h X 6 doses then 372 mg PO daily + aerosolized d-AmB Duration of prophylaxis: 3 to 4 months (median received: 3.1 months) **TDM not systematically performed**	Voriconazole 200 mg IV 12h, then 200 mg PO BID +/- aerosolized d-AmB Duration: 3 to 4 months (median received: 3.4 months) **TDM not systematically performed**	EORTC/MSG 2020 Duration of follow-up: 12 months

Legend
AFT: antifungal therapy
BAL: bronchoalveolar lavage
BD: twice a day
d-AmB: amphotericin B deoxycholate
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
GM: Galactomannan
IA: invasive aspergillosis
IPA: Invasive pulmonary aspergillosis
IV: parenteral
NR: not reported
PCR: Polymerase chain reaction
PO: oral
TDM: Therapeutic Drug Monitoring
TDS: three times a day

High-Risk of IA (see our criteria for targeted anti-*Aspergillus* prophylaxis)
*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.

Supplementary Table B1.3: Summary of Risk of bias of included study

Study	Overall Risk of bias	Confounding	Selection of participants into the study	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result
Samanta 2020	**Serious**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 5-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration are clearly defined.	Administration of aerosolized amphotericin B as part of the universal prophylaxis was not symmetrical (40% in the "before" vs "100% in the "after") and likely results in overestimating the potential benefit Isavuconazole prophylaxis.	No evidence of missing data.	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported and similar in both groups.	The outcome measurement and analyses are consistent with the Methods.

Legend
IA: invasive aspergillosis

Risk of bias judgment

Low	
Moderate	
Serious	
Critical	
No information	

Supplementary Figures B1.1: Forest plots for each patient-important outcome

Figure B1.1.a: Invasive aspergillosis (follow-up: 12 months)

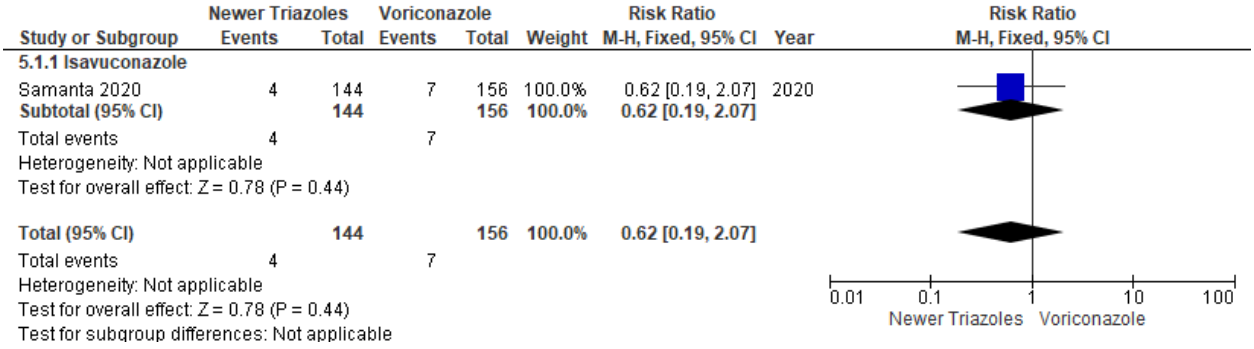


Figure B1.1.b: Breakthrough IA

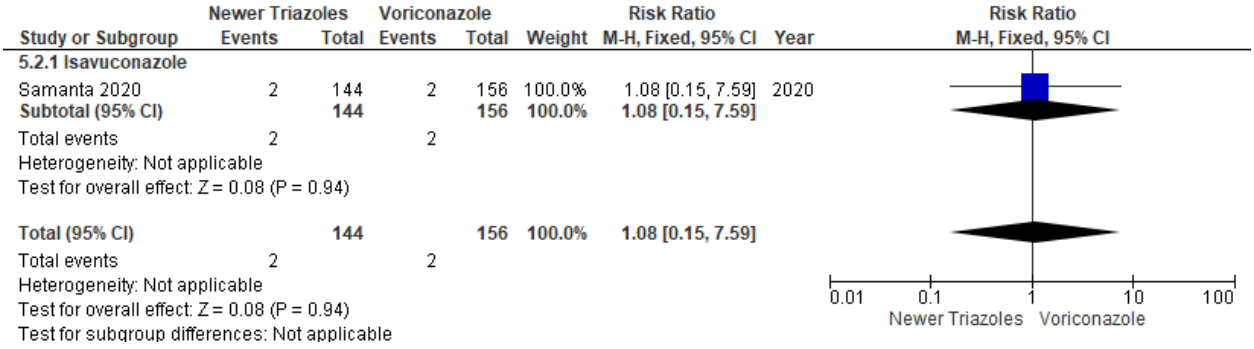


Figure B1.1.c: Invasive fungal infection (follow-up: 12 months)

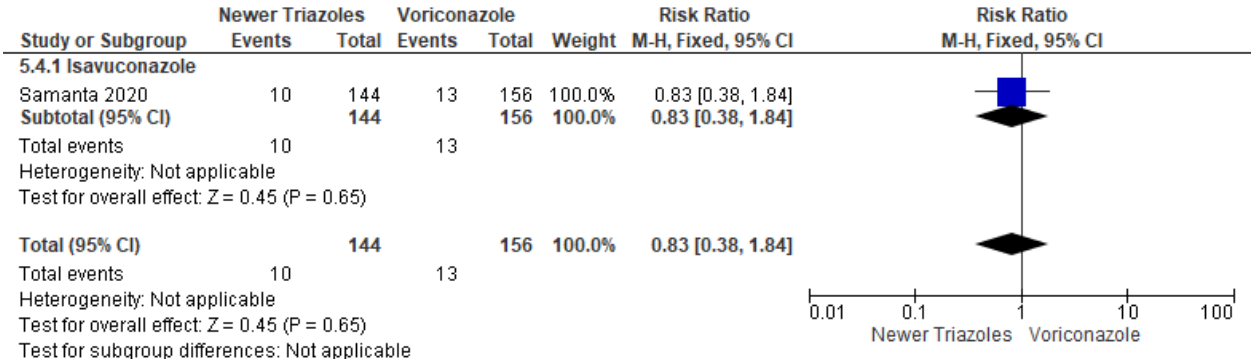


Figure B1.1.d: Mortality (all-cause)

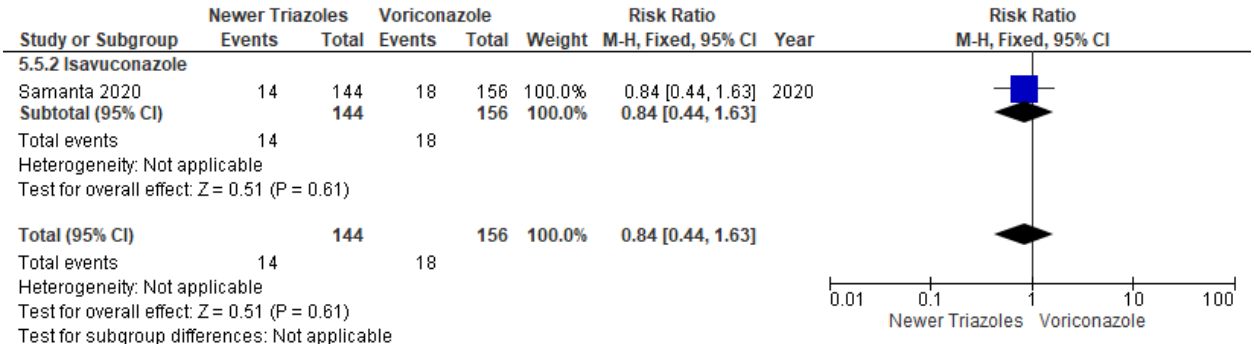
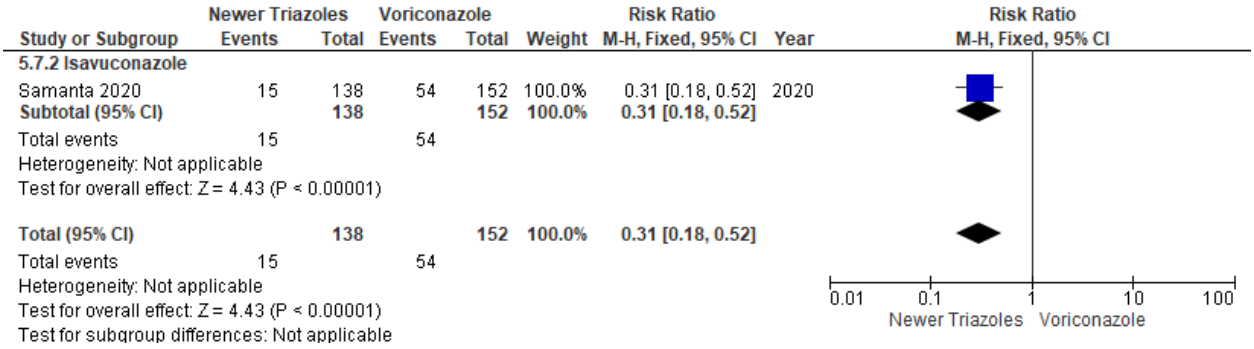


Figure B1.1.e: Serious adverse events



Other evidence comparing anti-mold triazoles

Direct comparisons between Posaconazole vs Voriconazole

Two studies were initially considered (Ju 2022 and Pennington 2022) but excluded since the comparison of interest was biased (i.e. selection bias due to the difference in indications for Voriconazole and Posaconazole which influenced their respective adverse event profiles).

