2026 IDSA Clinical Practice Guidelines on Prevention of Invasive Aspergillosis in Adult Solid Organ Transplant Recipients – Supplementary material for Liver, Kidney and Pancreas Transplant Recipients

Liver Transplant Recipients

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Methods

-PICO format
-Literature search strategy (same as Clinical Questions A1 & A2)
-Eligibility criteria for selection of the studies

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

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

Population: In adult liver transplant recipients in post-transplant period
Intervention: Universal anti-*Aspergillus* prophylaxis
= either echinocandins, triazoles, amphotericin B (AmB) or itraconazole
Comparator: No anti-*Aspergillus* 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
-Increase in serious adverse events (SAEs)
Important
-Increase in non-serious adverse events (AEs)
-Reduction in mortality (all-cause)
-Graft rejection
-Graft loss
Removed outcome
-Invasive fungal infection (not a good surrogate outcome of IA in this population; invasive fungal infection was mainly equivalent to invasive Candida infection)
-Need to change antifungal therapy (a poor surrogate outcome), given that this composite endpoint was defined heterogeneously across studies and does not reliably reflect either clinical efficacy or AE

Outcomes not reported:
-Length of hospital stay, readmission, quality of life

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 invasive aspergillosis between universal prophylaxis and no prophylaxis.

After assessing the impact on other outcomes (no effect on mortality), the impact on AEs (no effect for some classes of antifungal), and the potential downstream consequences on IA in liver transplant recipients (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 April 2nd, 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 (english[Filter])) AND (pre-emptive OR preemptive OR prophyla* AND (english[Filter])) AND (english[Filter])) AND ("Liver Transplantation"[Mesh] OR "liver transplant*" OR "hepatic transplant*") AND (2000:2024[pdat])) NOT (("Case Reports"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type]) AND (english[Filter]))

Limits: 2000-present; English, RCT
Search run on February 18th 2024
Rerun on April 2nd 2025

Embase

#1. 'invasive mold*'
#2. 'invasive mould*'
#3. 'invasive fung*'
#4. aspergill*
#5. aspergillus
#6. aspergillosis
#7. 'anti-fungal*'
#8. 'antifungal*'
#9. antimold*
#10. 'anti mold*'
#11. 'anti mould*'
#12. antimould*
#13. antiaspergill*
#14. 'anti aspergill*'
#15. voriconazole
#16. posaconazole
#17. isavuconazole
#18. amphotericin
#19. echinocandin
#20. caspofungin
#21. micafungin
#22. anidulafungin
#23. itraconazole
#24. triazole
#25. azole
#26. #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
#27. 'pre emptive' OR preemptive OR prophyla*
#28. 'liver transplantation'/exp OR 'liver transplant*' OR 'hepatic transplant*'
#29. #26 AND #27 AND #28 AND [english]/lim
#30. #29 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py)
#31. #30 AND ('Conference Abstract'/it OR 'Conference Paper'/it OR 'Conference Review'/it)
#32. #30 NOT #31

Limits: 2000-present; English, RCT
Search run on February 18th 2024
Rerun on April 2nd 2025

Cochrane
#1 invasive NEXT mold*
#2 invasive NEXT mould*
#3 invasive NEXT fung*
#4 aspergill*
#5 aspergillus
#6 aspergillosis
#7 anti-fungal*
#8 antifungal*
#9 antimold*
#10 anti-mold*
#11 anti-mould*
#12 antimould*
#13 antiaspergill*
#14 anti-aspergill*
#15 Voriconazole
#16 Posaconazole
#17 Isavuconazole
#18 Amphotericin
#19 Echinocandin
#20 Caspofungin
#21 Micafungin
#22 Anidulafungin
#23 Itraconazole
#24 triazole
#25 azole
#26 #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
#27 pre-emptive
#28 preemptive
#29 prophyla*
#30 #27 OR #28 OR #29
#31 MeSH descriptor: [Liver Transplantation] explode all trees
#32 liver NEXT transplant*
#33 hepatic NEXT transplant*
#34 #31 OR #32 OR #33
#35 #26 AND #30 AND #34
#36 MeSH descriptor: [Randomized Controlled Trial] explode all trees

Limits: 2000-present; English, RCT
Search run on February 18th 2024
Rerun on April 2nd 2025

Eligibility Criteria for Selection of the Studies

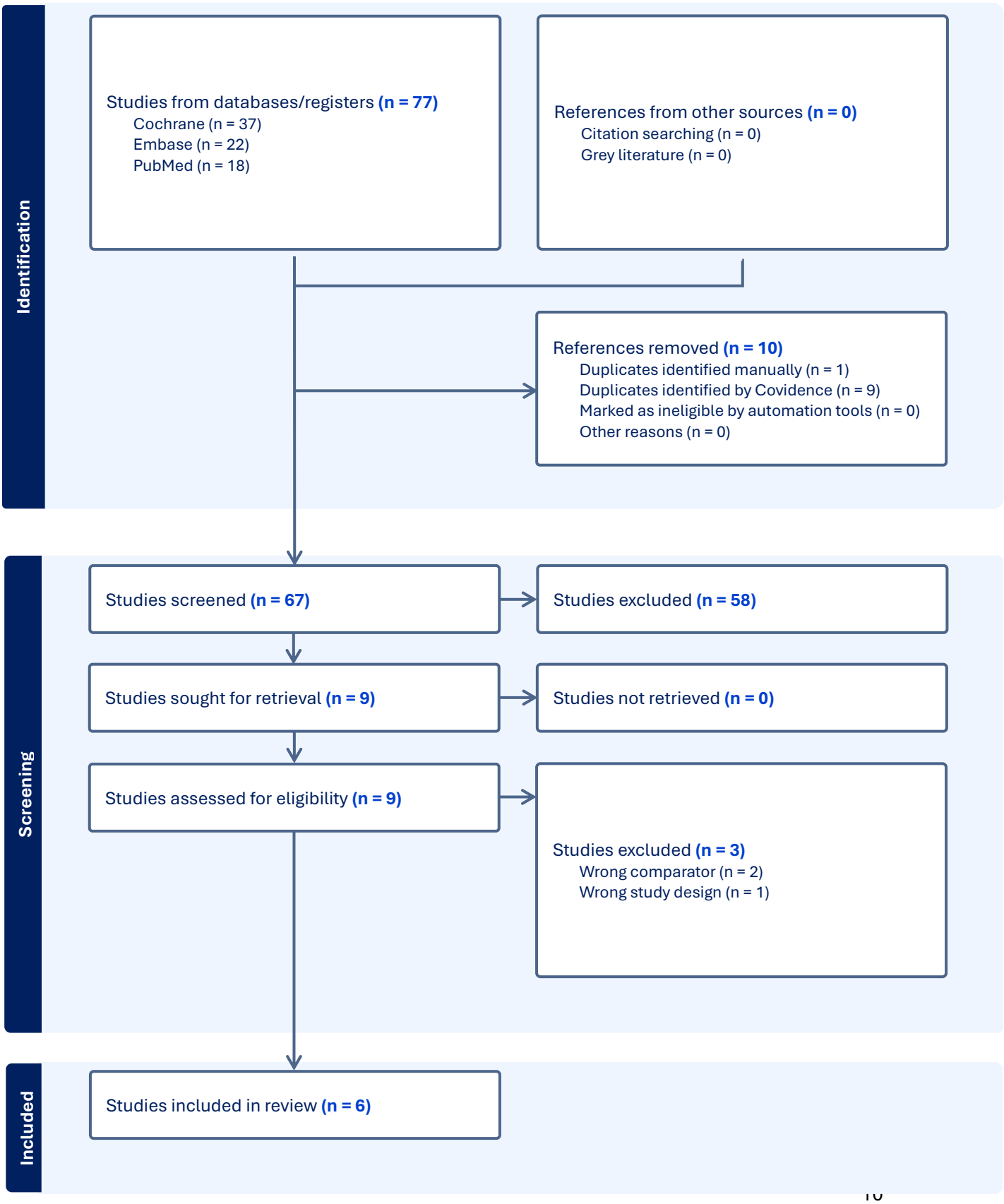
Inclusion criteria:

- Patient population: Adult liver transplant recipients in early post-transplant period
- Intervention: Universal anti-*Aspergillus* prophylaxis
  - -Echinocandins such as caspofungin, micafungin or anidulafungin
  - -Triazoles such as posaconazole, voriconazole or isavuconazole
  - -Amphotericin B (IV or inhaled)
  - -Itraconazole (any formulation)
- -Comparator: No anti-*Aspergillus* prophylaxis
  - -Fluconazole (any formulation)
  - -Absence of antifungal prophylaxis
- -Outcomes: study reporting on either incidence of IA or/and AEs associated with the use of anti-*Aspergillus* prophylaxis
- Study design: Randomized controlled trials (RCTs)
- 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
  - -Observational studies, 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 April 2nd, 2025)



Supplementary Table A1.1: GRADE evidence profile

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

P: Adult liver 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: 3 months)										MID*: at least 40 fewer per 1,000		
5[2-6]	randomized trials	serious[a]	not serious	not serious	serious[b]	None	4/340 (1.2%)	3/300 (1.0%)	**RR 1.11** (0.23 to 5.45)	**1 more per 1,000** (from 8 fewer to 45 more)	⊕⊕◯◯ Low	CRITICAL
								Estimated real-life baseline risk: 1.9% (1.4 to 2.6%)		**2 more per 1,000** (from 15 fewer to 85 more)		
Mortality (all-cause) (follow-up: range 1 months to 6 months)												
6[1-6]	randomized trials	serious[c]	not serious	not serious	very serious[d]	None	37/438 (8.4%)	33/390 (8.5%)	**RR 1.06** (0.67 to 1.69)	**5 more per 1,000** (from 28 fewer to 58 more)	⊕◯◯◯ Very Low	IMPORTANT
Attributable Mortality (follow-up: range 1 months to 6 months)										MID*: at least 20 fewer per 1,000		
6[1-6]	randomized trials	serious[c]	not serious	not serious	serious[b]	None	4/438 (0.9%)	5/389 (1.3%)	**RR 0.70** (0.18 to 2.72)	**4 fewer per 1,000** (from 11 fewer to 22 more)	⊕⊕◯◯ Low	CRITICAL
Serious Adverse Events										MID*: at least 40 fewer per 1,000		
6[1-6]	randomized trials	serious[e]	not serious	not serious	serious[b]	None	9/437 (2.1%)	7/388 (1.8%)	**RR 1.15** (0.40 to 3.30)	**3 more per 1,000** (from 11 fewer to 41 more)	⊕⊕◯◯ Low	CRITICAL
Non-serious Adverse Events												
5[1,2, 4-6]	randomized trials	serious[c]	not serious	not serious[f]	serious[b]	None	81/398 (20.4%)	48/359 (13.4%)	**RR 1.50** (0.96 to 2.35)	**67 more per 1,000** (from 5 fewer to 181 more)	⊕⊕◯◯ Low	IMPORTANT
Non-serious Adverse Events (*for Echinocandins ONLY*)												
2[1-2]	randomized trials	serious[g]	not serious	not serious	serious[b]	None	20/183 (10.9%)	18/186 (9.7%)	**RR 1.13** (0.62 to 2.06)	**13 more per 1,000** (from 37 fewer to 103 more)	⊕⊕◯◯ Low	IMPORTANT
Graft Rejection												
1[2]	randomized trials	not serious	not serious	not serious	very serious[h]	None	6/100 (6.0%)	4/100 (4.0%)	**RR 1.50** (0.44 to 5.15)	**20 more per 1,000** (from 22 fewer to 166 more)	⊕⊕◯◯ Low	IMPORTANT
Graft Loss												
1[2]	randomized trials	not serious	not serious	not serious	very serious[i]	None	13/100 (13.0%)	14/100 (14.0%)	**RR 0.93** (0.46 to 1.87)	**10 fewer per 1,000** (from 76 fewer to 122 more)	⊕⊕◯◯ 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
***MID = Minimal Important Difference or Decision Threshold (trivial vs small effect)**
****Estimated real-life baseline risk was based on a separate mapping review of the literature and the average and 95%CI was calculated using GLMM.**

Explanations

a. Judged at high risk of bias: Winston 2002 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest).
b. The upper boundary of the confidence interval crosses the decision threshold (minimal important difference for recommending or not the prophylaxis), thus providing evidence of serious imprecision around the estimates of effect.
c. Judged at high risk of bias: Winston 2002 and Kang 2020 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest) and Sharpe 2003 due to early stoppage (consequently causing serious concerns regarding adequate randomization and potential attrition bias).
d. 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.
e. Judged at high risk of bias: Winston 2002 and Kang 2020 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest).
f. Statistically significant noted in the meta-analysis (I2=35%, p-value=0.19) but clearly explained by the heterogeneity of the agents used and their side effect profile, as well as the definition of non-serious adverse events between studies.
g. Judged at high risk of bias: Kang 2020 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest).
h. The upper boundary of the confidence interval crosses the decision threshold (minimal important difference for recommending or not the prophylaxis) and the confidence interval is wide, thus providing evidence of very serious imprecision around the estimates of effect.
i. The lower boundary of the confidence interval crosses the decision threshold for important benefit while the upper boundary of the confidence interval crosses the decision threshold for important harm, thus providing evidence of very serious imprecision.

References

1. Kang et al. A Multicenter, Randomized, Open-Label Study to Compare Micafungin with Fluconazole in the Prophylaxis of Invasive Fungal Infections in Living-Donor Liver Transplant Recipients. J Gastrointest Surg Apr 2020;24(4):832-840.
2. Winston et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. Am J Transplant Dec 2014;14(12):2758-64.
3. Hadley et al. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. Transpl Infect Dis Feb 2009;11(1):40-8.
4. Sharpe et al. Efficacy and safety of itraconazole prophylaxis for fungal infections after orthotopic liver transplantation: a prospective, randomized, double-blind study. Transplantation Sep 2003;76(6):977-83.
5. Winston et al. Randomized controlled trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients. Transplantation Sep 2002;74(5):688-95.
6. Biancofiore et al. Antifungal prophylaxis in liver transplant recipients: a randomized placebo-controlled study. Transpl Int Jul 2002;15(7):341-7.