Supplementary Table B1.4: Indirect comparisons between anti-mold triazoles

Azoles/Study	Premature discontinuation	Hepatotoxicity	Neurotoxicity (including visual side effects)	Skin cancer (include both indications for prophylaxis and therapy)	Drug-drug interactions
Voriconazole					
Kuklinski 2023 [18]	-	-	-	16.5% (SCC) 4.5% (KC)	-
Ju 2022 [19]	9.9%	Elevated total bilirubin 4.9% Elevated liver enzymes 3.5%	2.1%	-	1.4% (tacrolimus toxicity)
Truong 2022 [20]	31.2%	-	-	-	-
Crone 2022 [21]	-	Elevated ALT 30% Elevated ALP 42%	-	-	Low CNI episode related to voriconazole discontinuation 37% Acute rejection related to low CNI episode 40% High creatinine related to high CNI episode 4%
Whitmore 2021 [22]	-	16.6% (need to switch therapy)	25% (visual side effects requiring azole change)	50% (photosensitivity requiring azole change)	-
Samanta 2021 [4]	41% (18% due to hepatotoxicity and 9% due to neurotoxicity)	18% hepatotoxicity led to discontinuation	9% neurotoxicity led to discontinuation	-	-
Pennington 2019 [23]	68.8%	-	-	-	3.9%
Cadena 2009 [24]	-	34% (all 34% required drug discontinuation)	-	-	-
D'Arcy 2020* [25]	-	-	-	aHR for SCC (compared to those without voricoanzole exposure) 1.09 (95%CI, 0.9-1.31) for 1-3 months, 1.42 (95%CI, 1.16-1.73) for 4-7 months, 2.04 (95%CI, 1.67-2.50) for 8-15 months, and 3.05 (95% CI, 2.37-3.91) for > 15 months of voriconazole exposure	-
Way 2020* [26]	-	-	-	IRR for SCC (compared to those without voriconazole exposure) 4.5 (95%CI, 1.3-15.3) for voriconazole exposure at least 4 months	-
Elnahas 2019* [27]	-	-	-	aOR for SCC 2.02 (95%CI, 1.04-3.93) for voriconazole exposure at least 100 days, compared to voriconazole exposure < 100 days	-
Hamandi 2018* [28]	-	-	-	aHR for SCC (compared to no azole exposure), 0.45 (95%CI, 0.1-2.1) for voriconazole exposure 1-90 days; 2.23 (95% CI, 0.26-2.49) for voriconazole exposure 91-180 days; 3.25 (95%CI, 1.59-7.79) for	-

				voriconazole exposure > 180 days	
Feist 2012* [29]	-	-	-	aOR 1.8 (95%, 1.3-2.6) for skin cancer and 2.1 (95%CI, 1.4-3.1) for aggressive skin cancer from voriconazole duration (years)	-
Posaconazole					
Kuklinski 2023* [18] (unspecified form)	-	-	-	7.1% (SCC) 7.8% (KC)	-
Ju 2022 [19] (oral suspension)	7.5%	0%	0%	-	0% (tacrolimus toxicity)
Truong 2022 [20] (delayed-release tablet)	3.7%	-	-	-	-
Whitmore 2021 [22] (delayed-release tablet)	-	-	1.3%	-	-
D'Arcy 2020* [25] (unspecified)	-	-	-	aHR for BCC (compared to those without posaconazole exposure) 1.55 (95%CI, 1.00-2.41)	-
Lewis 2020 [30] (unspecified form)	3.4% (due to drug-drug interaction leading to hepatotoxicity)	-	-	-	-
Pennington 2019 [23] (unspecified form)	18.3%		-	-	0%
Isavuconazole					
Truong 2022 [20]	9.8%	-	-	-	-
Samanta 2021 [4]	30% (6% due to hepatotoxicity)	-	-	-	-
Lewis 2020 [30]	0%	-	-	-	-
Itraconazole					
Truong 2022 [20]	5.3%				
Whitmore 2021 [22] (SUBA®-itraconazole)	-	0%	0%	-	-
D'Arcy 2020* [25]	-	-	-	aHR for BCC (compared to those without itraconazole exposure) 1.74 (95%CI, 1.27-2.37)	
Pennington 2019 [23]	61.8%	-	-	-	2.9%
Cadena 2009 [24]	-	0%	-	-	-

Legend: aHR: adjusted hazard ratio; BCC: basal cell carcinoma; CI: confidence interval; CNI, calcineurin inhibitor; IRR: incidence rate ratio; KC: keratinocyte cancer; SCC: squamous cell carcinoma.

*Data for skin cancer from azole exposure were derived from both treatment and prophylactic indications.

Stewardship considerations for prophylaxis with anti-mold triazoles

Voriconazole

-There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi.
-The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis, especially non-*C. albicans* species (especially *C. glabrata*), is not clear as only limited studies includes data on antifungal susceptibility in their report.
-The burden of azole-resistant *Aspergillus* spp. associated with mold-active azole prophylaxis was not calculable but may have geographic restrictions that limit visibility.
-One report noted of breakthrough infection of *Rhizopus*, *Alternaria*, and *Fusarium* during voriconazole mold-active azole prophylaxis (Husain 2006) [31].

Isavuconazole

-There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi.
-The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis, especially non-*C. albicans* species (especially *C. glabrata*), is not clear as only limited studies includes data on antifungal susceptibility in their report.
-The burden of azole-resistant *Aspergillus* spp. associated with mold-active azole prophylaxis was not calculable but may have geographic restrictions that limit visibility.

Posaconazole

-There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi.
-The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis, especially non-*C. albicans* species (especially *C. glabrata*), is not clear as only limited studies includes data on antifungal susceptibility in their report.
-The burden of azole-resistant *Aspergillus* spp. associated with mold-active azole prophylaxis was not calculable but may have geographic restrictions that limit visibility.

Itraconazole

-There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi.
-The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis, especially non-*C. albicans* species (especially *C. glabrata*), is not clear as only limited studies includes data on antifungal susceptibility in their report.
-The burden of azole-resistant *Aspergillus* spp. associated with mold-active azole prophylaxis was not calculable but may have geographic restrictions that limit visibility.

Between aerosolized amphotericin B formulations

Supplementary Table B2.1: GRADE evidence profile

Subquestion B2: In lung transplant recipients receiving anti-*Aspergillus* prophylaxis, should **lipid formulation of aerosolized Amphotericin B (L-AmB or ABLC)** be used rather than **aerosolized Amphotericin B deoxycholate (d-AmB)**?

P: Adult lung transplant recipients
I: Lipid formulation of aerosolized AmB
C: Aerosolized d-AmB
Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lipid formulation aerosolized AmB prophylaxis	Aerosolized AmB deoxycholate prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis										**MID*:** at least 40 fewer per 1,000		
ABLC (follow-up: 2 months)												
1	randomized studies	not serious	not serious	not serious	very serious[a]	none	1/51 (2.0%)	1/49 (2.0%)	**RR 0.96** (0.06 to 14.94)	**1 fewer per 1,000** (from 56 fewer to 54 more)	⨁⨁◯◯ Low	IMPORTANT
L-AmB (follow-up: 6 to 12 months)												
3	non-randomized studies	serious[b]	not serious	not serious	not serious	none	2/144 (1.4%)	4/100 (4.0%)	**RR 0.46** (0.11 to 1.98)	**22 fewer per 1,000** (from 36 fewer to 39 more)	⨁◯◯◯ Very low	IMPORTANT
Breakthrough IA												
ABLC												
1	randomized studies	not serious	not serious	not serious	very serious[a]	none	1/51 (2.0%)	1/49 (2.0%)	**RR 0.96** (0.06 to 14.94)	**1 fewer per 1,000** (from 56 fewer to 54 more)	⨁⨁◯◯ Low	IMPORTANT
L-AmB												
2	non-randomized studies	serious[b]	not serious	not serious	serious[c]	none	2/133 (1.5%)	2/82 (2.4%)	**RR 0.47** (0.07 to 3.25)	**13 fewer per 1,000** (from 23 fewer to 55 more)	⨁◯◯◯ Very low	IMPORTANT
Invasive Fungal Infection												
ABLC (follow-up: 2 months)												
1	randomized studies	not serious	not serious	not serious	very serious[a]	none	6/51 (11.8%)	7/49 (14.3%)	**RR 0.82** (0.30 to 2.28)	**25 fewer per 1,000** (from 157 fewer to 107 more)	⨁⨁◯◯ Low	IMPORTANT
L-AmB (follow-up: 6 to 12 months)												
2	non-randomized studies	serious[b]	not serious	not serious	very serious[d]	none	1/40 (2.5%)	2/51 (3.9%)	**RR 0.47** (0.07 to 3.25)	**7 fewer per 1,000** (from 35 fewer to 210 more)	⨁◯◯◯ Very low	IMPORTANT
Serious Adverse Events										**MID*:** at least 40 fewer per 1,000		
ABLC												
1	randomized studies	not serious	not serious	not serious	very serious[a]	none	3/51 (5.9%)	6/49 (6.4%)	**RR 0.48** (0.13 to 1.82)	**64 fewer per 1,000** (from 176 fewer to 49 more)	⨁⨁◯◯ Low	CRITICAL
L-AmB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lipid formulation aerosolized AmB prophylaxis	Aerosolized AmB deoxycholate prophylaxis	Relative (95% CI)	Absolute (95% CI)		
3	non-randomized studies	serious[b]	not serious	not serious	very serious[a]	none	4/144 (2.8%)	12/100 (12.0%)	**RR 0.43** (0.10 to 1.92)	**68 fewer per 1,000** (from 108 fewer to 110 more)	⨁◯◯◯ Very low	CRITICAL
Dyspnea												
ABLC												
1	randomized studies	not serious	not serious	not serious	serious[e]	none	1/47 (2.1%)	9/47 (19.1%)	**RR 0.11** (0.01 to 0.84)	**170 fewer per 1,000** (from 290 fewer to 50 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
L-AmB												
3	non-randomized studies	serious[b]	serious[f]	not serious	very serious[a]	none	14/144 (9.7%)	18/100 (18.0%)	**RR 0.75** (0.25 to 2.27)	**45 fewer per 1,000** (from 135 fewer to 229 more)	⨁◯◯◯ Very low	IMPORTANT
Cough												
ABLC												
1	randomised studies	not serious	not serious	not serious	very serious[g]	none	1/47 (2.1%)	5/47 (10.6%)	**RR 0.20** (0.02 to 1.65)	**85 fewer per 1,000** (from 182 fewer to 12 more)	⨁⨁◯◯ Low	IMPORTANT
L-AmB												
3	non-randomized studies	serious[b]	not serious	not serious	serious[c]	none	23/144 (16.0%)	14/100 (14.0%)	**RR 0.75** (0.25 to 2.27)	**17 fewer per 1,000** (from 71 fewer to 83 more)	⨁◯◯◯ Very low	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **RR:** risk ratio; ABLC: amphotericin B lipid complex; L-AmB: liposomal amphotericin B; d-AmB: amphotericin B deoxycholate
*MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)