Supplementary Table A1.2: Characteristics of the included studies

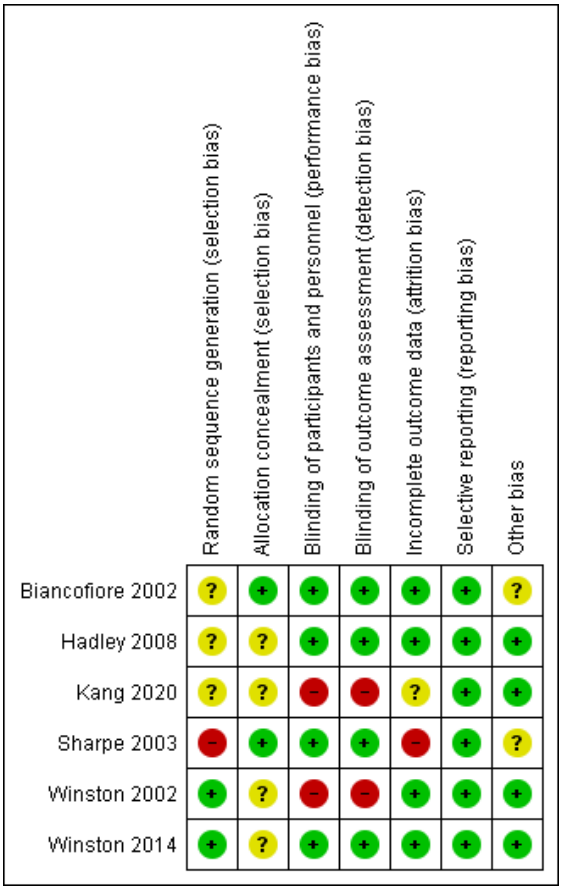
Study *(lead author, year of publication, location)*	**Population** *(type of patients, year of enrollment, n randomized, age, exclusion*)*	**Study design** *(NI margin if applicable, primary outcome with its timing)*	**Risk assessment for IFI and/or IA** *(definition and %)*	**Baseline risk for IA and mortality** *(% in the comparator group)*	**Intervention** *(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**
Kang 2020 Seoul, Republic of Korea Multicentric (5 centers)	Living donor liver transplant recipients 2012 – 2015 N = 172 (PP = 144) Age (mean): 54.2y Exclusion: -Systemic AFT within 14 days of randomization -Proven/ probable IFI -Re-transplantation -Deceased donor whole liver	Non-inferiority trial Margin 10% for rate of clinical success (lack of a proven or probable IFI and no additional antifungal therapy including an increase in the study medication dosage) until the end of prophylaxis	All comers were included in the cohort High risk for IFI: NR	Baseline risk for IA: NR Baseline risk for mortality: 1.1%	Micafungin 100mg daily Duration: 21 days or until hospital discharge (median days received= 20)	Fluconazole 100-200mg daily (IV/PO) Duration: 21 days or until hospital discharge (median days received= 21)	Proven or Probable IFI according to EORTC/MSG 2008 Total duration of follow-up: 3 months
Winston 2014 California, USA Multicentric (6 centers)	Liver transplant recipients **with high risk of IFI** 2010 - 2011 N = 200 (mITT = 197) Age (median): 58y Exclusion: -Life expectancy less than 72h -Systemic AFT for an IFI within 4 weeks preceding transplantation	Superiority trial Primary outcome: Incidence of proven or probable IFI within 90 days post-transplant	High risk of IFI = inclusion criteria (defined as re-transplantation; transplantation for fulminant hepatic failure; receipt of corticosteroids for at least 2 weeks within 4 weeks preceding transplantation; hospitalization for at least 48 h in ICU at the time of transplantation; colonization with *Candida* spp. at least at 2 sites within 4 weeks preceding transplantation; at least 15U of intraoperative packed red blood cell transfusions and operative time >6 h; requirement of any form of renal replacement therapy at the time or within 7 days of transplantation; and re-operation involving the intraabdominal cavity). High risk of IA: NR but correspond to at least 60% of the entire cohort (requiring RRT)	Baseline risk for IA: 2.0% Baseline risk for mortality: 12.0%	Anidulafungin IV 200mg load, then 100mg daily Duration: 21 days or until hospital discharge *(In patients with ongoing need for renal replacement therapy, persistent liver allograft dysfunction, continued ICU stay, or increased immunosuppressio n for rejection in the previous 21 days, study drug could be continued beyond 21 days for a maximum of 42 days).* (median days received= 21)	Fluconazole 400mg IV daily (or adjusted for renal function) Duration: 21 days or until hospital discharge *(In patients with ongoing need for renal replacement therapy, persistent liver allograft dysfunction, continued ICU stay, or increased immunosuppressio n for rejection in the previous 21 days, study drug could be continued beyond 21 days for a maximum of 42 days).* (median days received= 21)	Proven or Probable IFI according to EORTC/MSG 2008 Total duration: 90 days
Hadley 2009 California, USA Multicentric (13 centers)	Liver transplant recipients **with high risk of IFI** 1999 - 2001 N = 68 (mITT = 64) Age (mean): 49.9y Exclusion: NR	Superiority trial Primary outcome: Incidence of proven IFI at 100 days post-transplant	High risk of IFI = inclusion criteria (defined as 2 or more of the following criteria within 5 days of OLT: a) choledochojejunostomy anastomosis; b)re-transplantation c) intra-operative administration of >40 units of cellular blood products (platelets or packed red blood cell); d) return to operating room within 5 days for laparotomy for bleeding/bile leak or viscous leak, vascular accident or graft failure; e) serum Cr >2 mg/dL or need for RRT within 48h prior to OLT; f) *Candida* spp. isolated from cultures obtained within 48h before or after OLT from one or more of: sputum, urine, wound, JP drains, intra-op	Baseline risk for IA: 0% Baseline risk for mortality: 13.3%	L-AmB2mg/kg IV Duration: 14 days (median days received= NR)	Fluconazole 400mg PO/IV Duration: 14 days (median days received= NR)	Proven or Probable IFI according to EORTC/MSG 2008 Total duration: 100 days post-transplant

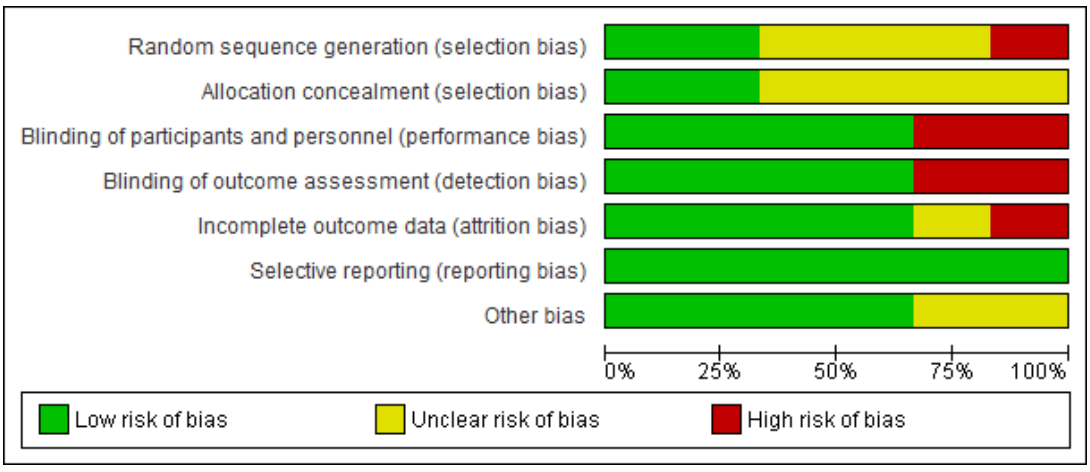
			recipient bile/biliary tree or T-tube drainage) High risk of IA: NR but correspond to at least 45% of the entire cohort (requiring RRT)				
Sharpe 2003 Ontario, Canada Single center	OLTs Years of enrollment: NR N = 71 Age (mean): 46y Exclusion: -Receiving AFT for IFI at the time of transplantation -Receiving AFT within 2 weeks or oral AFT within 1 week -Prior IFI unresponsive to azole -Receiving other medications with potential drug-drug interactions	Phase III restricted sequential design trial Primary outcome: Incidence of disseminated fungal infection post-transplantation	All comers were included in the cohort High risk for IFI: NR	Baseline risk for IA: 0% Baseline risk for mortality: 15.8%	Itraconazole 5mg load followed by 2.5mg/kg BD Duration: until endpoint, discharge or 56 days (median days received= NR)	Placebo Duration: until endpoint, discharge or 56 days (median days received= NR)	Suspected or proven deep fungal infections (defined as at least one of the following: 1) positive histology on biopsy form deep tissue, 2) at least one positive blood culture for yeast, 3) clinical signs and radiological lesions in combination with the presence of *Aspergillus* spp. or other filamentous fungi in bronchoalveolar lavage fluid). Total duration: 56 days
Biancofiore 2002 Pisa, Italy Single center	All OLTs 1999 - 2000 N = 129 Age (mean) ranging from 46.2 to 50.3y in the intervention groups vs 51.5y in the comparator group Exclusion: -Systemic AFT prior to transplant	Explorative trial Primary outcome: Incidence of mycotic infections at 30 days post-transplant	All comers were included in the cohort High risk for IFI: NR	Baseline risk for IA: 0% Baseline risk for mortality: 6.8%	L-AmB 1mg/kg/day for 7 days followed by 200mg PO Itraconazole for 21 days OR 400mg/day IV Fluconazole for 7 days followed by 200mg PO Itraconazole for 21 days Duration: 28 days (median days received= NR)	Placebo IV for 7 days then PO for 21 days Duration: 28 days (median days received= NR)	Mycotic infection (defined as: 1) histological evidence of tissue invasion at biopsy or autopsy; 2) a positive culture from a deep tissue specimen, such as blood, peritoneal fluid, or biopsy specimen; 3) positive cultures from multiple peripheral sites (three or more); and 4) the presence of budding yeast, pseudohyphae, or a positive culture from a bronchoalveolar lavage specimen with clinical and/or radiological evidence of pneumonitis) Total duration: 30 days post-transplant
Winston 2002 California, USA Single center	Liver transplant recipients Years of enrollment: NR N = 188 Age (median): 53y in the intervention group vs 50y in the comparator group Exclusion: -Receiving other medications with potential drug-drug interactions	Explorative trial Primary outcome: Incidence of IFI post-transplantation	All comers were included in the cohort High risk for IFI: NR	Baseline risk for IA: 1.1% Baseline risk for mortality: 7.7%	Itraconazole oral solution 200mg TID, then 200mg BD Duration: 10 weeks (median days received= 70)	Fluconazole 400mg (IV/PO) daily Duration: 10 weeks (median days received= 69)	Invasive fungal infections (defined by the presence of fungus in the blood, pulmonary tissues or secretions, sinuses, soft tissues, peritoneal cavity, or other organ structure in association with symptoms and signs of infection not explainable by other pathogens) Total duration: 70 days

Legend
AFT: antifungal therapy
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
IA: Invasive Aspergillosis
ICU: intensive care unit
IFI: Invasive Fungal Infection
L-AmB: liposomal amphotericin B
NR: not reported
OLT: orthotopic liver transplant
PP: Per Protocol, mITT: modified Intent-To-Treat
PO: oral, IV: parenteral, BD: twice a day, TDS: three times a day
RRT: renal replacement therapy

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 Figure A1.2: Summary of risk of bias of included studies

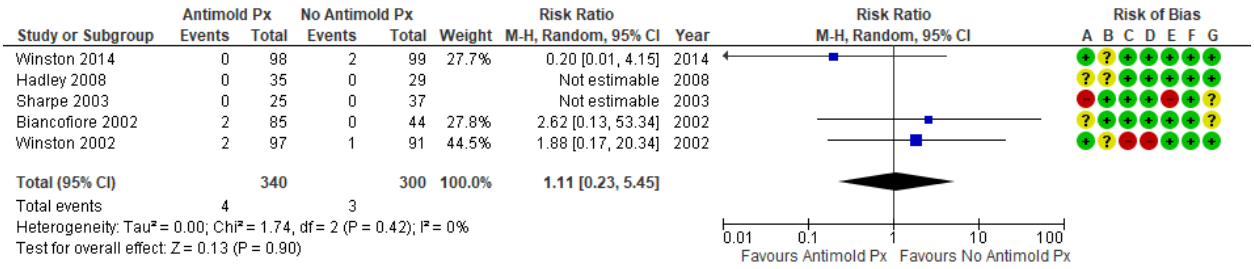




Supplementary Figures A1.3: Forest plots for each patient-important outcome

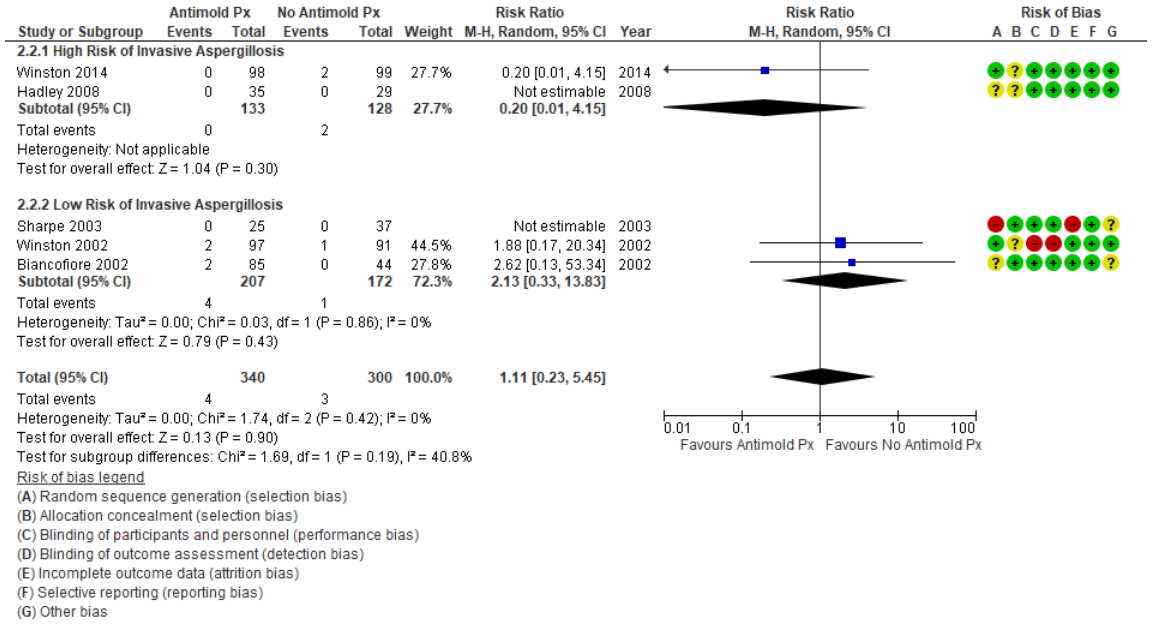
Please note that all studies are presented from the most recently published to the oldest in other to assess the generalizability of the data. Furthermore, only important subgroup analyses for decision-making purposes are presented here.