Explanations

a. The boundaries of the confidence interval cross the decision threshold (minimal important difference) for both important benefit and important harm, thus providing evidence of very serious imprecision.
b. All 3 studies were designed as pre/post-intervention studies, and they were all considered at serious risk of bias (ROBINS-I) mainly due to potential residual confounding and selection bias (potential unmeasured changes in enrolled participants and changes in standard of care overtime).
c. The confidence interval includes both trivial benefits and small but important harms, thus providing evidence of serious imprecision around the estimates of effect.
d. The confidence interval includes both trivial benefits and large harms, thus providing evidence of very serious imprecision around the estimates of effect.
e. The upper boundary of the confidence interval crosses the decision threshold (minimal important difference) for important benefit à, thus providing evidence of serious imprecision.
f. Statistical significant noted in the meta-analysis (I2=58%, p-value=0.10). The heterogeneity between studies is likely related to various definition of dyspnea used in each individual study.
g. The confidence interval includes both large benefits and trivial harms, thus providing evidence of very serious imprecision around the estimates of effect.

References

1. Drew RH et al. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung transplant recipients. Transplantation. 2004 Jan 27;77(2):232-7.
2.Umemura K and al. Comparison of the safety and cost-effectiveness of nebulized liposomal amphotericin B and amphotericin B deoxycholate for antifungal prophylaxis after lung transplantation. Journal of Infection and Chemotherapy 30 (2024) 741-5.

3. Monforte V and al. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for *Aspergillus* infection prevention in lung transplantation. J Heart Lung Transplant. 2010 May;29(5):523-30.
4. Lowry CM and al. Safety of aerosolized liposomal versus deoxycholate amphotericin B formulations for prevention of invasive fungal infections following lung transplantation: a retrospective study. Transpl Infect Dis. 2007 Jun;9(2):121-5.

Supplementary Table B2.2: Characteristics of the included studies

Study *(lead author, year of publication, location)*	**Population** *(type of patients, year of enrollment, n randomised, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(anti-Aspergillus prophylaxis with lipid formulation of aerosolized AmB, total duration)*	**Comparator** *(anti-Aspergillus prophylaxis with d-AmB, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
Aerosolized ABLC vs d-AmB							
Drew 2004 **North Carolina, US** Single Center	Adult lung or heart-lung transplant recipients 1999-2002 N = 100 (16 single lung, 81 double lungs, 1 heart-lung) Age (median): 50y aerosolized ABLC group vs 52 aerosolized d-AmB group Exclusion: pregnant or lactating women, patients with hypersensitivity to AmB or liposomal preparations, those unwilling or unable to comply with aerosolized drug administration, documented prior active IFIs (excluding colonization), mycetomas, or concomitant systemic antifungal therapy	Randomized controlled trial, double-blind Sequential assignment computer-generated randomization 1:1 Intent-to-Treat analysis Descriptive statistic (no sample size calculation) Primary outcome measures: (1) incidence of study drug intolerance requiring treatment discontinuation and (2) number of subjects experiencing one or more adverse events. Funding: This project was supported by an unrestricted educational grant from Elan Pharmaceuticals (which was manufacturing ABLC at the time).	No stratification for risk of IA or IFI	Baseline risk for IA (in the d-AmB group): 2.0% Mortality rate in the entire cohort: 25.8%	Aerosolized ABLC 100 mg daily x 4 days, then once a week X 7 weeks (total of 11 doses) Duration received: 35 days (range 0 to 58 days) Number of treatments received: 6.7 +/- 2.3	Aerosolized d-AmB 50mg daily x 4 days, then once a week X 7 weeks (total of 11 doses) Duration received: 39 days (range 1 to 56 days) Number of treatments received: 6.8 +/- 2.7	IFI definitions adapted from Ascioglu 2002 Duration of follow-up: 2 months after initiation of study drug administration Attrition was symmetrical and frequent because the duration for the study drug administration (not total prophylaxis duration) was determined largely on the logistics of patients likely returning to their local care providers which would limit study-related data collection and study drug administration.
Aerosolized L-AmB vs d-AmB							
Umemura 2024 Kyoto, Japan Single Center	All lung transplant recipients Before: 2021-2022 After: 2022-2023 N= 62 (45 double lung, 17 single lung) Age (median): 44y Exclusion: NR	Before – after retrospective cohort study Primary outcomes: Efficacy on IFI at 6 months and safety evaluations during or immediately after inhalation	No stratification for risk of IA or IFI	Baseline risk for IA: d-AmB 3.3% Baseline risk for mortality: NR	Aerosolized L-AmB 25mg (adults) or 10mg (children under 20kg) three doses/ week with oral itraconazole (doses not reported but TDM performed) Duration of prophylaxis with aerosolized L-AmB: until discharge (median received:53 days, ranging from 32-193)	Aerosolized d-AmB 5mg TDS with oral itraconazole (doses not reported but TDM performed) Duration of prophylaxis with aerosolized d-AmB: until discharge (median received:42 days, ranging from 5-148 days)	Defined as: Fungal infections were regularly monitored using chest radiography, computed tomography, sputum culture, and serum β-(1,3)-D glucan and *Aspergillus* galactomannan antigens Duration of follow-up: 6 months

Monforte 2010 Barcelona, Spain Two Centers	All lung transplant recipients Before: 2000-2001 After: 2003-2005 N = 153 (48 single lung, 101 double lung, 4 heart-lung) Age (median): 48y in L-AmB group vs 51 in d-AmB group Exclusion: less than 18 years, died within 24 hours of transplantation	Before – after retrospective cohort study Primary outcomes: Efficacy on IA at 12 months	No stratification for risk of IA or IFI	Baseline risk for IA: d-AmB 4.1% Baseline risk for mortality: d-AmB 30.6%	Aerosolized L-AmB 25 mg 3 times/ week X 60 days, then 25 mg once a week between 60 and 180 days, and 25 mg once every 2 weeks for life (median received: NR)	Aerosolized d-AmB 6mg TDS x 120 days, then 6mg daily for life (median received: NR)	*Aspergillus* infection was defined as invasive if either: 1. Ulcerative tracheobronchitis if bronchial biopsy and/or bronchoscopy findings of necrotic ulcers or pseudomembrane in the anastomosis or in the tracheobronchial tree that disappeared after treatment. 2. Invasive pulmonary aspergillosis if evidence of tissue damage on lung histopathology or radiological signs of IA. Duration of follow-up: 12 months
Lowry 2007 Massachusetts, US Single Center	All lung transplant recipients N = 38, of which 9 received both agents (26 single lung, 12 double lung) 2002-2004 (before, during and after d-AmB shortage) Age (median): 58y in L-AmB group vs 58 in d-AmB group Exclusion: records missing	Before – after retrospective cohort study Primary outcomes: Safety and tolerability	No stratification for risk of IA or IFI	Baseline risk for IA: d-AmB 5.6% Baseline risk for mortality: NR	Aerosolized L-AmB 20 mg BD (median received: 24 days, range from 5 5o 128 days))	Aerosolized d-AmB 10mg BD (median received: 20 days, range from 4 to 68 days))	IA was not defined Duration of follow-up: NR

Legend
ABLC: amphotericin B lipid complex
AFT: antifungal therapy
BAL: bronchoalveolar lavage
BD: twice a day
d-AmB: amphotericin B deoxycholate
GM: Galactomannan
IFI: invasive fungal infection
IA: invasive aspergillosis
IV: parenteral
L-AmB: liposomal amphotericin B
NR: not reported
PCR: Polymerase chain reaction
PO: oral
TDM: Therapeutic Drug Monitoring
TDS: three times a day

High-Risk of IA (see our criteria for targeted prophylaxis)
*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.