Figures A1.3.a: Invasive aspergillosis (at 3 months)

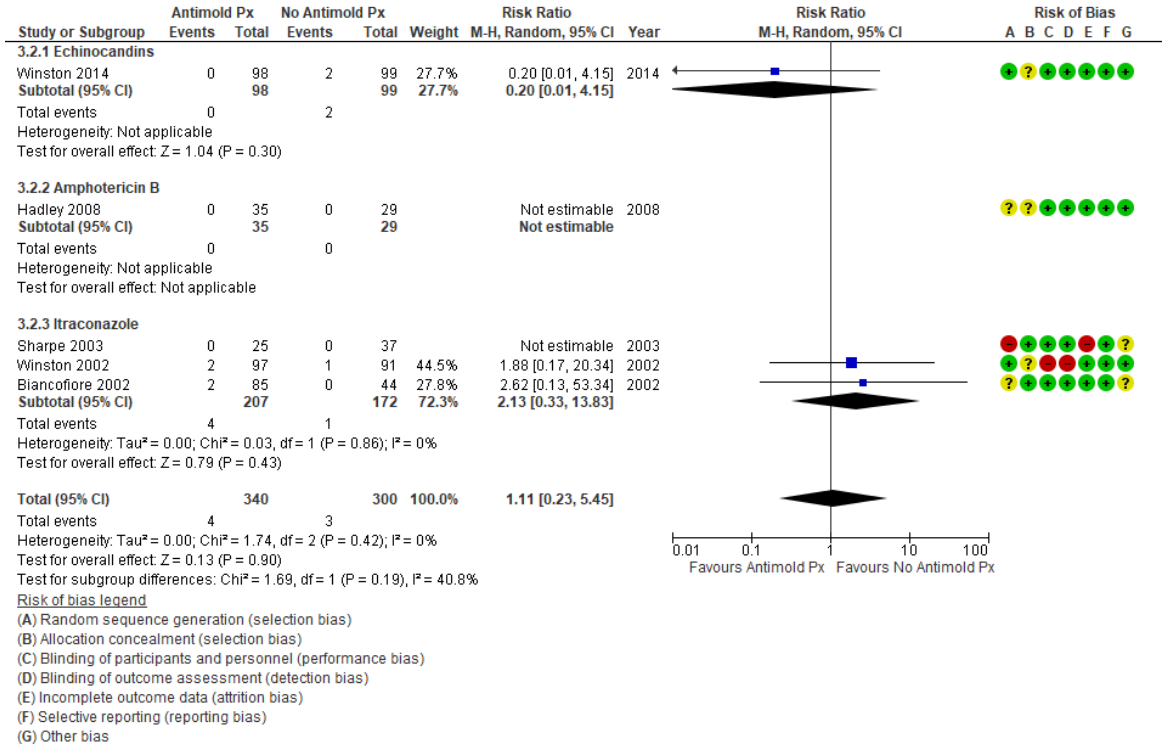


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Subgroup analysis for higher risk vs lower risk invasive aspergillosis

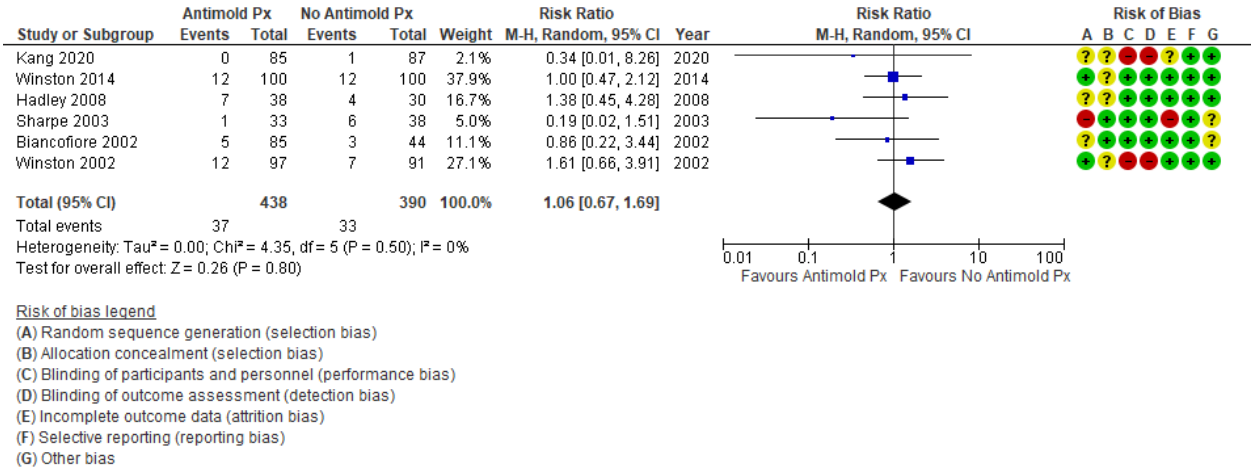


Subgroup analysis per class of antifungal agents



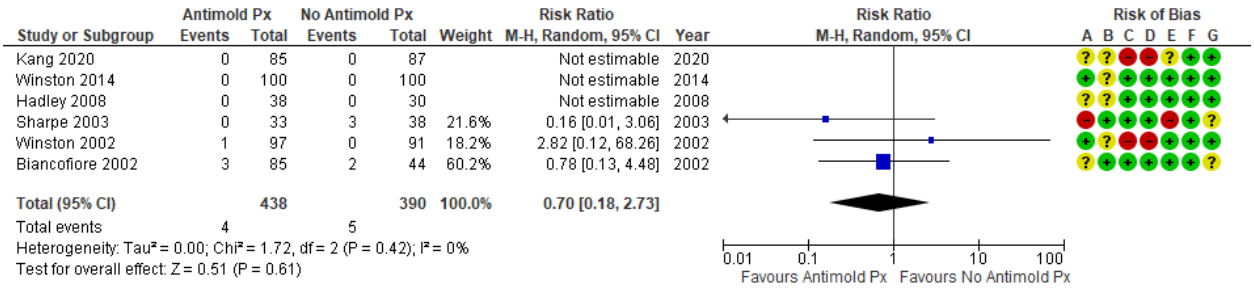
In summary, subgroup analyses are not providing a clear explanation why Winston 2014 reported a better RR than the other studies (**hypothesis**: improvement in standard of care with time, use of universal prophylaxis in a cohort at higher risk of IA, possible difference in the baseline risk factors between the 2 cohorts, and/or use of an echinocandins as compared to AmB or itraconazole).

Figure A1.3.b: All-cause mortality (ranging 1-6 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

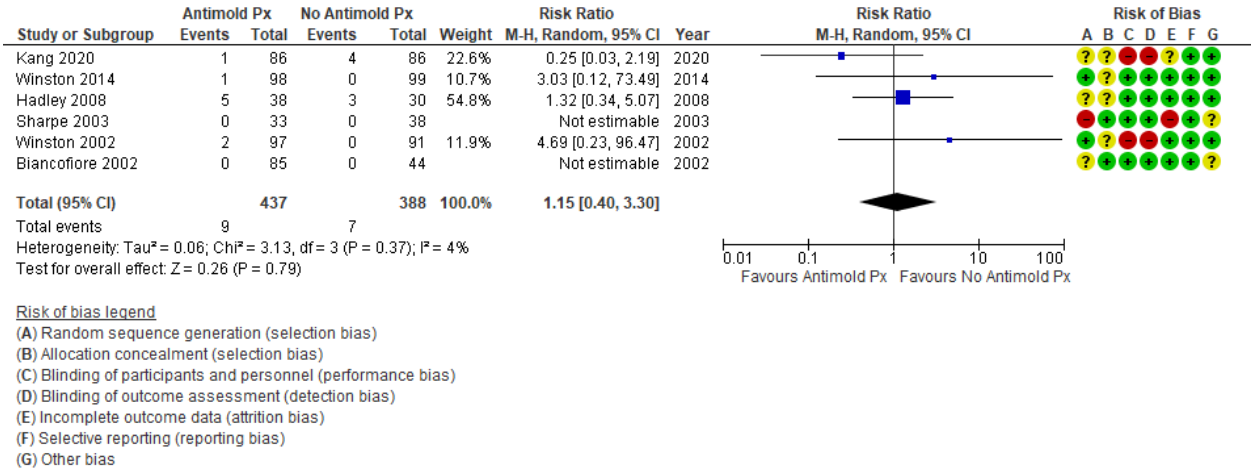
Figure A1.3.c: Attributable mortality (ranging 1-6 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

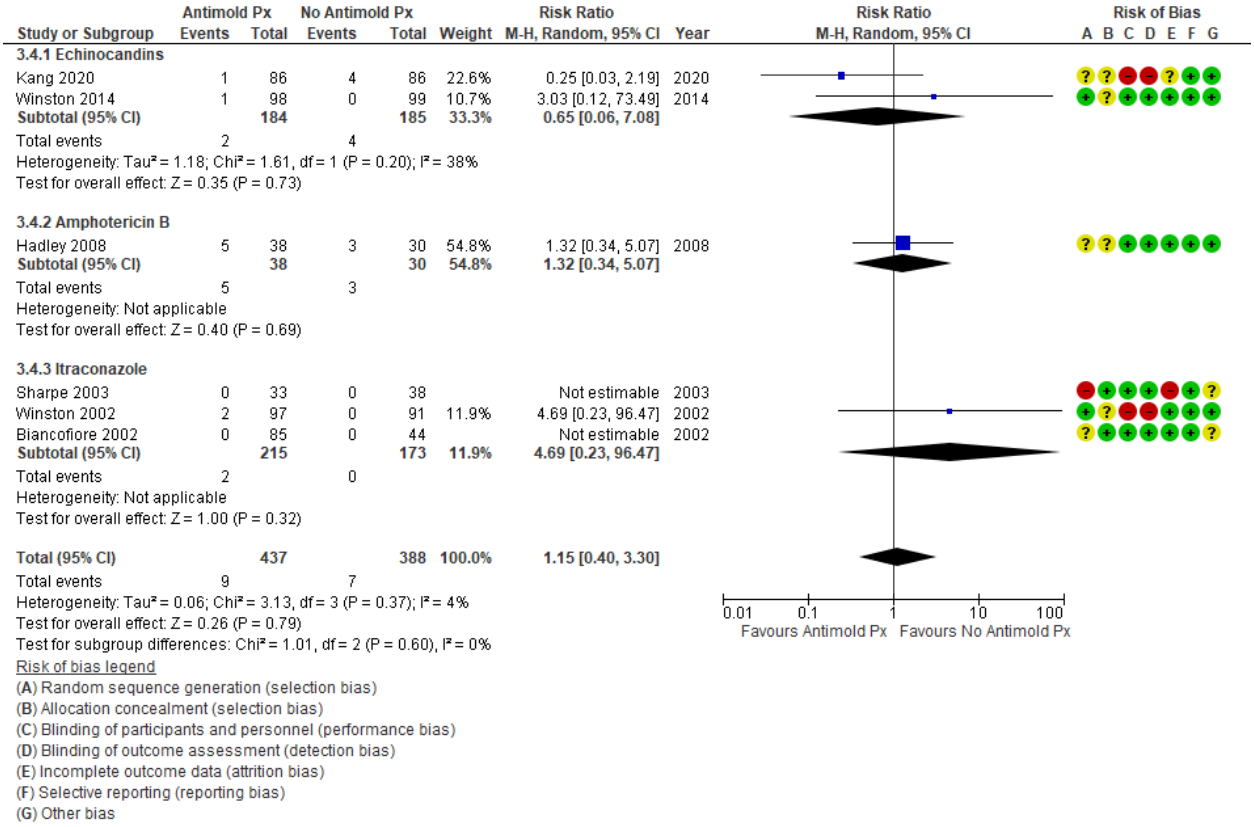
Of note, no mortality was attributed to IA in the 3 more recent studies (published after 2008).

Figures A1.3.d: Serious adverse events (up to 3 months)



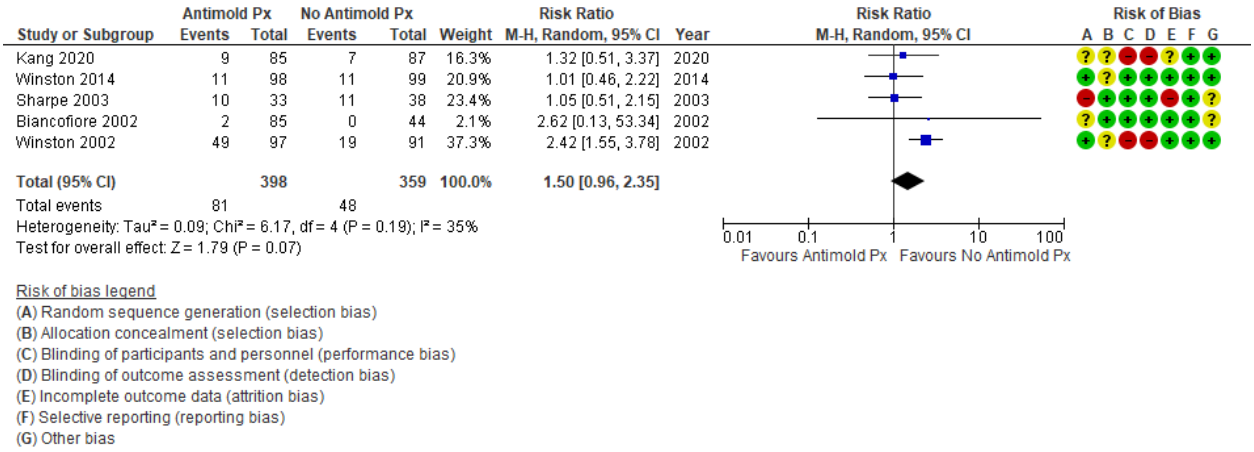
SAEs were defined as SAEs leading to discontinuation except for Sharpe 2003 which use the standard definition of defined as fatal or life threatening, disabling, requiring intervention to prevent permanent impairment or damage, or resulting in or prolonging hospitalization.