Supplementary Tables B2.3: Summary of risk of bias of included studies

Study (randomized controlled trial) *(lead author, year of publication, name of trial, countries)*	**Random sequence generation** (selection bias)	**Allocation concealment** (selection bias)	**Blinding of participants and personnel** (performance bias)	**Blinding of outcome assessment** (detection bias)	**Incomplete outcome data** (attrition bias)	**Selective reporting** (reporting bias)	**Other bias** (e.g. sources of funding)
Drew 2004 **North Carolina, US** Single Center	Low RoB -Sequential assignment computer-generated randomization 1:1 -Comparison of patients' characteristics at baseline seems appropriate but small sample size	Unclear RoB -Not reported	Low RoB -Double-blind	High RoB -Double-blind	Unclear RoB -Attrition was symmetrical and frequent due to the logistical issues unrelated to the comparison of interest in this study.	Low RoB	Low RoB -Industry-funded but through an unrestricted educational grant
Legend: RoB: risk of bias							

Study (non-randomized study)	**Overall Risk of bias**	**Confounding**	**Selection of participants into the study**	**Classification of interventions**	**Deviation from intended interventions**	**Missing data**	**Measurement of outcomes**	**Selection of the reported result**
Umemura 2024	**Serious**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	Selection bias is possible due to potential changes in enrolled participants over time (i.e. over a 2-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration are clearly defined.	Administration of itraconazole was administered in both groups (except for 2 patients in d-AmB group due to death, and 3 patients in the L-AmbB group due to prior IA treated with Voriconazole) potentially overestimating the potential benefit of the L-AmB; nevertheless, this is unlikely to influence measured adverse events.	No evidence of missing data.	Diagnosis of IA was not based on standard definitions and diagnostic interventions were not clearly reported, this is unlikely to influence measured adverse events.	The outcome measurement and analyses are consistent with the Methods.
Monforte 2010	**Serious**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 5-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care).	Intervention status and planned duration are clearly defined.	Patients identified as being colonized with *Aspergillus* were switched to systemic antifungals (L-AmB 5/104 (4.8%) vs d-AmB 1/49 (2.0%)) potentially overestimating the potential benefit of the L-AmB; nevertheless, this is unlikely to influence measured adverse events.	No evidence of missing data.	Diagnosis of IA was based on standard definitions and diagnostic interventions were clearly reported.	The outcome measurement and analyses are consistent with the Methods.
Lowry 2007	**Serious**	Possible residual confounding is expected due to unmeasured and uncontrolled factors due to the study design (such as environmental or practice changes potentially influenced by the implementation of the intervention and that could influence the	Selection bias is possible due to potential changes in enrolled participants over time (i.e. over a 2-year period, participants in the before vs after the intervention may have differed due to	Intervention status and planned duration seem to be directly related to the d-AmB shortage but not detailed when both L-AmB vs d-AmB were available.	Unclear	Missing data is likely minimal.	Diagnosis of IA was not defined, and diagnostic interventions were not clearly reported, this is unlikely to influence measured adverse events.	The outcome measurement and analyses are consistent with the Methods.

		outcomes (e.g. modifying the incidence of IA due to breakthrough/ resistance in the post-intervention period)	unmeasured changes in standard of care).					

Legend:
d-AmB: amphotericin B deoxycholate
IA: invasive aspergillosis
L-AmB: liposomal amphotericin B,

Risk of bias judgment

Low	
Moderate	
Serious	
Critical	
No information	

Supplementary Figures B2.1: Forest plots for each patient-important outcome

Figure B2.1.a: Invasive aspergillosis (follow-up: 2 to 12 months)

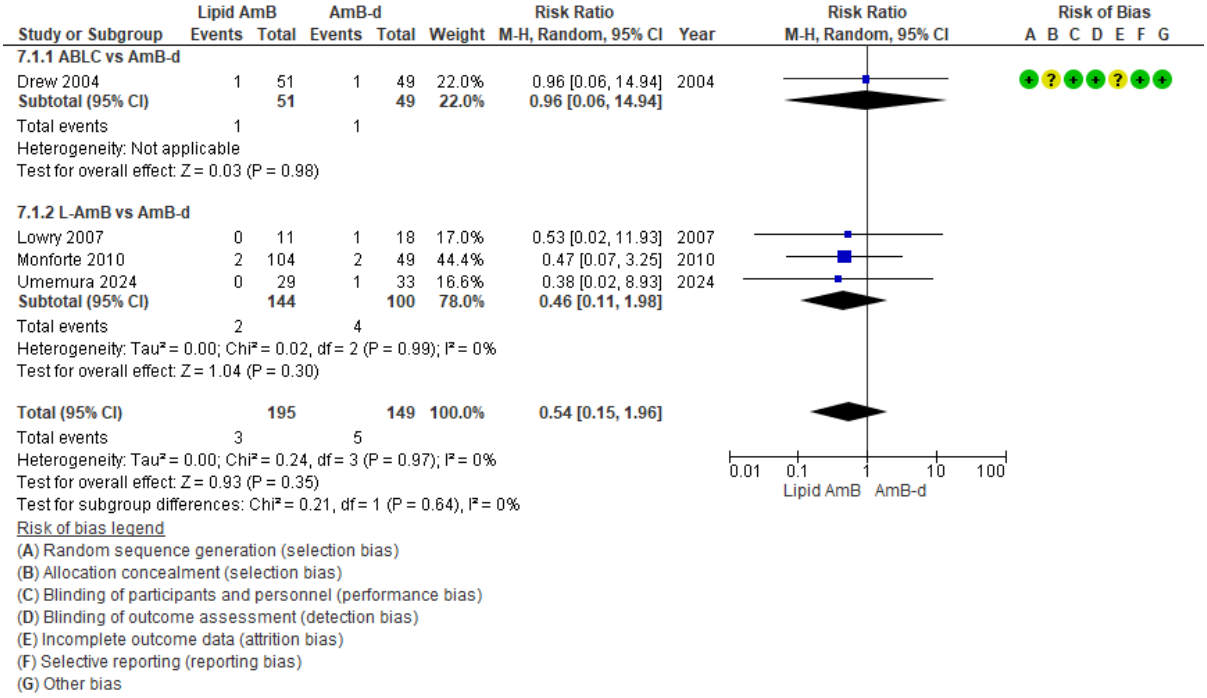


Figure B2.1.b: Breakthrough IA

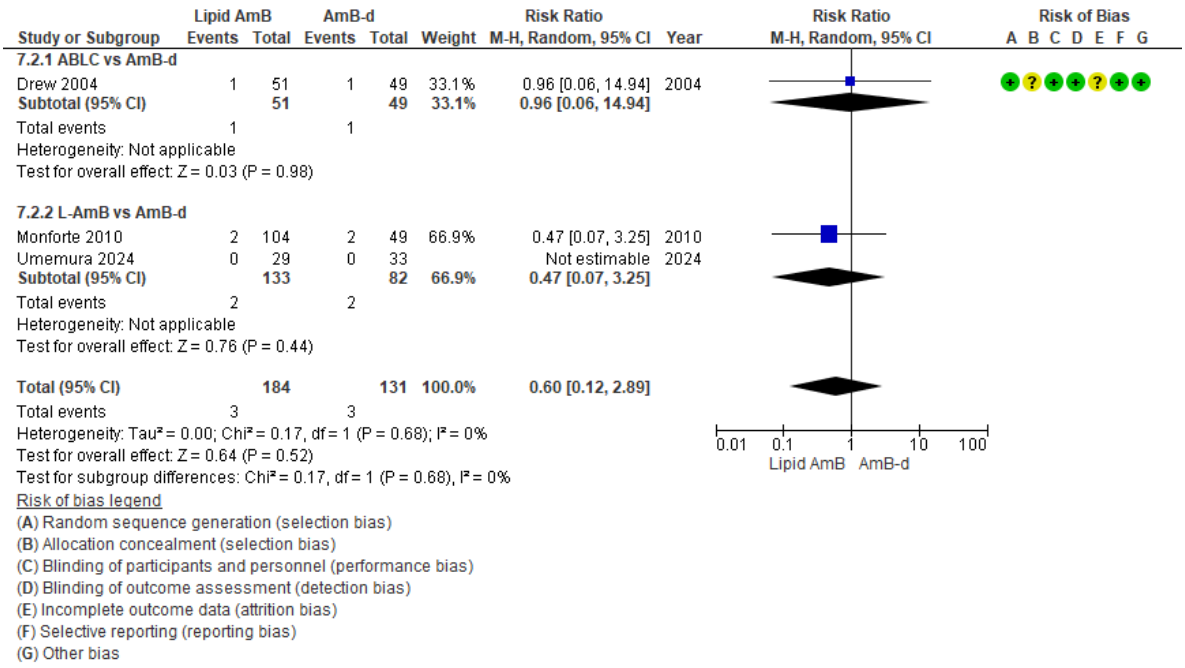
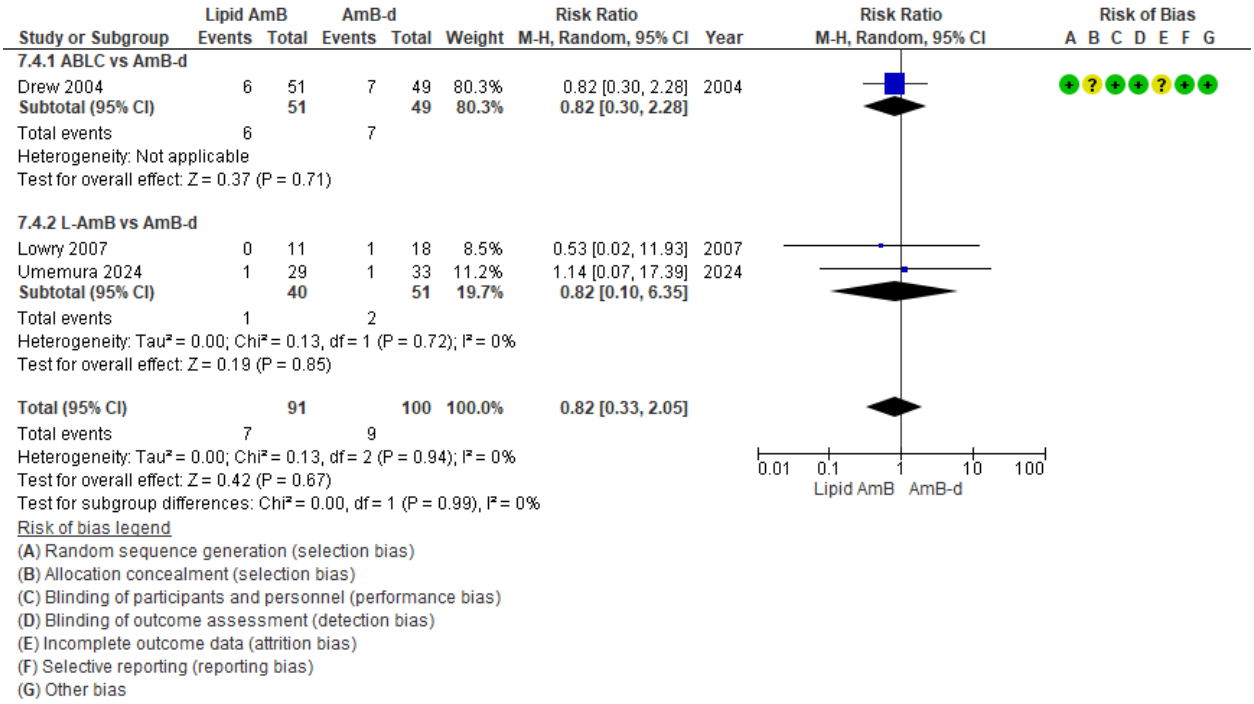


Figure B2.1.c: Invasive fungal infection (follow-up: 2 to 12 months)



Mortality (all-cause): NR

Attributable mortality: NR

Graft loss / Graft rejection: NR

Figure B2.1.d: Serious adverse events (adverse events leading to discontinuation)

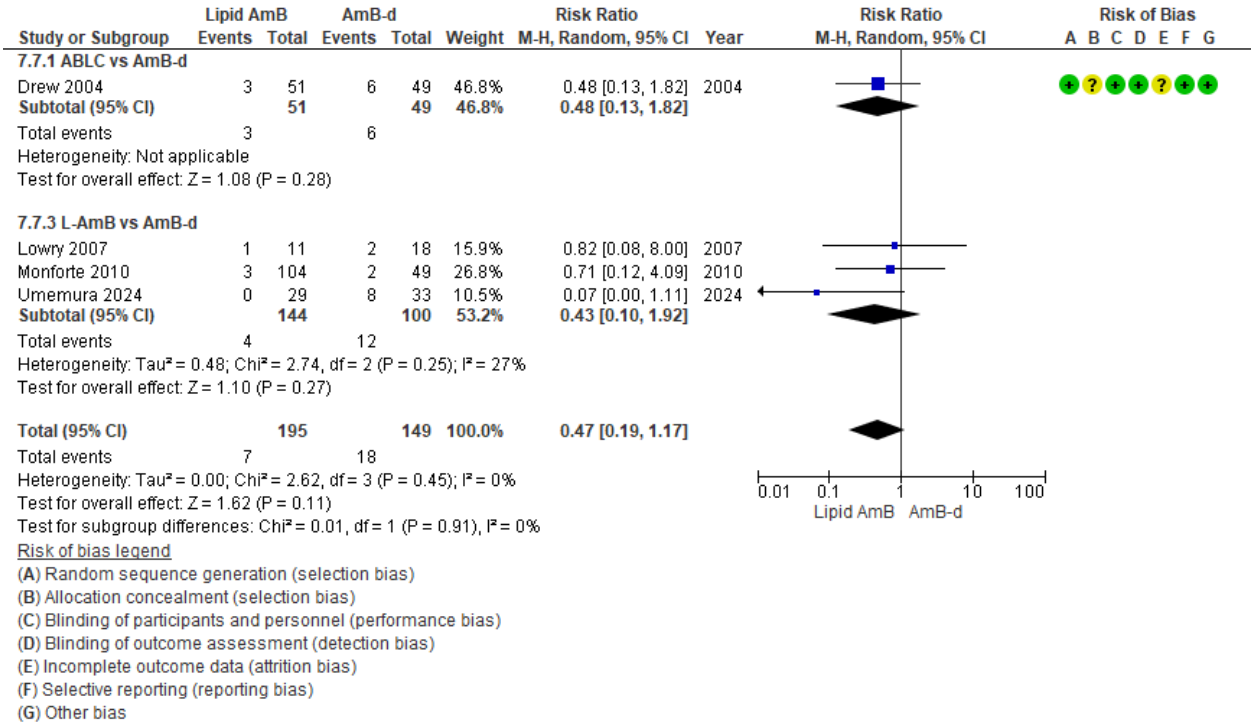


Figure B2.1.e: Adverse events: Dyspnea

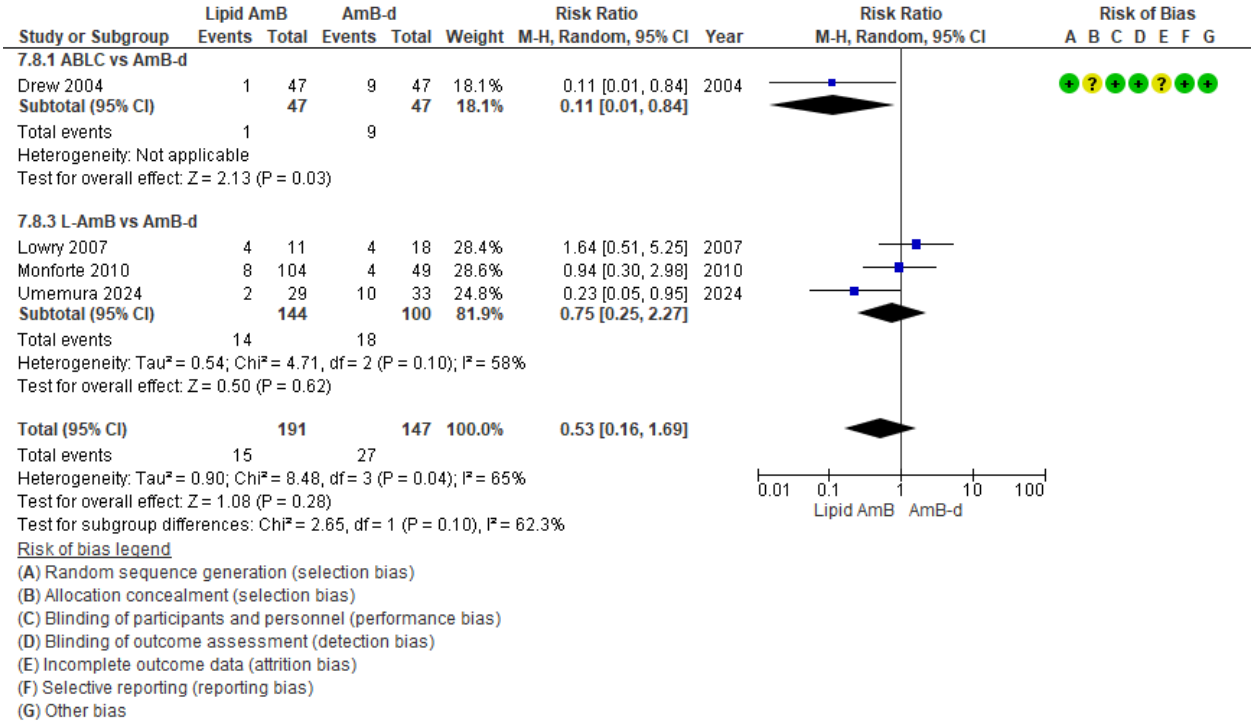
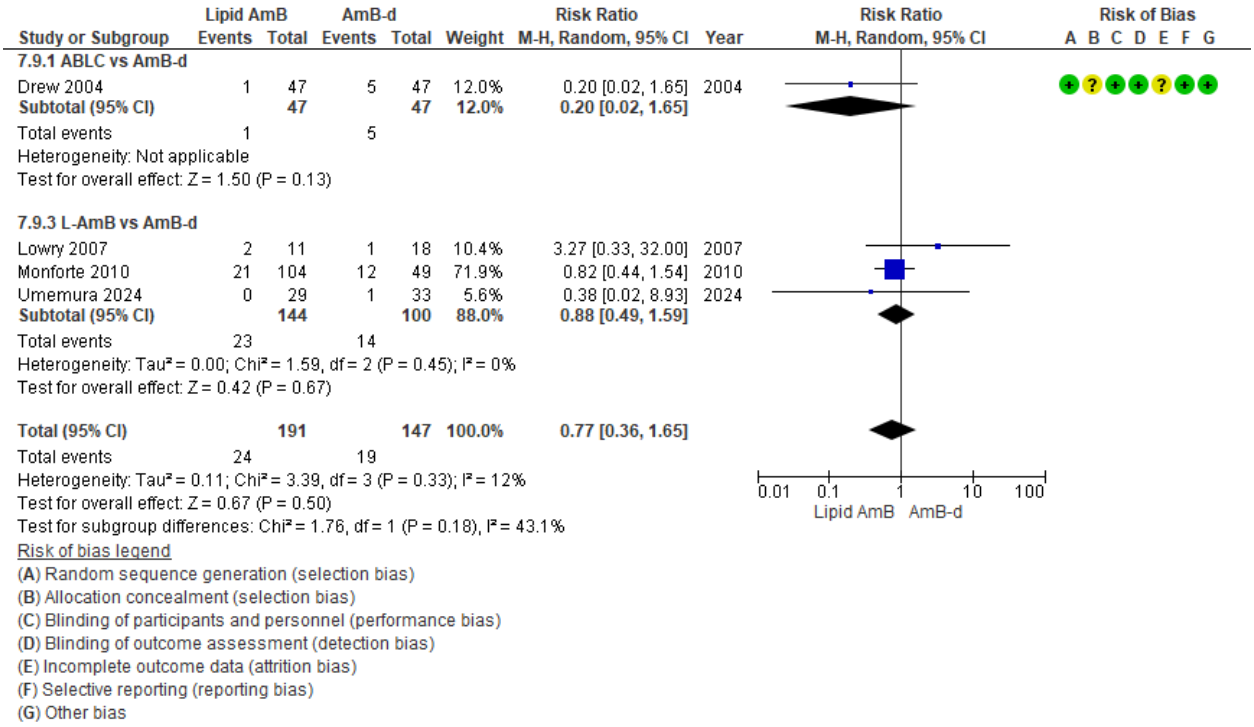