Subgroup analysis per class of antifungal agents

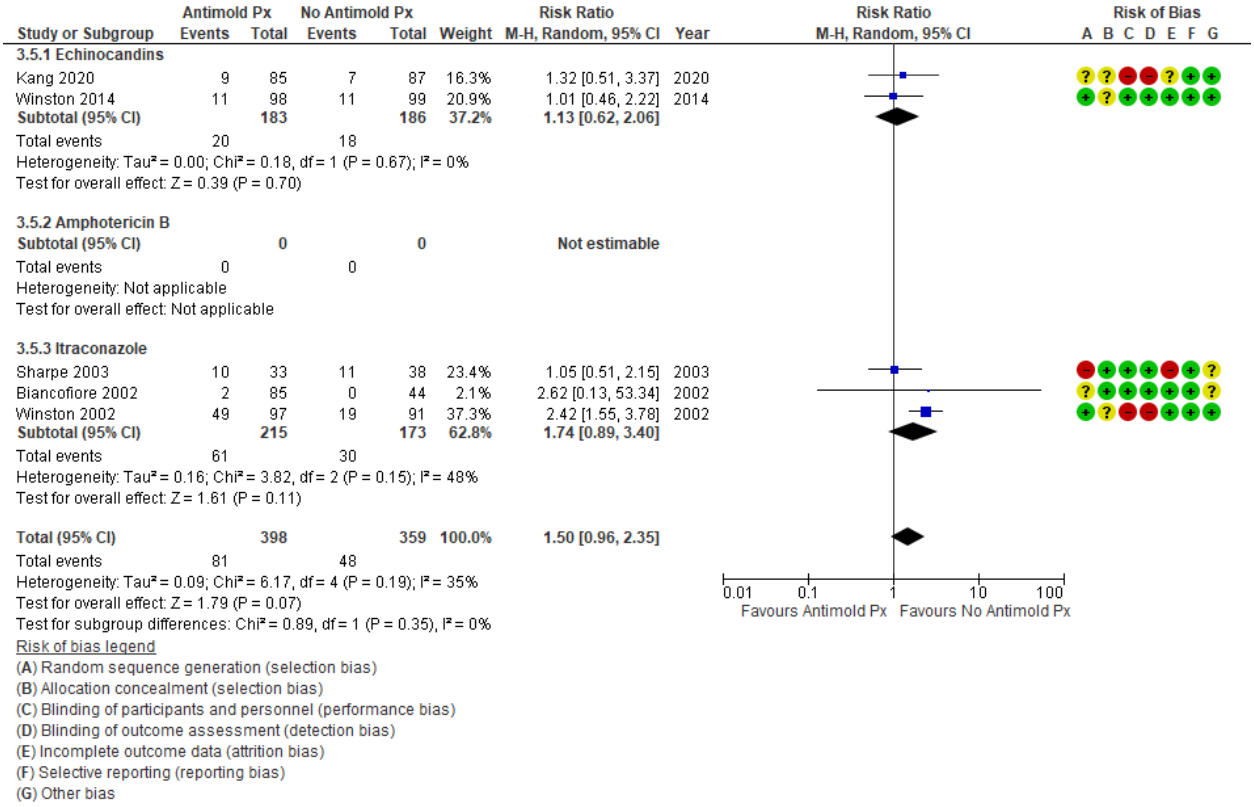


In summary, this subgroup analysis a trend towards less SAEs between classes (more frequently SAEs reported in itraconazole, than AmB, and echinocandins)

Figure A1.3.e: Non-serious adverse events (up to 3 months)

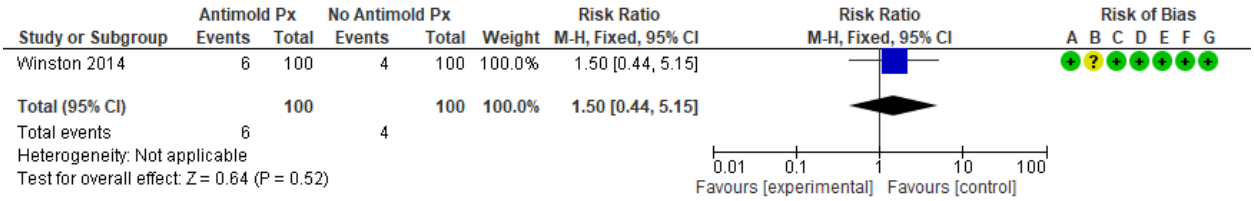


Subgroup analysis per class of antifungals



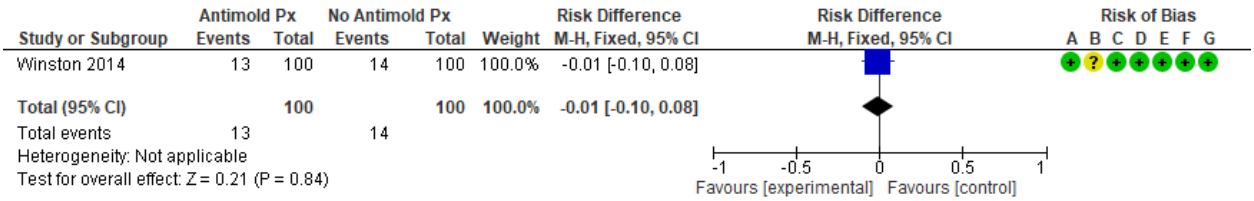
In summary, this subgroup analysis a trend towards less non-serious AEs between classes (more frequently reported in itraconazole, than echinocandins)

Figure A1.3.f: Graft loss (at 3 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure A1.3.g: Graft rejection (at 3 months)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplementary Table A1.3: 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	When comparing universal anti-*Aspergillus* prophylaxis with no anti-*Aspergillus* prophylaxis, the desirable consequences are trivial: there is no evidence that universal anti-*Aspergillus* prophylaxis significantly reduce the incidence of invasive aspergillosis or mortality (all-cause or attributable).	

Undesirable effects

How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ **Small** ○ **Trivial** ○ Varies ○ Don't know	When considering the use of anti-*Aspergillus* prophylaxis with no anti-*Aspergillus* prophylaxis, the undesirable consequences were judged trivial to small: -no significant increase serious adverse events -small increase in non serious adverse events by 6.7%, 95%CI (0.5 to 18.1%) but when stratified by class of agents this increase was judged small to moderate for itraconazole and trivial for echinocandins.	

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	In absence of desirable consequences and evidence of trivial to small undesirable consequences, the balance of effects probably favors not using anti-*Aspergillus* prophylaxis in liver transplant recipients with a baseline risk for IA approximating 2%.	

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	No studies identified. No patient representatives were identified for this section of the guideline.	The panel assumes that patients enrolled for liver transplant recipients would generally support interventions that would provide a favorable balance of benefits and harms.

○ **Probably no important uncertainty or variability** ○ 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-*Aspergillus* 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)

Echinocandins	Daily dose	Cost per day (US$)	
		AWP	AC
Micafungin	100 mg (IV)	$58 to 224	$59
Caspofungin	50 mg (IV)	$83 to 405	$53
Anidulafungin	100 mg (IV)	$229	$211

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

Amphotericin B	Daily dose (for 70 kg)	Cost per day (US$)	
		AWP	AC
Liposomal Amphotericin B	3 mg/kg or 210mg (IV)	$1,285 to 1,558	$257
Amphotericin B lipid complex	5mg/kg or 350mg (IV)	$441	$240
Amphotericin deoxycholate	0.5 to 1 mg/kg or 35 to 70 mg (IV)	$42 to 84	$36

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

Daily costs (US$ per day) of fluconazole prophylaxis (AWP versus AC in a single center, US November 2024)

	Daily dose	Cost per day (US$)	
		AWP	AC
Fluconazole	400 mg (PO / IV)	$ 5 to 150 / 0.05 to 1	$ 3 / 8 to 16

The prices presented are AWP for daily dose for generic brand of antifungal except for anidulafungin and isavuconazole which generic formulations are 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. These direct costs are not including the costs associated with specific therapeutic drug monitoring 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.

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 unfavorable balance of effects, using universal anti-*Aspergillus* prophylaxis could not be cost-effective.

Other considerations were not judged key factors for the development of the recommendation in the context that the intervention did not provide a favorable balance of desirable / undesirable consequences:

-Acceptability / Stewardship (Is the intervention acceptable to key stakeholders?)

-Feasibility (Is the intervention feasible to implement?)

-Equity (What would be the impact on health equity?)

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 ○

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

Background

End-stage liver disease by itself is a risk factor for aspergillosis, so liver transplant candidates and liver transplant recipients are at some risk for IA early after transplant on that basis. The liver transplant procedure itself maintains a risk for Candida infection (during liver retrieval when the common bile duct is dissected and the gallbladder emptied / flushed, or during liver implantation when the biliary anastomosis is created as either a duct-to-duct or a Roux-en-Y hepaticojejunostomy when the recipient bile duct is diseased, etc). The antifungal Candida prophylaxis may or may not have concurrent mold coverage. Non-operative factors that are associated with aspergillosis include re-transplantation, receipt of corticosteroids, fulminant hepatic failure as cause of transplant, and the requirement for renal replacement therapy.

Literature Review

Pubmed was searched from January 2000 to April 2025 for studies reporting infectious outcomes among liver 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 the incidence of IA.

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

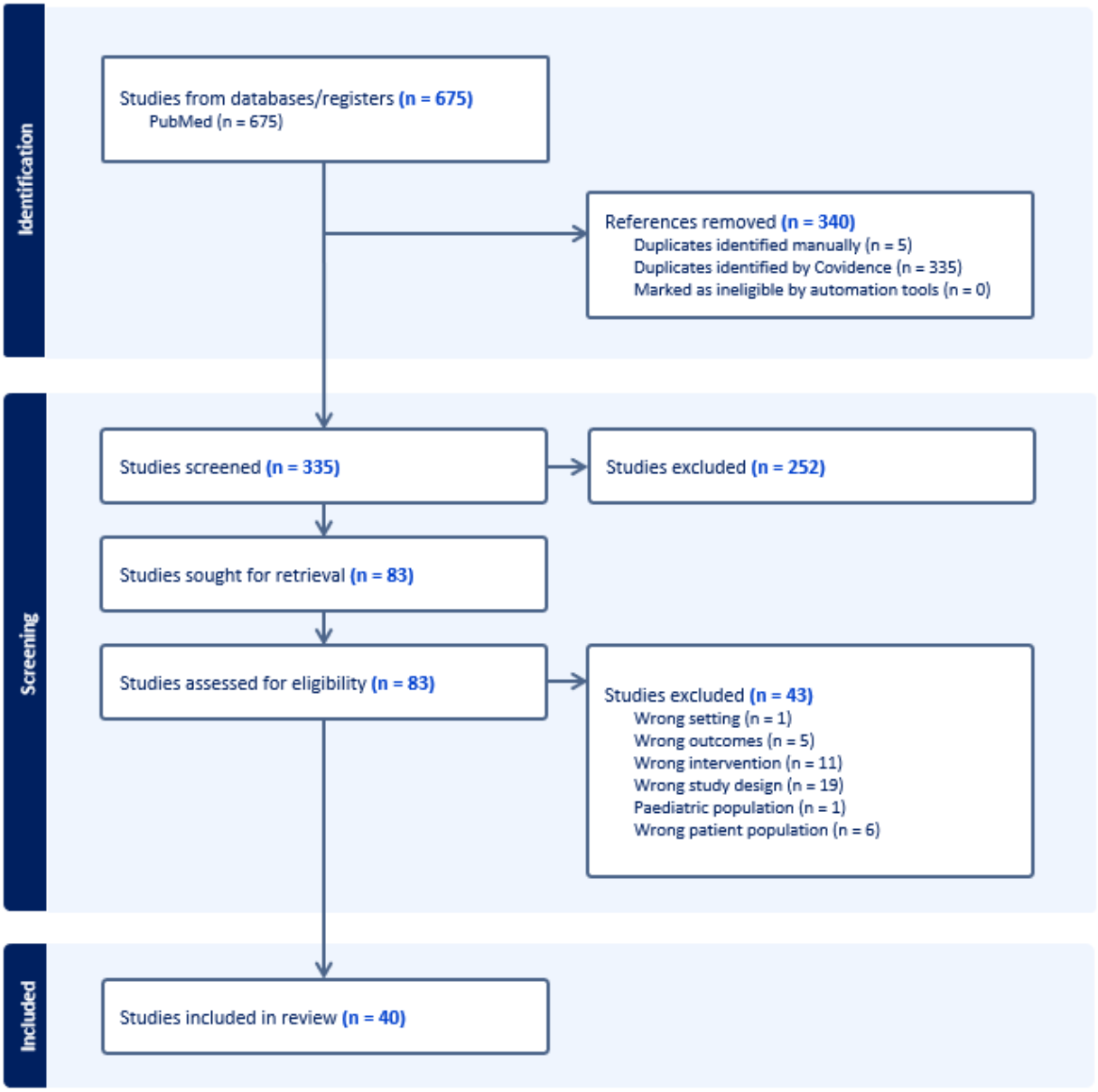
((("invasive mold*") OR ("invasive mould*") OR ("invasive fung*") OR (aspergill*) OR (aspergillus) OR (aspergillosis)) OR (("anti-fungal*" OR "antifungal*" OR antimold* OR anti-mold* OR anti-mould* OR antimould* OR antiaspergill* OR anti-aspergill* OR Voriconazole OR Posaconazole OR Isavuconazole OR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

AND
("Liver Transplantation"[Mesh] OR "liver transplant*" OR "hepatic 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 A1.4: PRISMA Flow diagram of study identification and selection (last updated on 1st April 2025)



Among 335 non-duplicate articles identified, most (252) were excluded by review of the title and abstract. After 43 further articles were excluded after full text review, 40 articles had data extracted [1-40].

The analysis assembled 40 studies where the methods section provided enough detail such that infectious IA outcomes could be identified, with 2 of the studies having 2 separate time cohorts [5, 11].

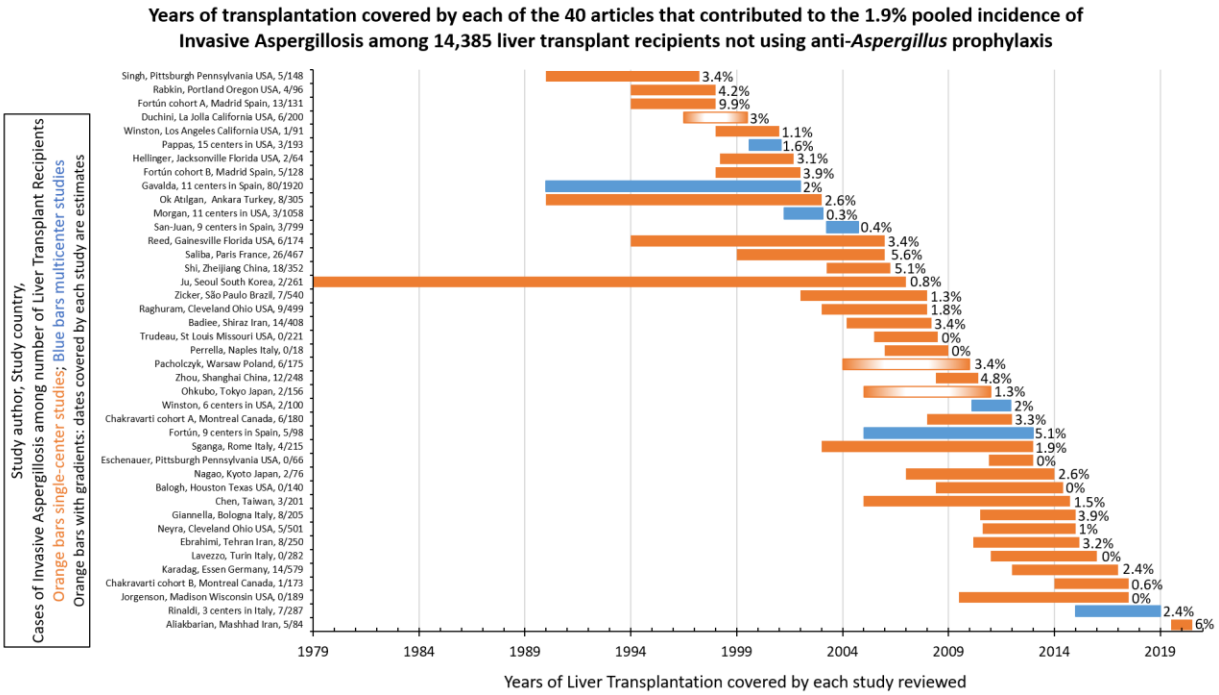
Supplementary Table A1.4. Source of definitions of proven or probable invasive aspergillosis

	Source of definitions	Year of publication	Author	Country
Single center studies	EORTC/MSG (De Pauw 2008 or Segal 2008 or Donnelly 2020)	2010 2013 2015 2016 2016 2016 2019 2019 2020 2020 2021 2021 2024	Badiee * Saliba Eschenauer Balogh Giannella Nagao Jorgenson Lavezzo Ebrahimi Neyra Chakravarti Karadag Aliakbarian	Shiraz, Iran France Pittsburgh, USA Houston, USA Bologna, Italy Kyoto, Japan Madison, USA Turin, Italy Tehran, Iran Cleveland, USA Montreal, Canada Germany Mashhad, Iran
	Pappas 2006	2008 2011	Shi Zicker	Zhejiang, China Brazil
	EORTC/MSG initial version (Ascioglu 2002)	2005 2009 2011 2012 2012	Hellinger Ju Zhou Ohkubo Raghuram	Jacksonville, USA South Korea Shanghai, China Tokyo, Japan Rochester, USA
	Denning 1994	2003 2007	Fortún Reed	Madrid, Spain Gainesville, USA
	Clinical criteria with no red flags to indicate inclusion of possible IA	2000 2001 2002 2002 2002 2011 2012 2013 2014 2014 2016	Rabkin Singh ** Duchini ** Biancofiore *** Winston Pacholczyk Perrella Trudeau Ok Atilgan Sganga Chen	Portland, USA Pittsburgh, USA La Jolla, USA Pisa, Italy Los Angeles, USA Poland Naples, Italy St. Louis, USA Turkey Rome, Italy Taiwan
Multicenter studies	EORTC/MSG (De Pauw 2008 or Segal 2008 or Donnelly 2020)	2014 2016 2021	Winston Fortún Rinaldi	6 centers, USA 9 centers, Spain 3 centers, Italy
	EORTC/MSG initial version (Ascioglu 2002)	2005 2005	Gavalda Morgan	11 centers, Spain 11 centers, USA
	Detailed clinical criteria with no red flags to indicate inclusion of possible IA	2006 2011	Pappas San-Juan	15 centers, USA 12 centers, Spain

Notes:
* Also referenced Pappas 2006.
** Clinical definitions and also referring back to Pittsburgh publications by Paterson and/or Singh.
*** Clinical definitions and also referring back to Castaldo 1991.
EORTC/MSG: The European Organization for Research and Treatment of Cancer and the Mycoses Study Group

Although the studies were published in 2000 or later, the number of years of lookback was as long as 28 years for a single study [16], so patients transplanted as early as 1979 were included.

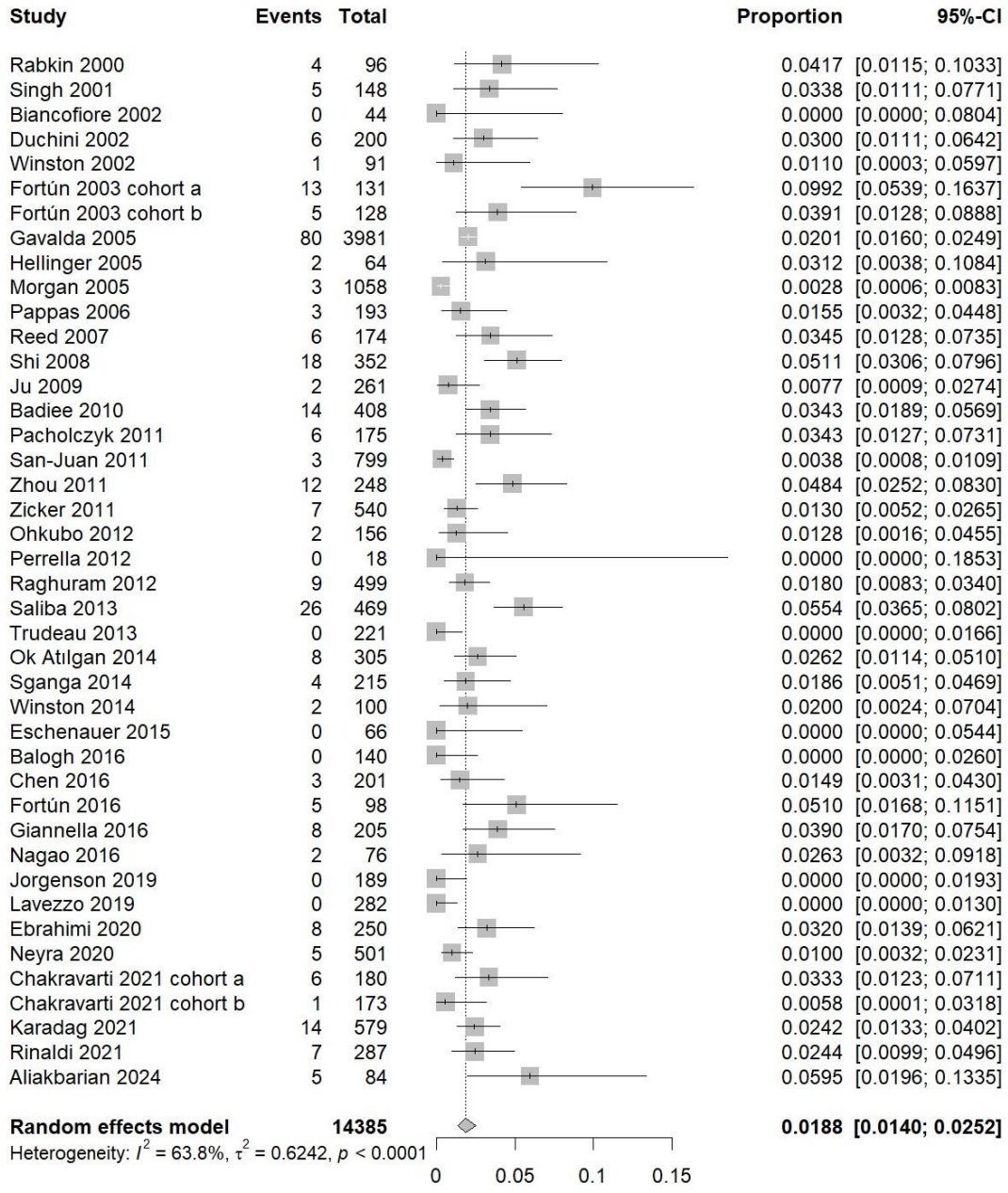
Supplementary Figure A1.5: Incidence of invasive aspergillosis by years of transplantation covered by each included study



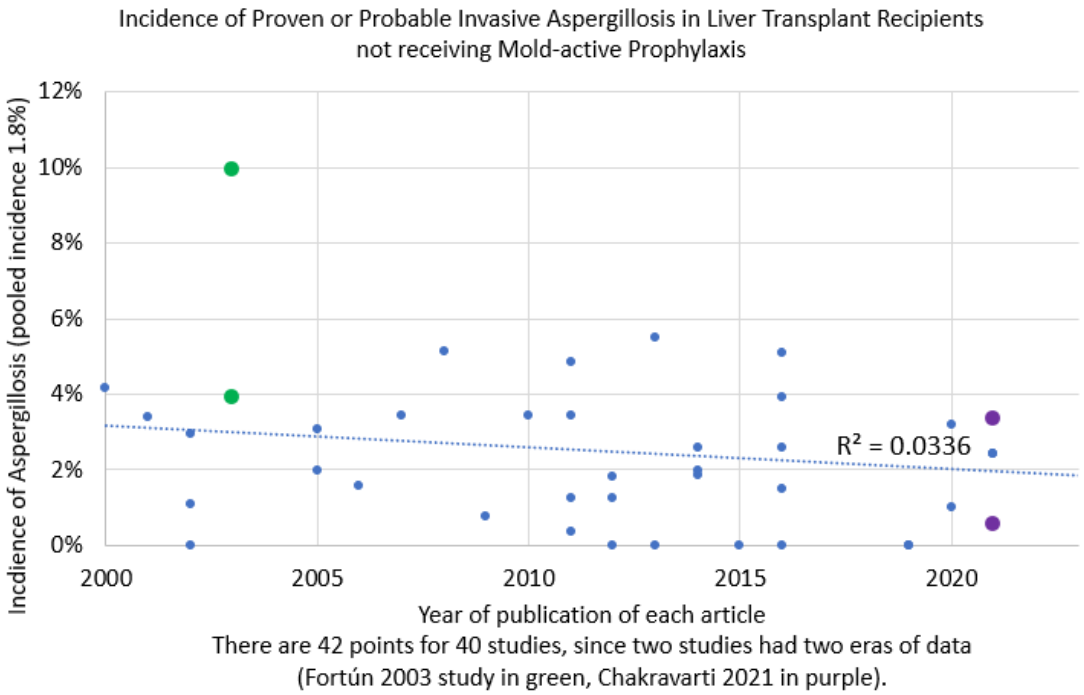
Notes: Multicenter studies colored blue, single center studies colored orange. Bars with gradients indicate that the dates covered by the study are estimated from data in the article.

Among 14,385 liver transplant recipients not using anti-*Aspergillus* prophylaxis, 305 cases of proven or probable IA were identified (using EORTC/MSG criteria, a similar definition, or clinical criteria without red flags for the inclusion of possible IA). **The pooled incidence for IA was 1.9% (95% confidence interval (CI) 1.4 to 2.5%)** using a generalized linear mixed-effects model. The median incidence for IA was 2.2% (Interquartile range (IQR), 0.72%, 3.4%).

Supplementary Figure A1.6: Forest plot of incidence of invasive aspergillosis in liver transplant recipients not receiving anti-*Aspergillus* prophylaxis



Supplementary Figure A1.7: Incidence of invasive aspergillosis by year of publication

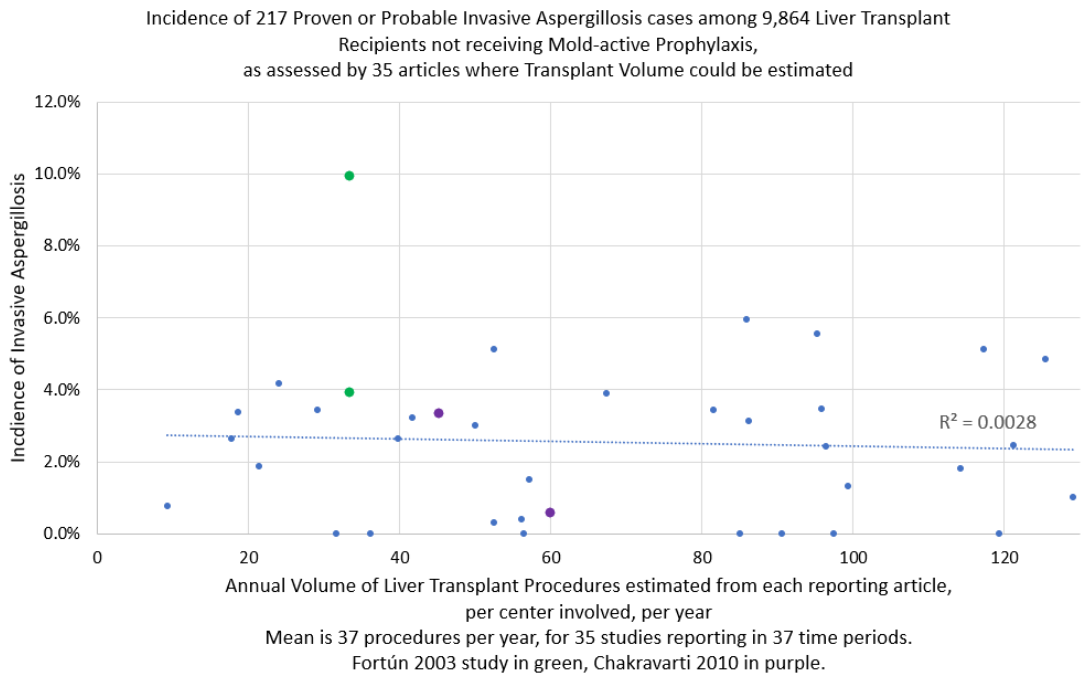


No correlation was observed between IA incidence and the year of publication of the articles, since the R-squared value is 0.0336 and an R-squared value closer to 1 represents a better fit.

The one-year all-cause mortality rate for IA was 65% among 146 cases where survival outcome was recorded.

Additionally, 35 of the 40 studies (87.5%) contained information that allowed for an approximate estimation of annual transplant volumes at the reporting centers. The studies evaluated represented a wide range of transplant procedures per center. For the two studies with two separate no -prophylaxis cohorts, Chakravarti 2021 had transplant volume numbers reported for each cohort separately, while Fortún 2016 from 2003 had a single volume reported that spanned the time of both cohorts.

Supplementary Figure A1.8: Incidence of invasive aspergillosis by annual volume of liver transplant procedures



No correlation was observed between IA incidence and the volume of liver transplant procedures performed at these centers, with an R-squared value of 0.0028.

One article reported an IA incidence of 9.9% in the first of two reported cohorts in the article [10]. Cohort A had no use of anti-*Aspergillus* prophylaxis, only fluconazole to prevent yeast infection. In the second time period during this article, high risk liver transplant recipients were given prophylaxis, so Cohort B represents low risk patients during the second time period. Fortún considered patients high risk if they had four or more of the following factors: high number (>30 units) of packed red cells required during the transplantation procedure; renal failure (creatinine clearance <25 mg/mL or creatinine serum level >2.5 mg/dL); dialysis requirement (or hemofiltration); re-transplantation; surgical reintervention (with a general anesthesia); positive cytomegalovirus (CMV) antigenemia (>10 cells/200 000) or CMV disease; acute rejection episode; mold colonization; prolonged antibiotic therapy (>5 days); and intensive care unit stay before transplantation.

33 of 40 studies were retrospective, observational single-center studies, while 7 studies reviewed patients from groups of hospitals within their country (Spain, Italy, and the United States) [11, 12, 19, 25, 32, 38, 40].