Figure B2.1.f: Adverse events: Cough



Other considerations for prophylaxis with aerosolized amphotericin B

Mechanism of action

1. Deoxycholate is a detergent that disrupt cell membrane → irritation of the resp epithelium; dAmB release unbound AmB→ irritation
2. L-AmB: AmB is encapsulated in liposomes of PL and cholesterol → shields AmB from direct interaction with lung epithelium → less irritation; slow drug release thus longer indwelling time → less frequent administration; smaller size than ABLC thus more cellular uptake
3. ABLC: AmB intercalated into a ribbon-like complex with 2 PL; larger particle size than L-AmB thus not as much cellular uptake

Efficacy and Adverse events

-Variability in formulations, nebulizers, and dosing regimens across trials makes it difficult to draw definitive conclusions about efficacy and safety.
-While generally well-tolerated, aerosolized AmB can cause local side effects such as cough, bronchospasm, bad taste, nausea, and airway irritation. These side effects are observed much more common when with deoxycholate formulation.
-Some patients may experience bronchospasm or airway irritation with aerosolized AmB, especially those lung transplant recipients with asthma or other respiratory conditions.
-Lack of large, well-designed clinical trials, particularly RCTs, specifically evaluating the effectiveness and safety of aerosolized AmB products, especially for **different durations**. Determining the ideal duration of aerosolized AmB prophylaxis, particularly in lung transplant recipients, remains a challenge.

Costs and Resources and Cost-effectiveness

Cost of antifungal drug (AmB) for aerosolized treatment

Aerosolized Amphotericin B	Typical doses	AWP product cost	Estimated cost (US$)		
			Per dose during intubation	Daily	For the first 3 months
Liposomal Amphotericin B	25 mg thrice weekly	$188 per 50 mg vial		(given three times weekly)	$4,512
Amphotericin Lipid Complex (ABLC)	50 mg weekly. Some study includes 100 mg X4 given during intubation	$135 per 50 mg (10 ml vial) $230 per 100 mg (20 ml vial)	$920	(given once weekly)	$2,540
Amphotericin B Deoxycholate	20 mg three times daily. Some study includes 50 mg X4 given during intubation	$12 per 50 mg (10 ml vial)	$48	$36	$1,344

All AWP pricing data were extracted from the 2006 Drug Topics Redbook (Published by Medical Economics, Inc. (E):http://www.medec.com). Note that costs are subject to change based on institutional contracts, local pricing, and drug availability, and the availability of generic formulation. Of note, amphotericin B lipid complex (ABLC; Abelcet) was discontinued from manufacturing in August 2025, and pricing may no longer apply depending on market availability.

These direct costs are not including the costs associated with equipment (nebulizer purchase, cleaning), consumables (nebulizer cups, mouthpiece or masks, tubing), and supplies (sterile diluents or water, syringes, etc). Costs associated with an episode of IA (either related to diagnosis, management or treatment): no recent data available.

Compared to other antifungal prophylaxis options, the cost of aerosolized AmB, particularly lipid formulations, can be higher, necessitating careful consideration of cost-effectiveness, especially for prolonged use. Cost-effectiveness between various AmB formulations should include factors such as incidence of adverse effects, the cost of managing these complications, and the overall clinical efficacy in preventing IA.

Acceptability / Stewardship

Ease of administration

-Choosing the right nebulizer to achieve optimal drug deposition in the desired lung regions is important for therapeutic efficacy.
-Delivering sufficient doses to the lungs efficiently is difficult with nebulizers, as a significant portion of the drug is often lost during administration. In addition, in single lung transplant, reduced airflow to the native lung may reduce the amount of drug reaching the distal airways compared with the allograft lung.
-Optimizing the delivery of aerosolized AmB requires proper nebulizer technique and administration protocols, which can vary across institutions and settings.
-D-AmB can disrupt pulmonary surfactant, potentially causing respiratory distress.

-Some patients may experience bronchospasm or airway irritation with aerosolized AmB, especially those lung transplant recipients with asthma or other respiratory conditions.
-Nebulized therapy can be time-consuming and requires patient cooperation, impacting adherence, particularly in long term prophylaxis.
-Most agents used for prophylaxis are administered not more than once or twice daily

Drug-drug interactions
-AmB have poor solubility and stability, making it difficult to formulate suitable for inhalation, especially in dry powder form. Achieving optimal particle size for deep lung deposition (1-5 μm) while maintaining stability and avoiding agglomeration is a key hurdle. Many aerosolized amphotericin B formulations are adapted from intravenous products, which are not optimized for lung delivery.
-Although minimal systemic absorption is generally reported, there are reports of trace amounts of AmB in the serum following aerosol administration, raising concerns about potential systemic effects, especially with prolonged use.
-Aerosolized AmB could potentially interact with other medications administered concurrently, although this is not felt to be common.

Stewardship
-Long term exposure to any antimicrobial agent, including aerosolized AmB could potentially contribute to the development of antifungal resistance, although this is less well-defined for aerosolized formulations compared to systemic use.
-Long term use of aerosolized AmB could potentially alter the respiratory microbiome, which might have unintended consequences.
-Effective stewardship requires a collaborative approach involving physicians and physician extenders, pharmacists, and respiratory therapists to ensure appropriate prescribing, monitoring, and management.

Acceptability
-D-AmB is more acceptable in terms of upfront cost, but its higher incidence of adverse effects can complicate implementation and reduce patient adherence.
-Lipid formulations are easier to implement from a clinical and patient acceptance perspective due to their better tolerability and less frequent administration, but face significant barriers in cost, payor approval and equipment needs.
-Patients: prioritize tolerability and cost. Lipid formulations have fewer side effects and are administered less frequently, thus increase acceptability among patients. Cost might be barrier.
-Healthcare providers: prioritize efficacy, safety and adherence. While there is no clear evidence of superiority among different AmB formulations, lipid formulations are favored due to better tolerability. Nevertheless, their higher cost often necessitates additional documentation and justification to secure insurance coverage, adding administrative burdens.
-Payers: focus on cost-effectiveness and evidence of clinical benefit. The lack of robust clinical trial data supporting the efficacy and safety of aerosolized AmB formulations can make approval challenging, particularly for lipid-based products. This regulatory hesitation directly influences the acceptability of these formulations among stakeholders, including institutions and insurance providers.

Feasibility

-The choice of formulation depends on the resources and infrastructure available in the healthcare setting.
-Choosing the appropriate nebulizer compatible with the formulation use may optimize lung deposition and minimize drug degradation and device clogging (to achieve optimal drug deposition in the desired lung regions is important for therapeutic efficacy).
-Although more expensive than d-AmB, the retention of drug in the airways are longer for L-AmB and ABLC such that administration requirement is less (once or twice a week for ABLC/L-AmB vs BID or TID for d-AmB).
-D-AmB is generally easier to implement in terms of compatibility with nebulizers, simplicity of preparation, and lower cost.
-Lipid formulations face feasibility challenges due to the need for advanced nebulization equipment, more complex preparation, and higher costs.
-ABLC and L-AmB dwell longer in the airway so once or twice a week administration is sufficient – this might increase compliance.
-Issues like manufacturing capacity, import restrictions, and distribution challenges can disrupt the supply chain, leading to shortages and delays in access to aerosolized AmB.

Equity

-There may be disparities in access for those in resource-limited areas, particularly after transition from a specialized inpatient hospital setting to an outpatient setting.
-On an individual patient level, affordability of the medication itself, the necessary nebulizers and the disposable equipment for administering it.
- The lack of robust clinical trial data supporting the use of aerosolized AmB might hinder its approval and reimbursement by Medicare and private insurance approval providers, leading to barriers in patient access. Efforts to enhance equity should focus on reducing the cost of lipid formulations, increasing insurance coverage.
-The choice of AmB formulation has profound implications for health equity. While d-AmB offers a lower-cost option, its higher toxicity profile disproportionately affects vulnerable populations who may lack access to comprehensive care. Lipid formulations, though safer, are often inaccessible due to cost, perpetuating disparities.

Heart Transplant Recipients

Table of Contents

Descriptive question: In heart transplant recipients, what is the baseline risk of invasive aspergillosis in patients not receiving anti-*Aspergillus* prophylaxis and which factors increase this risk of invasive aspergillosis?

Background

Heart transplant recipients are at risk for opportunistic infections, including IA. The risk of IA arises primarily from post-transplant immunosuppression therapy, leaving patients vulnerable to opportunistic fungal infections from environmental exposures. Most IA cases occur within the first 90 days, though late-onset infections are reported. Additional risk factors include prior cardiac surgeries, mechanical circulatory support devices, and cytomegalovirus (CMV) infection. Whether the overall risk in this population is sufficient to warrant universal antifungal prophylaxis is uncertain.

Literature Review

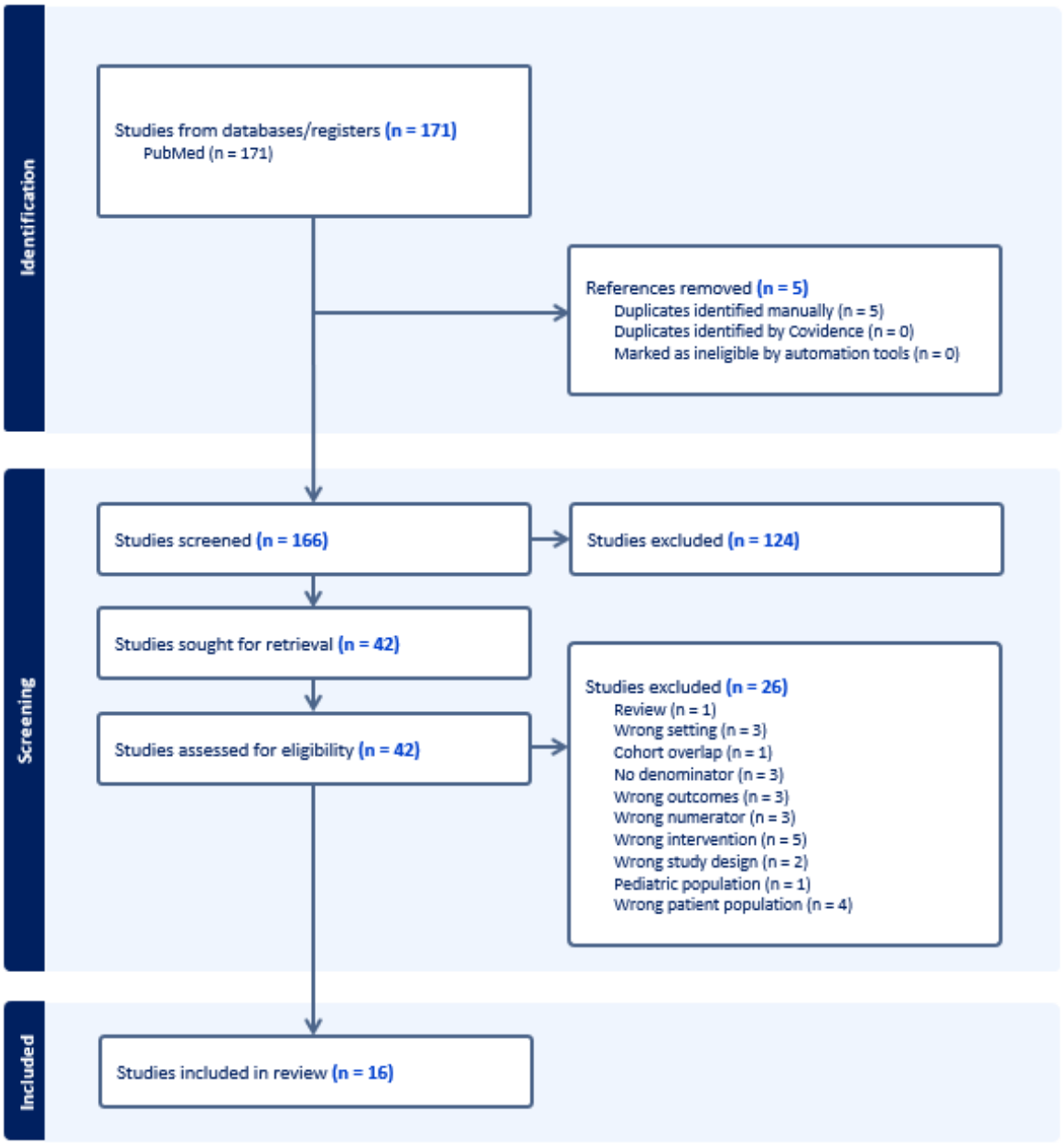
PubMed was searched from January 2000 to April 2025 for studies reporting infectious outcomes among heart transplant recipients not receiving anti-*Aspergillus* prophylaxis. Studies were retained if their data could possibly identify IA among the outcomes of the patients in their examined cohort, even if no IA was specifically found, to minimize overestimation of IA incidence.

Literature Search Strategy (last updated on April 1st, 2025)

((((("invasive mold*") OR ("invasive mould*") OR ("invasive fung*") OR (aspergill*) OR (aspergillus) OR (aspergillosis)) OR (("anti-fungal*" OR "antifungal*" OR antimold* OR anti-mold* OR anti-mould* OR antimould* OR antiaspergill* OR anti-aspergill* OR Voriconazole OR Posaconazole OR Isavuconazole OR Amphotericin OR Echinocandin OR Caspofungin OR Micafungin OR Anidulafungin OR Itraconazole OR triazole OR azole) AND (prophyla*)) AND (english[Filter])) AND ("Heart Transplantation"[Mesh] OR "cardiac transplant*" OR "heart transplant*")) NOT ((("Case Reports" [Publication Type]) OR "Editorial" [Publication Type]) OR "Comment" [Publication Type] AND (English[Filter]))

Limits: English; 2000-present
Search run on August 28th, 2023
Rerun on April 1st, 2025

Supplementary Figure 1: PRISMA flow diagram pf study identification and selection (last updated on 1st April 2025)



Among 171 articles identified, 124 were excluded by review of the title and abstract, and 26 further articles were excluded after full text review (see Prisma flow diagram below). The 16 remaining articles had data extracted [32-47].

The analysis was based on 16 studies where the methods section provided enough detail such that infectious IA outcomes could be identified. Among 6,005 heart transplant recipients, 232 cases of proven

or probable IA were identified (using EORTC/MSG criteria, a similar definition, or clinical criteria without red flags for the involvement of possible IA).

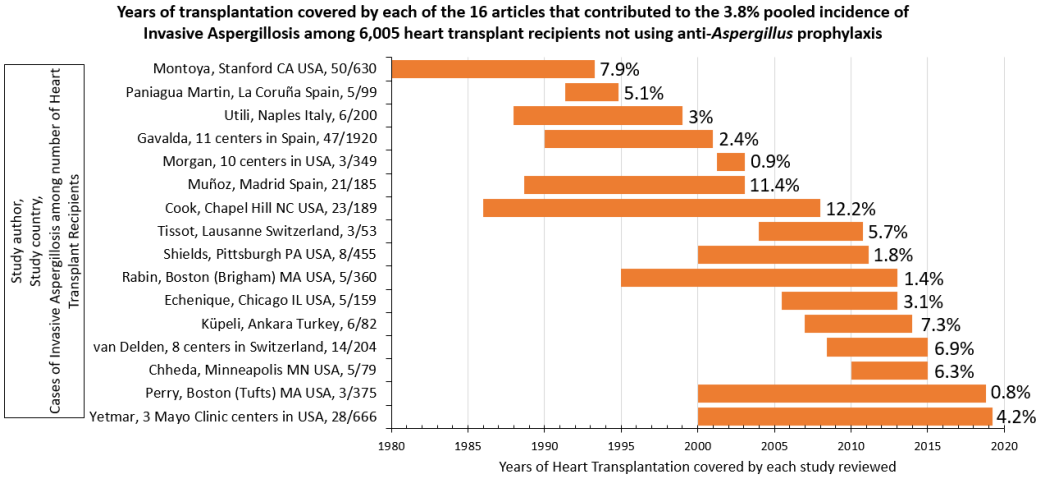
Supplementary Table 1. Source of definitions of proven or probable invasive aspergillosis

	Source of definitions	Year of publication	Author	Country
Single center studies	EORTC-MSG (De Pauw 2008 or Segal 2008 or Donnelly 2020)	2012 2014 2015 2017 2018 2019 2023	Shields Tissot Rabin Echenique Cook Chheda Perry	Pittsburgh, USA Switzerland Boston, USA Chicago, USA Chapel Hill, USA Minneapolis, USA Boston, USA
	Walsh 2008	2015	Küpeli	Turkey
	Clinical with no red flags to indicate inclusion of possible IA, also referencing Walsh 2008	2010	Paniagua Martin	La Coruña, Spain
	Ascioglu 2002	2003	Montoya	USA
	Patterson 2000	2004	Muñoz	Madrid, Spain
	Horvath 1996	2000	Utili	Italy
Multiple center studies	EORTC-MSG (De Pauw 2008 or Segal 2008 or Donnelly 2020)	2020 2021	van Delden Yetmar	Switzerland USA
	Ascioglu 2002	2005 2005	Gavalda Morgan	Spain USA

EORTC/MSG: The European Organization for Research and Treatment of Cancer and the Mycoses Study Group; IA: invasive aspergillosis

Although the studies were published after 2000, the number of years of lookback was as long as 22 years, so patients transplanted as early as 1980 were included. The incidence was not provided by year among the studied patients in any of the papers. Year of transplant was not analyzed as a risk factor in any of the studies.