Risk factors for IA infections after liver transplantation had been analyzed by Phoompoung and colleagues from 28 studies published through to 2019 [41]. They found that risk factors for invasive candidiasis differed from IA, with IA risk factors including post-transplant renal replacement therapy (OR 9.2; 95% CI 4.2–20.4), re-operation (OR 8.0; 95% CI 2.9–21.7), and CMV infection (OR 6.2; 95% CI 2.0–19.3). Of the articles we examined that were published after 2019, no new risk factors were noted.

Conclusion

There may be a role for anti-*Aspergillus* prophylaxis among specific hospital systems with a high number of recognized cases of IA, or for unique patients with individual generalized risk factors for IA that may include re-operation, renal replacement therapy, CMV, or augmented immunosuppression.

Research gaps

Significant research gaps remain in understanding *Aspergillus* prophylaxis in liver transplant recipients, primarily due to inconsistent practices, diagnostic challenges, drug-related complexities, and a lack of high-quality, large-scale clinical trial data. A key gap is confirming whether prophylaxis improves overall survival and not just reduces the incidence of fungal infection. While some centers use universal prophylaxis, most employ a targeted approach for high-risk patients as outlined in the manuscript. The best antifungal agent for prophylaxis is unclear because fluconazole, echinocandins, and mold-active azoles have all been used in different settings. The ideal duration of therapy is also debated, as many guidelines are based on limited data. The low incidence of IA in liver transplant recipients makes conducting large, multicenter RCTs challenging, yet these studies are needed to provide high-level for treatment recommendations. Research on the impact of prophylaxis on patient-reported outcomes, such as quality of life and side effects, is lacking.

Research is lacking on the efficacy of a pre-emptive strategy, which involves monitoring for early signs of infection in high-risk patients and starting treatment only when evidence of infection is detected.

There is limited evidence to guide the duration of secondary prophylaxis after a patient successfully recovers from an IA episode.

Clinical question A2: In liver transplant recipients, should targeted anti-*Aspergillus* prophylaxis be used rather than no anti-*Aspergillus* prophylaxis?

Population: Adult liver transplant recipients in early post-transplant period
Intervention: Targeted anti-*Aspergillus* prophylaxis
= either echinocandins, triazoles, AmB or itraconazole
= In liver transplant recipients considered at high risk of IA
Comparator: No anti-*Aspergillus* prophylaxis
= either anti-yeast prophylaxis (fluconazole) or no anti-*Aspergillus* prophylaxis
Outcomes (patient-important outcomes as per panel voting and reassess by subgroup)
Critical
-Reduction in IA
-Reduction in mortality (all-cause/overall and attributable)
-Increase in SAEs
Important
-Increase in non-serious AEs
Removed outcome
-IFIs (not a good surrogate outcome of IA in this population since IFIs were mainly equivalent to invasive Candida infections)
Outcomes not reported:
-Need to change antifungal therapy
-Length of hospital stay, readmission, quality of life
-Graft rejection, Graft loss

Literature Search Strategy (last updated April 4th, 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
(pre-emptive OR preemptive OR prophyla*)
AND
("Liver Transplantation"[Mesh] OR "liver transplant*" OR "hepatic transplant*")
NOT
("Case Reports"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type])
NOT RCTs

Limits: English; 2000-present
Search run on February 27th, 2024
Rerun on April 4th, 2025

Embase

#1. 'invasive mold*'
#2. 'invasive mould*'
#3. 'invasive fung*'
#4. aspergill*
#5. aspergillus
#6. aspergillosis
#7. 'anti-fungal*'
#8. 'antifungal*'
#9. antimold*
#10. 'anti mold*'
#11. 'anti mould*'
#12. antimould*
#13. antiaspergill*
#14. 'anti aspergill*'
#15. voriconazole
#16. posaconazole
#17. isavuconazole
#18. amphotericin
#19. echinocandin
#20. caspofungin
#21. micafungin
#22. anidulafungin
#23. itraconazole
#24. triazole
#25. azole
#26. #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
#27. 'pre emptive' OR preemptive OR prophyla*
#28. 'liver transplantation'/exp OR 'liver transplant*' OR 'hepatic transplant*'
#29. #26 AND #27 AND #28 AND [english]/lim
#30. #29 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py)
#31. #30 AND ('Conference Abstract'/it OR 'Conference Paper'/it OR 'Conference Review'/it)
#32. #30 NOT #31

Limits: English; 2000-present

Search run on February 27th, 2024
Rerun on April 4th, 2025

Cochrane
#1 invasive NEXT mold*
#2 invasive NEXT mould*
#3 invasive NEXT fung*
#4 aspergill*
#5 aspergillus
#6 aspergillosis
#7 anti-fungal*
#8 antifungal*
#9 antimold*
#10 anti-mold*
#11 anti-mould*
#12 antimould*
#13 antiaspergill*
#14 anti-aspergill*
#15 Voriconazole
#16 Posaconazole
#17 Isavuconazole
#18 Amphotericin
#19 Echinocandin
#20 Caspofungin
#21 Micafungin
#22 Anidulafungin
#23 Itraconazole
#24 triazole
#25 azole
#26 #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
#27 pre-emptive
#28 preemptive
#29 prophyla*
#30 #27 OR #28 OR #29
#31 MeSH descriptor: [Liver Transplantation] explode all trees
#32 liver NEXT transplant*
#33 hepatic NEXT transplant*
#34 #31 OR #32 OR #33
#35 #26 AND #30 AND #34

Limits: English; 2000-present
Search run on February 27th, 2024
Rerun on April 4th, 2025

Web of Science
"invasive mold*"(All Fields) OR "invasive mould*"(All Fields) OR "invasive fung*"(All Fields) OR aspergill*(All Fields) OR aspergillus (All Fields) OR aspergillosis (All Fields) OR "anti-fungal*"(All Fields) OR "antifungal*"(All Fields) OR antimold*(All Fields) OR anti-mold*(All Fields) OR anti-mould*(All Fields) OR antimould*(All Fields) OR antiaspergill* (All Fields) OR anti-aspergill*(All Fields) OR Voriconazole(All Fields) OR Posaconazole (All Fields) OR Isavuconazole (All Fields)OR Amphotericin (All Fields) OR Echinocandin (All Fields) OR Caspofungin(All Fields) OR Micafungin (All Fields)OR Anidulafungin(All Fields) OR Itraconazole (All Fields) OR triazole (All Fields) OR azole (All Fields)
AND
pre-emptive (All Fields) OR preemptive (All Fields) OR prophyla* (All Fields)
AND
"Liver Transplantation" (All Fields) OR "liver transplant*" (All Fields) OR "hepatic transplant*" (All Fields)
NOT
"randomized control* trial" OR randomi*
Also Exclude: Editorial Material, Letter, Meeting Abstract, Meeting Summary

Limits: English; 2000-present
Search run on February 27th, 2024
Rerun on April 4th, 2025

Eligibility Criteria for Selection of the Studies

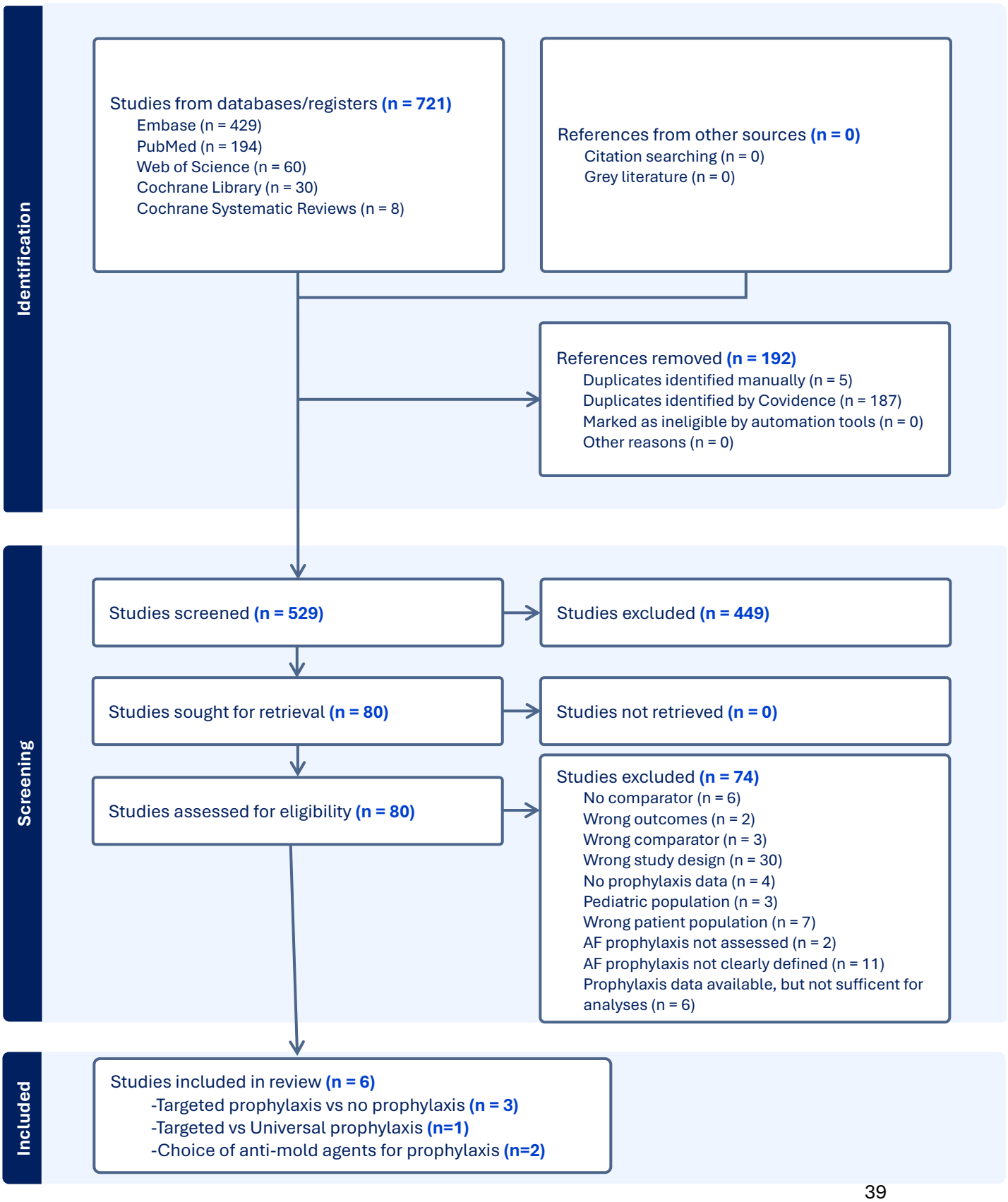
Inclusion criteria:

- Patient population: Adults liver transplant patients in early post-transplant period
- Intervention: Targeted anti-*Aspergillus* prophylaxis
  = Patients at high risk of IA which is classically defined as presenting at least one of the recognized risk factors, such as:
    1) RRT in peri-transplantation period
    2) re-transplantation
    3) transplantation for fulminant liver failure
    4) *Aspergillus* colonization prior to transplant
  = Anti-*Aspergillus* prophylaxis
    -Echinocandins such as caspofungin, micafungin or anidulafungin
    -Triazoles such as posaconazole, voriconazole or isavuconazole
    -AmB (IV or inhaled)
    -Itraconazole (any formulation)
- -Comparator: No anti-*Aspergillus* prophylaxis
  -Fluconazole (any formulation)
  -Absence of antifungal prophylaxis
- -Outcomes: study reporting on either incidence of IA or/and AEs associated with the use of anti-*Aspergillus* prophylaxis
- Study design: Observational studies (including pre / post-intervention studies)
- Year: published from 2000 up to present
- Language: English only

Exclusion criteria:

- -Patient population:
  -Pediatric population
  -Liver transplant patients not specifically at high risk of IA (for example, studies reporting on patients at high risk of invasive Candida infection but not at high risk of IA were not included)
- -Intervention / Comparator
  -Comparison: any comparison where the comparator group is not classified at similar risk of IA (e.g. high risk with targeted anti-*Aspergillus* prophylaxis vs low risk without anti-*Aspergillus* prophylaxis)
- -Study design
  -One-arm studies (including case series and case reports)
  -Conference proceedings, abstracts, letters to editor, and comments

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



Supplementary Table A2.1: GRADE evidence profile

Clinical question A2: In liver transplant recipients, should **targeted anti-*Aspergillus* prophylaxis** be used rather than **no anti-*Aspergillus* prophylaxis**?

P: Adult liver transplant recipients
I: Targeted anti-*Aspergillus* prophylaxis (i.e. in liver transplant recipients at high risk of invasive aspergillosis)
C: No 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	No anti-*Aspergillus* prophylaxis **	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (follow-up: 3 to 12 months months)										**MID*:** at least 40 fewer per 1,000		
3[1-3]	non-randomized studies	not serious[a]	not serious	not serious	very serious[b]	none[c]	3/86 (3.5%)	10/59 (16.9%)	**RR 0.19** (0.06 to 0.66) ***	**137 fewer per 1,000** (from 159 fewer to 58 fewer)	⊕◯◯◯ Very low	CRITICAL
Invasive Aspergillosis (follow-up: 3 months) &										**MID*:** at least 40 fewer per 1,000		
2[5,6]	randomized trials	not serious	not serious	serious[d]	serious[e]	none	0/133 (0%)	2/128 (1.6%)	**RR 0.20** (0.01 to 4.15)	**13 fewer per 1,000** (from 15 fewer to 49 more)	⊕⊕◯◯ Low	CRITICAL
Mortality (all-cause) (follow-up: 12 months)												
1[3]	non-randomized studies	not serious[a]	not serious	not serious	extremely serious[f]	none	6/11 (54.5%)	12/22 (54.5%)	**RR 1.00** (0.52 to 1.94)	**0 fewer per 1,000** (from 262 fewer to 513 more)	⊕◯◯◯ Very low	IMPORTANT
Attributable Mortality (follow-up: 12 months)										**MID*:** at least 20 fewer per 1,000		
3[1-3]	non-randomized studies	not serious[a]	not serious	not serious	very serious[g]	none	1/86 (1.2%)	8/59 (13.6%)	**RR 0.18** (0.03 to 1.00)	**111 fewer per 1,000** (from 132 fewer to 0 more)	⊕◯◯◯ Very low	CRITICAL
Serious Adverse Events £										**MID*:** at least 40 fewer per 1,000		
6[4-9]	randomized trials	serious[h]	not serious	not serious	serious[e]	None	9/437 (2.1%)	7/388 (1.8%)	**RR 1.15** (0.40 to 3.30)	**3 more per 1,000** (from 11 fewer to 41 more)	⊕⊕◯◯ Low	CRITICAL
Non-serious Adverse Events £												
5[4,5,7-9]	randomized trials	serious[i]	not serious	not serious[j]	serious[e]	None	81/398 (20.4%)	48/359 (13.4%)	**RR 1.50** (0.96 to 2.35)	**67 more per 1,000** (from 5 fewer to 181 more)	⊕⊕◯◯ Low	IMPORTANT
Non-serious Adverse Events (*for Echinocandins ONLY*) £												
2[4,5]	randomised trials	serious[k]	not serious	not serious	serious[e]	None	20/183 (10.9%)	18/186 (9.7%)	**RR 1.13** (0.62 to 2.06)	**13 more per 1,000** (from 37 fewer to 103 more)	⊕⊕◯◯ 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
***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.**
*****This estimate represents the effect in the intend to treat population (rather than the per protocol) and is likely underestimating the incidence of aspergillosis since most studies reported a high rate of deviation from the intervention and simultaneous cointerventions.**
& This row is reporting on the effect of anti-Aspergillus prophylaxis from the 2 RCTs included in clinical question A1 where a significant proportion of the population were considered at higher risk of Invasive Aspergillosis. The pooled relative effects were comparable between the 2 RCTs and the 3 non-randomised studies included in clinical question A2, but the baseline incidence of IA and thus the absolute effect differs greatly. The panel judged that this consistency in relative effect of anti-Aspergillus prophylaxis between different study designs further supports that this pooled effect reported in the 3 included non-randomised studies is not likely to be overestimated.
£ Adverse Events were not reported in the 3 non-randomised studies included in clinical question A2, but the panel judged that the reported Serious Adverse Events in the 6 RCTs included in clinical question A1 were generalizable to this clinical question as the included populations, antifungal agents and comparators were similar.