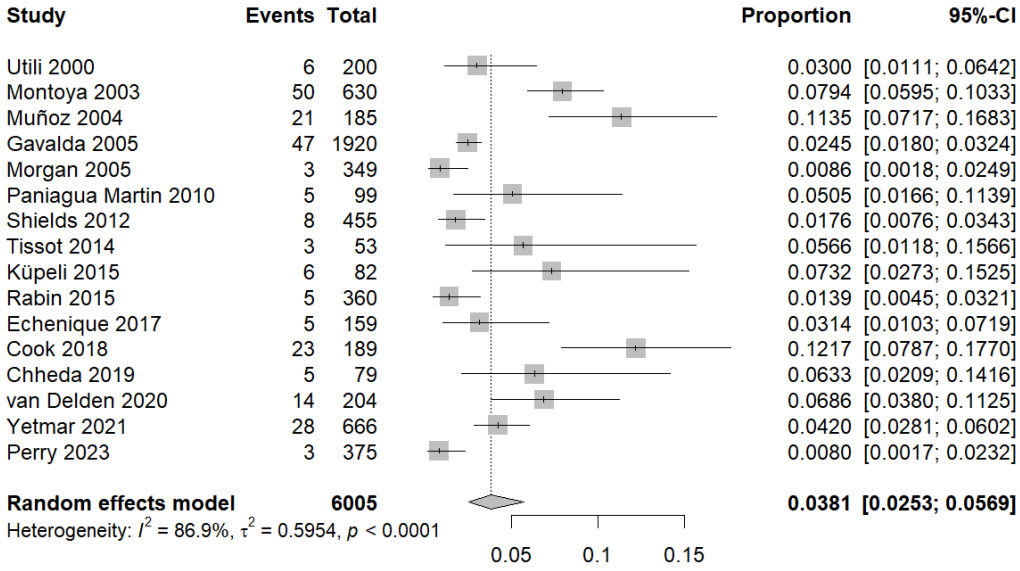
Supplementary Figure 2: Incidence of Invasive Aspergillosis by years of transplantation covered by each included study



The pooled incidence for IA was 3.8% (95% confidence interval (CI) 2.5 to 5.7%) using a generalized linear mixed model. The median incidence for IA was 3.9%. For the seven studies where transplant cohorts included patients from 1999 and prior, the median incidence was 5.1% (Interquartile range (IQR),

2.4%, 11.4%). For the nine studies where transplant cohorts included patients from 2000 and after, the median incidence was a little lower at 4.2%, with a tighter IQR (IQR, 1.3%, 6.6%). The incidence of IA among heart transplant recipients does not decline if the three studies not using 2002 or later EORTC definitions for their retrospective cohorts are removed.

Supplementary Figure 3: Forest plot of incidence of invasive aspergillosis in heart transplant recipients not receiving anti-*Aspergillus* prophylaxis



Reported mortality among heart transplant recipients who developed IA is high. In the 72 cases for which one-year survival outcomes were available, approximately 46% of patients died within one year of diagnosis. It is important to note that this represents all-cause mortality among those with IA, and comparative mortality among heart transplant recipients without IA was generally not reported

Twelve of 16 studies were retrospective, observational single center studies [32-35, 37-40, 43-45, 47] while four studies reviewed patients from groups of hospitals within their country (Spain, Switzerland, and the United States) [36, 41, 42, 46].

If studies identified a subset of patients who received mold-active prophylaxis, those individual patients were excluded from the denominator. Four retrospective studies had a second era where mold-active fungal prophylaxis was started; however, only the initial era without prophylaxis was assessed for IA incidence [32, 33, 35, 41].

Few studies provided an analysis of risk factors. For 23 cases reported by Cook et al, IA patients had a lower white blood count than non-IA infected patients, but they were not neutropenic (odds ratio (OR) 0.74 (95% CI 0.57,0.97)) [33]; infected patients also had lower albumin (OR 0.13 (95% CI 0.03,0.52)), more pre-transplant hospital admissions (OR 1.81 (95% CI 1.19,2.76)), and more rejection episodes (OR 1.99 (95% CI 1.06,3.75)). For 21 cases reported by Muñoz et al, risk factors included post-operative RRT (relative risk (RR) 4.9 (95% CI 1.2,18)), CMV disease in the first 3 months (RR 5.2 (95% CI 2,13.9)), reoperation (RR 5.8 (95% CI 1.8,18)), and another IA case in the heart transplant program 2 months before or after the case being addressed (RR 4.6 (95% CI 1.5,14.4)) [35]. CMV disease consisted of the detection of signs or symptoms attributable to viral syndrome or CMV focal end organ disease. For 28 cases reported by Yetmar et al, the only significant risk factor for mold infections (not just IA) was post-transplant RRT (adjusted Hazard Ratio 3.0 (95% CI 1.29,6.97) [41].

Two articles reported an IA incidence over 10% [33, 35]. The cohorts they examined both started with patients transplanted prior to 1990. Cook evaluated their patients, transplanted from 1986 to 2008, in

case-control fashion and identified risk factors for IA that included an increased number of pretransplant hospitalizations and post-transplant acute cellular rejection episodes (a marker of augmented immunosuppression) [33]. Muñoz identified that 18 of 24 IA cases occurred within 2 months of another case before or after the transplant date but it was not considered an “outbreak” situation [35]. IA in an additional patient in that article was associated with the recovery of *Aspergillus* from a malfunctioning room ventilation system in the hospital. That patient was also reported separately as a case report [48]. In the discussion of their paper, Muñoz and colleagues recommended that the diagnosis of any case of IA shortly before or after the transplantation date should be considered an environmental alarm risk. Their center would then implement an analysis of the environment and consider providing prophylaxis during this assessment. In 2013, they reported on the effect of echinocandin prophylaxis from 2003 to 2010 that was provided to 13 targeted heart transplant recipients with one or more of the above four risk factors and not to 120 non-high-risk recipients. Prophylaxis was started from the beginning of the risk factor(s) and continued for 3 to 4 weeks after their resolution. During these 8 years, a portion of which was during a period with high concentrations of *Aspergillus* spores in the intensive care unit, the incidence of IA reduced from 8.6% (no prophylaxis) to 2.2% (targeted echinocandin prophylaxis) (p=0.01) and *Aspergillus*-related mortality trended down from 5.8% to 1.5% (p=0.06) [49].

Three studies reported common clinical findings among their IA cases, although these were not specifically risk factor analyses. For five cases presented by Shields et al that occurred within 3 months of transplant, patients had greater than one week of intubation, a second thoracic operation, or hemodialysis [40]. Three cases with onset after 3 months, had hemodialysis and augmented immunosuppression, with two of the three cases occurring more than 1 year after transplant [40]. For three cases presented by Tissot et al, common clinical findings included extracorporeal membrane oxygenation, RRT, reoperation, and *Aspergillus* colonization [43]. For six cases presented by Utili et al, two had CMV, two had neutropenia, and three received therapy for graft rejection [34].

The IA incidence range is wide among the centers. A few studies [32, 43, 45] have a follow-up time of $\geq$ 2 years, and perhaps this is contributing to the higher incidence. In Shields, there were 2 IA cases within 3-4 months when there was construction in the vicinity of the transplant center, and that prompted the case review [40]. We feel that there may be some bias toward evaluating and publishing the incidence of IA when there are small groups of cases at individual centers, since only 16 articles could be retrieved to review the incidence of IA among patients not receiving anti-*Aspergillus* prophylaxis, over a 25-year publication window.

Conclusion

The overall reported incidence of IA in heart transplant recipients does not meet our threshold for recommending universal prophylaxis, and no studies in this population have demonstrated the effectiveness and safety of such approach. Although overall incidence of IA is relatively low, IA mortality IA is high. The risk is concentrated among patients with identifiable factors, particularly those who require post-operative RRT, undergo reoperation, develop CMV infection, or receive intensified immunosuppression. Thus, there may be a role for targeted prophylaxis in centers experiencing higher incidence or outbreak-level risk, particularly among patients with these high-risk features described above. Environmental monitoring and control measures may complement these targeted approaches. 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.

Research gap

The impact of ECMO, 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 highest risk heart transplant recipients are needed, as is quantification of the IA attributable mortality in this population.

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