Explanations

a. All 3 studies were designed as pre/post-intervention studies, and they were all considered at serious of bias (ROBINS-I) mainly due to potential residual confounding and selection bias. Of note, the following potential biases might cause underestimation of the effect of prophylaxis: 1) derivation from the intended intervention in 2 of the included studies where patients in the prophylaxis group did not receive it (Chakravarti 2021 and Hellinger 2005), 2) administration of an anti-*Aspergillus* agent in the control group in one study (Hellinger 2005).

b. The boundaries of the confidence interval are on the same side of their decision-making and do not cross the clinical decision threshold between recommending and not recommending prophylaxis (meaning that different decisions could be recommended at the lower vs the upper boundary of the confidence interval). Nevertheless, the sample size does not meet the OIS (optimal information size), thus providing evidence of very serious imprecision around the estimates of effect.

c. Despite the possible publication bias, this outcome was not rated down since the reported effect was very similar to what was reported in clinical trials (which are usually at lower risk for publication).

d. For each of these 2 studies, only a proportion of the cohorts was considered to be higher risk of invasive *Aspergillus* infection, thus rated down for indirectness.

e. The upper boundary of the confidence interval crosses the decision threshold (minimal important difference for recommending or not the prophylaxis), thus providing evidence of serious imprecision around the estimates of effect.

f. The lower boundary of the confidence interval crosses the decision threshold for important benefit and the confidence interval likely includes moderate to large benefit while the upper boundary of the confidence interval crosses the decision threshold for important harm and the confidence interval likely includes moderate to large harm, thus providing evidence of extremely serious imprecision.

g. The lower boundary of the confidence interval crosses the decision threshold (minimal important difference for recommending prophylaxis or not) and the confidence interval likely includes moderate and large effect, thus providing evidence of very serious imprecision around the estimates of effect.

h. Judged at high risk of bias: Winston 2002 and Kang 2020 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest).

i. Judged at high risk of bias: Winston 2002 and Kang 2020 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest) and Sharpe 2003 due to early stoppage (consequently causing serious concerns regarding adequate randomization and potential attrition bias).

j. Statistically significant noted in the meta-analysis (I^2=35%, p-value=0.19) but clearly explained by the heterogeneity of the agents used and their side effect profile, as well as the definition of non-serious adverse events between studies.

k. Judged at high risk of bias: Kang 2020 due to the lack of blinding (i.e. investigators might have judged clinical outcomes differently in both groups, which could have led to difference in investigations, in change of antifungal therapy, and ultimately affecting the outcome of interest).

References

1. Chakravarti et al. Targeted caspofungin prophylaxis for invasive aspergillosis in high-risk liver transplant recipients, a single-center experience. Transplant Infectious Disease 2021;23(4):e13568.
2. Hellinger et al Risk stratification and targeted antifungal prophylaxis for prevention of aspergillosis and other invasive mold infections after liver transplantation. Liver Transplantation 2005;11(6):656-662.
3. Singh et al. Preemptive prophylaxis with a lipid preparation of amphotericin B for invasive fungal infections in liver transplant recipients requiring renal replacement therapy. Transplantation 2001;71(7):910-913.
4. Kang et al. A Multicenter, Randomized, Open-Label Study to Compare Micafungin with Fluconazole in the Prophylaxis of Invasive Fungal Infections in Living-Donor Liver Transplant Recipients. J Gastrointest Surg Apr 2020;24(4):832-840.
5. Winston et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. Am J Transplant Dec 2014;14(12):2758-64.
6. Hadley et al. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. Transpl Infect Dis Feb 2009;11(1):40-8.
7. Sharpe et al. Efficacy and safety of itraconazole prophylaxis for fungal infections after orthotopic liver transplantation: a prospective, randomized, double-blind study. Transplantation Sep 2003;76(6):977-83.
8. Winston et al. Randomized controlled trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients. Transplantation Sep 2002;74(5):688-95.
9. Biancofiore et al. Antifungal prophylaxis in liver transplant recipients: a randomized placebo-controlled study. Transpl Int Jul 2002;15(7):341-7.

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, total duration)*	**Comparator** *(No anti-Aspergillus prophylaxis, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and Duration of follow-up**
Chakravarti 2021 Quebec, Canada Single center	Liver transplant recipients (**with stratification for high risk of IA**) Before: 2008-2011 After: 2014 - 2017 N = 256 (at high risk of IA = 70) Age (median): 54y in the intervention group vs 57y in the comparator group Exclusion: -Multi-visceral transplantation -Death within 24 hours -All liver transplants in 2012 and 2013	Before – after retrospective cohort study Primary outcomes: Incidence of proven or probable IA in high-risk patients within 90 days	High risk for IA = criteria for inclusion in the targeted prophylaxis group in the post-intervention phase (defined as at least one of the following criteria: acute liver failure, requirement for renal replacement therapy within 30 days of transplantation (prior or after OLT), re-transplantation or colonization with *Aspergillus* prior to transplantation).	**In patients at high risk of IA:** Baseline risk for AI: 16.7% Baseline risk of mortality: NR (but was 3.9% in the entire pre-intervention cohort)	**In patients at high risk of IA**: Caspofungin 70mg IV loading dose followed by 50mg daily Duration: 28 days or until discharge (whichever was sooner) (median days received= NR)	No antifungal prophylaxis	Proven or Probable IFI according to EORTC/MSG 2008 Total duration: 90 days
Hellinger 2005 Florida, USA Single center	Liver transplant recipients (**with stratification for high risk for IMI**) Before: 1998-1999 After: 1999 - 2001 n = 308 (at high risk of IMI = 42) Age (median): 52y in the intervention group vs 51y in the comparator group Exclusion: NR	Before – after retrospective cohort study Primary outcomes: Incidence of invasive mold or yeast infection at 12 months	High risk for invasive mold infection = criteria for inclusion in the targeted prophylaxis group in the post-intervention phase (defined as : (1) hemodialysis at the time of transplantation; (2) hospital discharge delayed beyond 7 days after transplantation because of allograft or renal insufficiency; (3) transplantation for fulminant hepatic failure; and (4) re-transplantation; recipients at HIGH RISK = who had either or both of the first 2 risk factors / recipients at INTERMEDIATE RISK = who had either or both of the latter 2 risk factors).	**In the group at high risk of IMI:** Baseline risk for AI: 28.6% Baseline risk of mortality: NR	**In patients at high or intermediate risk of IMI:** 5mg/kg/day of ABLC continued Duration: until hospital discharge (median days received= NR)	No antifungal prophylaxis	Proven, Probable or Possible IFI according to EORTC/MSG 2002 Total duration: 12 months
Singh 2001 Pennsylvania, USA Single center	Liver transplant recipients requiring RRT Before: 1990-1997 After: 1997- 2000 n = 33 Age (mean): 48y Exclusion: NR	Before – after retrospective cohort study Primary outcomes: Incidence of IFI	All patients on renal replacement therapy (thus, **all considered at high risk of IA**)	**In the group at high risk of IA:** Baseline risk for AI: 13.6% Baseline risk of mortality: 54.5%	5mg/kg/day of L-AmB or ABLC Duration: until discharge, death or discontinuation of RRT	No antifungal prophylaxis	IA (defined as evidence of tissue invasion on biopsy or autopsy plus isolation of *Aspergillus* species in culture) and Invasive candidiasis (defined as histopathologic evidence of tissue invasion by biopsy, or on autopsy, or isolation of *Candida* species in one or more blood cultures, or isolation of *Candida* in normally sterile body fluid or sites, with samples collected intra-operatively or by percutaneous needle aspirate).

							Total duration: 12 months

Legend:
ABLC: amphotericin B lipid complex
IA: invasive aspergillosis IFI: invasive fungal infection
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
L-AmB: liposomal amphotericin IMI: invasive mold infection
NR: not reported
OLT: orthotopic liver transplant
RRT: renal replacement therapy

*Exclusion: the exclusion criteria listed were those considered important for generalizability of the data but are not exhaustive.

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

Studies	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
Chakravarti 2021	**Serious**	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 expected due to potential changes in enrolled participants over time (i.e. over a 10-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	Derivation from the intended intervention: 15% proportion of the cohort identified at high risk of IA did not receive prophylaxis. Nevertheless, the deviation would be expected to drive the effect towards the null.	Missing data was described and likely not significant.	Diagnosis of IA was based on EORTC/MSG (diagnosis criteria probably not changing with time throughout the study period)	The outcome measurement and analyses are consistent and well described in the Methods.
Hellinger 2005	**Serious**	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	Derivation from the intended intervention: 49% proportion of the cohort identified at HR of IA did not receive prophylaxis. Administration of an antifungal treatment for yeast infections (but with anti-*Aspergillus* activity) occurred in 14% of the pre-intervention group. Nevertheless, the deviation would be expected to drive the effect towards the null.	No information on missing data or potential for data to be missing	Diagnosis of IA was based on EORTC/MSG (diagnosis criteria probably not changing with time throughout the studied period)	The outcome measurement and analyses are incompletely described in the Methods.
Singh 2001	**Serious**	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 expected due to potential changes in enrolled participants over time (i.e. over a 10-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	No deviation from the intervention reported.	No information on missing data or potential for data to be missing	Diagnosis of IA required evidence of tissue invasion on biopsy or autopsy plus isolation of *Aspergillus* species in culture (diagnosis criteria probably not changing with time throughout the studied period)	No description of the planned outcomes and analyses.

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

Risk of bias judgment

Low	
Moderate	
Serious	
Critical	
No information	

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

Please note that all studies are presented from the most recently published to the oldest in other to assess the generalizability of the data.

Figure A2.2.a: Invasive aspergillosis (3 to 12 months)

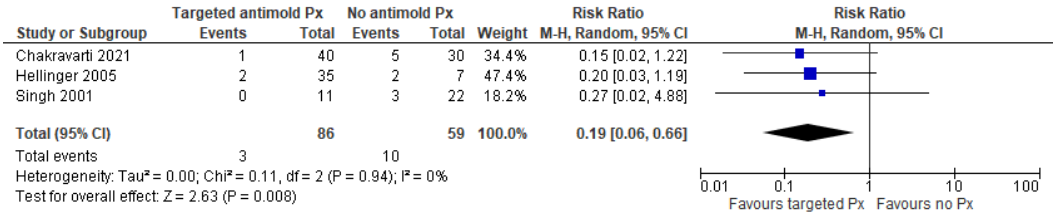


Figure A2.2.b: Mortality (12 months)

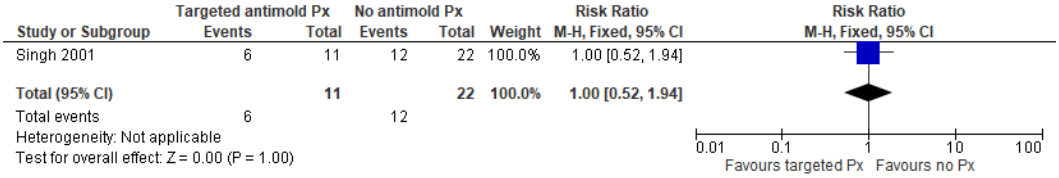


Figure A2.2.c: Attributable mortality (12 months)

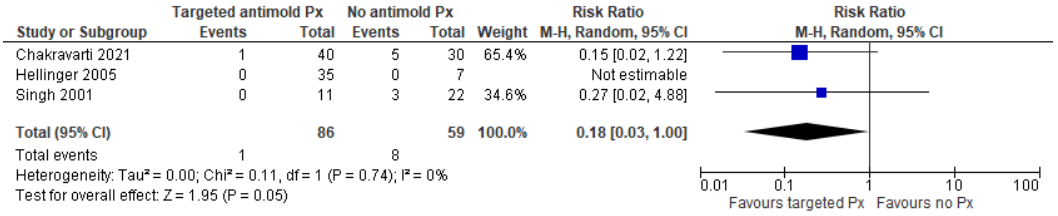
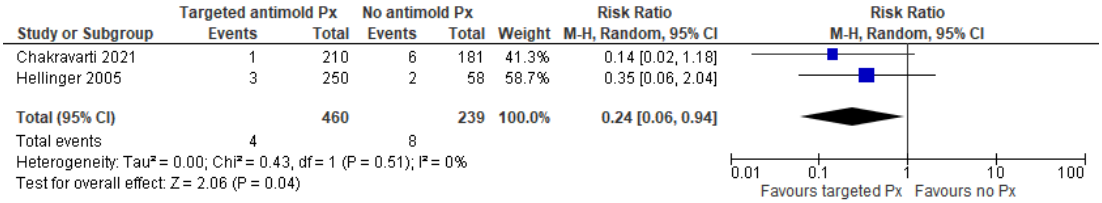


Figure A2.2.d: Serious and non-serious Adverse Events: not reported

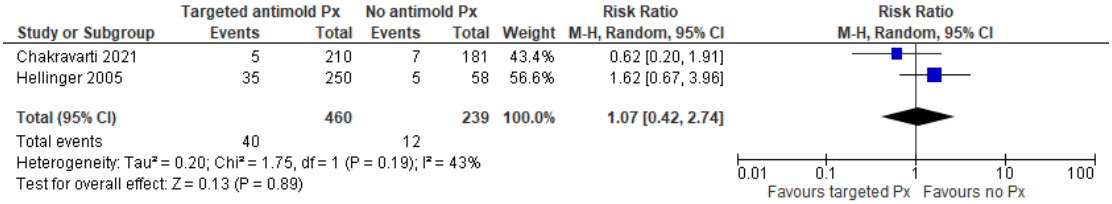
<u>Impact of using targeted anti-*Aspergillus* prophylaxis on the entire cohort of liver transplant recipients</u> (assuming the patients at low-risk IA group are not receiving antifungal prophylaxis)

Figure A2.2.e: Invasive aspergillosis (3 to 12 months)



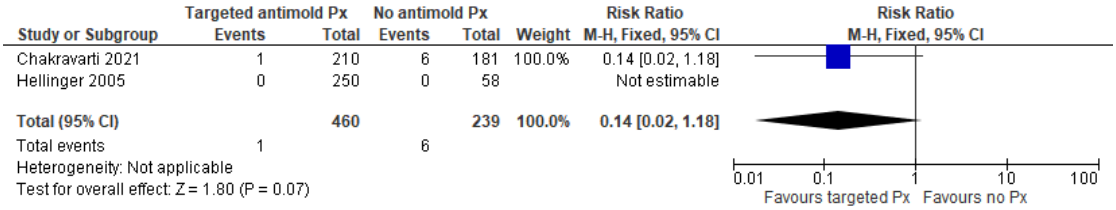
In the entire cohort (with a baseline risk of 3.3% (i.e. in the comparator group), which was 16.9% in the high risk group and 0.5% in low risk group), and RD = -2.5%, 95% CI (from -3.1% to -0.2%)

Figure A2.2.f: Mortality (12 months)



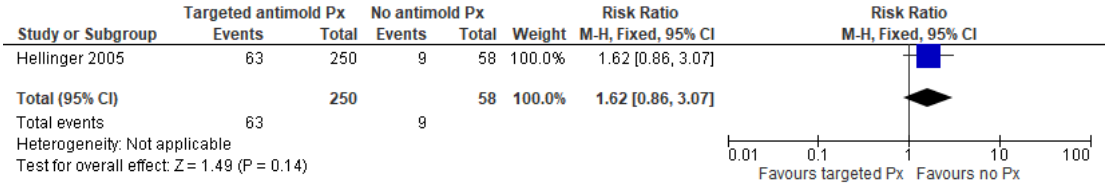
In the entire cohort (with a baseline mortality of 5.0%), RD = 4.0%, 95% CI (from -2.9% to 8.7%)

Figure A2.2.g: Attributable mortality (12 months)



In the entire cohort (with a baseline IA attributable mortality of 2.5%), RD = - 2.2%, 95% CI (from -2.5% to -0.5%)

Figure A2.2.h: Graft loss



In the entire cohort (with a baseline graft loss rate of 15.5%), RD = 9.6%, 95% CI (from 2.2% to 32.1%), but selection bias very likely for this outcome according to authors.

Figure A2.2.i: Serious and non-serious Adverse Events: not reported

Supplementary Table A2.4: 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	When comparing targeted anti-*Aspergillus* prophylaxis with no anti-*Aspergillus* prophylaxis, the desirable consequences of in patients at high risk of invasive aspergillosis were judged substantial: -moderate to large reduction in incidence of invasive aspergillosis (risk difference of -13.7%, 95%CI (-15.9% to -5.8%) when a minimal reduction in incidence of IA by **4% was judged to be a small and important difference (decision threshold).** -moderate to large reduction in attributable mortality, without a reduction in all-cause mortality.	A risk difference of -13.7%, 95%CI (-15.9% to -5.8%) translate in a **number needed to prevent** (nnp) of 7 patients, with 95% (6 to 17) in a population with a baseline risk of 16.9%. With a relative risk of 0.19, with 95%CI (0.06 to 0.66), If we are aiming at bringing the baseline risk around 2% (baseline risk in liver transplant recipients), then targeted anti-*Aspergillus* prophylaxis would be beneficial on reducing the incidence of IA in a population with a **baseline risk** of IA approximating 10.5%, with 95%CI (3.03 to 33.3).

Undesirable effects

How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ **Small** ○ **Trivial** ○ Varies ○ Don't know	When considering the use of anti-*Aspergillus* prophylaxis with no anti-*Aspergillus* prophylaxis, the undesirable consequences were judged trivial to small: -no significant increase serous adverse events -small increase in non serious adverse events by 6.7%, 95%CI (0.5 to 18.1%) but when stratified by class of agents this increase was judged small to moderate for itraconazole and trivial for echinocandins.	The panel underlined the echinocandins are usually the preferred anti-*Aspergillus* prophylaxis due the observed tolerability as well as its favorable drug-drug interaction profile.

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	In liver transplant patients at high risk for invasive aspergillosis, the evidence shows moderate desirable consequences with trivial to small adverse events, thus favoring using targeted prophylaxis rather than not.	

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 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 liver transplant recipients would generally support interventions that would provide a favorable balance of benefits and harms.

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	Two studies (Balogh 2016 and Reed 2007) reporting on direct costs of anti-*Aspergillus* prophylaxis in liver transplant recipients were identified from our mapping review. Nevertheless, the reported data was judged not to be generalizable to current time (i.e. reported costs of agents were from 1994-2005 and 2008-2014 while the costs associated with an episode of IA was derived from older literature).	Daily costs (US$ per day) of anti-*Aspergillus* agents (average wholesale prices (AWP) versus acquisition costs (AC) in a single center, US November 2024) **Echinocandins** Daily dose Cost per day (US$) AWP AC Micafungin 100 mg (IV) $58 to 224 $59 Caspofungin 50 mg (IV) $83 to 405 $53 Anidulafungin 100 mg (IV) $229 $211 **Amphotericin B** Daily dose (for 70 kg) Cost per day (US$) AWP AC Liposomal Amphotericin B 3 mg/kg or 210mg (IV) $1,285 to 1,558 $257 Amphotericin B lipid complex 5mg/kg or 350mg (IV) $441 $240 Amphotericin B deoxycholate 0.5 to 1 mg/kg or 35 to 70 mg (IV) $42 to 84 $36 The prices presented are AWP for daily dose for generic brand of antifungal except for anidulafungin and isavuconazole which generic formulations are 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. These direct costs are not including the costs associated with specific therapeutic drug monitoring (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.

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**		

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**	No evidence identified	The real cost-effectiveness was not estimable by the panel due to the lack of available evidence.

Acceptability / Stewardship

Is the intervention acceptable to key stakeholders?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	**Stewardship issues** **1) Mold-active azole prophylaxis:** -There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi, especially non-*C. albicans* species (especially *Nakaseomyces glabratus (*formerly known as *Candida glabrata)*). The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis in orthotopic liver transplant is not clear as only limited studies includes data on antifungal susceptibility in their report. -Anecdotal reports noted breakthrough infection of *Rhizopus* spp. during mold-active azole prophylaxis. **2) Echinocandin prophylaxis:** -Several recent reports raise concerns of emergence of breakthrough *Candida* infection during echinocandin (micafungin) prophylaxis in liver transplant recipients. It should point out that these studies did not link breakthrough *Candida* to echinocandin resistance. This signal was not observed in clinical trials. -In the papers reviewed, there were rare cases of breakthrough *Rhizopus* spp. during echinocandin prophylaxis. -Cryptococcal disease is an uncommon but fatal disease in patients with liver cirrhosis. Echinocandin has no activity against *Cryptococcus*.	**Ease of administration** -most agents used for prophylaxis are administered not more than once or twice daily -some agents have interchangeable route of administration for switching from parenteral to oral (e.g. triazoles) **Management of drug-drug interactions and adverse events** -most drug-drug interactions and adverse events are limited (echinocandins) or easily predictable (e.g. triazoles and hepatotoxicity)

Feasibility

Is the intervention feasible to implement?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	No evidence identified	In most inpatient settings where liver transplantation is performed, administration of anti-*Aspergillus* prophylaxis (either parenteral or oral) as well as monitoring organ function and blood levels should be feasible.

Equity

What would be the impact on health equity?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	No evidence identified regarding targeted vs no fungal prophylaxis, but some on evidence around the transplant procedure (PMID: 32043822,	Assuming that:

○ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	PMID: 38100220, PMID: 29266108, PMID: 29266108, PMID: 29266108)	1) anti-*Aspergillus* prophylaxis is administered until discharge or up to 28 days (duration of hospitalization being usually of 10 days in uncomplicated vs 21 days in complicated liver transplant recipients), without requirement for prolonged duration of prophylaxis after discharge 2) these agents are usually widely available for inpatient settings (unless limited by local formulary issues), = then, the panel judged that implementing this recommendation should not have any impact on equity.

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**
ACCEPTABILITY / STEWARDSHIP	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know

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 A3: In liver transplant recipients, should targeted anti-*Aspergillus* prophylaxis be used rather than universal anti-*Aspergillus* prophylaxis?

Population: Adult liver transplant recipients in early post-transplant period
Intervention: Targeted anti-*Aspergillus* prophylaxis
= either echinocandins, triazoles, AmB or itraconazole
= In liver transplant recipients considered at high risk of IA
Comparator: Universal anti-*Aspergillus* prophylaxis
= all liver transplant recipients
= either same anti-*Aspergillus* prophylaxis as in the intervention group
Outcomes (patient-important outcomes as per panel voting and reassess by subgroup)
Critical
-Reduction in IA
-Reduction in mortality (all-cause/overall and attributable)
-Increase in SAEs
Important
-Increase in non-serious AEs
Removed outcome
-IFIs (not a good surrogate outcome of Invasive Aspergillosis in this population since IFIs were mainly equivalent to invasive Candida infections)
Outcomes not reported:
-Need to change antifungal therapy
-Length of hospital stay, readmission, quality of life
-Graft rejection, graft loss

Literature Search Strategy (same as Clinical Question A2)

Eligibility Criteria

Inclusion criteria:

- Patient population: Adults liver transplant patients in early post-transplant period
- Intervention: Targeted anti-*Aspergillus* prophylaxis
  - = Patients at high risk of IA which is classically defined as presenting at least one of the following recognized risk factors, such as:
    1) RRT in peri-transplantation period
    2) re-transplantation
    3) transplantation for fulminant liver failure
    4) *Aspergillus* colonization prior to transplant
  - = Anti-*Aspergillus* prophylaxis
    - -Echinocandins such as caspofungin, micafungin or anidulafungin
    - -Triazoles such as posaconazole, voriconazole or isavuconazole
    - -AmB (IV or inhaled)
    - -Itraconazole (any formulation)
- -Comparator: Universal anti-*Aspergillus* prophylaxis
  - = All liver transplant recipients
  - = **Same anti-*Aspergillus* prophylaxis as in the intervention group**
    - -Echinocandins such as caspofungin, micafungin or anidulafungin
    - -Triazoles such as posaconazole, voriconazole or isavuconazole
    - -AmB (IV or inhaled)
    - -Itraconazole (any formulation)
- -Outcomes: study reporting on either incidence of IA or/and AEs associated with the use of anti-*Aspergillus* prophylaxis
- Study design: Observational studies (including pre / post-intervention studies)
- Year: published from 2000 up to present
- Language: English only

Exclusion criteria:

- -Patient population:
  - -Pediatric population
- -Intervention / Comparator
  - -Comparison: any comparison where the comparator group is not classified at similar risk of IA (e.g. high risk with targeted anti-*Aspergillus* prophylaxis vs low risk without anti-*Aspergillus* prophylaxis)
- -Study design
  - -One-arm studies (including case series and case reports)
  - -Conference proceedings, abstracts, letters to editor, and comments

PRISMA Flow Diagram of Study Identification and Selection (same as Clinical Question A2)

Supplementary Table A3.1: GRADE evidence profile

Clinical Question A3: In liver transplant recipients, should **targeted anti-*Aspergillus* prophylaxis** be used rather than universal anti-*Aspergillus* prophylaxis?

P: Adult liver transplant recipients
I: Targeted anti-*Aspergillus* prophylaxis (i.e. in liver transplant recipients at high risk of IA)
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 **	Universal anti-*Aspergillus prophylaxis*	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (at 100 days post-transplant)										**MID*:** at least 40 fewer per 1,000		
1	non-randomized studies	not serious[a]	not serious	not serious	not serious[b]	None	1/145 (0.7%)	0/237 (0.0%)	not estimable	**7 more per 1,000** (from 7 fewer to 20 more)	⊕⊕◯◯ Low[a,b]	CRITICAL
Mortality (at 100 days post-transplant)												
1	non-randomized studies	not serious[a]	not serious	not serious	very serious[c]	none	15/145 (10.3%)	17/237 (7.2%)	**RR 1.44** (0.74 to 2.80)	**32 more per 1,000** (from 28 fewer to 91 more)	⊕◯◯◯ Very low[a,c]	IMPORTANT
Attributable Mortality (at 100 days post-transplant										**MID*:** at least 20 fewer per 1,000		
1	non-randomized studies	not serious[a]	not serious	not serious	not serious[b]	none	1/145 (0.7%)	0/237 (0.0%)	not estimable	**7 more per 1,000** (from 7 fewer to 20 more)	⊕⊕◯◯ Low[a,b]	CRITICAL
Serious and Non-serious Adverse Events (at 100 days post-transplant))										**MID*:** at least 40 fewer per 1,000		
1	non-randomized studies	not serious	not serious	not serious	serious[d]	none	2/145 (1.4%)	5/237 (2.1%)	**RR 0.65** (0.13 to 3.33)	**7 fewer per 1,000** (from 34 fewer to 19 more)	⊕◯◯◯ Very low[b]	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 intervention group used a stratification approach, where patients considered at low risk of invasive aspergillosis AND high risk of yeast infection received anti-yeast prophylaxis.**

Explanations

a. The included study was designed as before and after intervention study and considered at serious of bias (ROBINS-I) mainly due to potential residual confounding and selection bias.
b. The boundaries of the confidence interval do not cross the clinical decision threshold between recommending and not recommending prophylaxis (meaning that different decisions could be recommended at the lower vs the upper boundary of the confidence interval). In the context where the baseline risk is very small (less than 1%), the certainty of evidence was not rated down for imprecision.
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. The boundaries of the confidence interval do not cross the clinical decision threshold between recommending and not recommending prophylaxis (meaning that different decisions could be recommended at the lower vs the upper boundary of the confidence interval). In the context where the baseline risk is not very small (2.1%) and the OIS (optimal information size) is not met, the certainty of evidence was rated down for imprecision.

References

1. Eschenauer et al. Targeted versus universal antifungal prophylaxis among liver transplant recipients. American Journal of Transplantation 2015; 15(1):180-189.

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** *(Targeted 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**
Eschenauer 2015 Pennsylvania, USA Single center	Liver transplant recipients (**with stratification for high risk of IMI**) Before: 2008-2010 After: 2010 - 2012 N = 382 (at high risk of IA in the intervention group = 78) Age (median): 55.7y **Exclusion:** -Multi-visceral transplantation -IFI at time of transplant -Death on day of transplant	Before – after retrospective cohort study Primary outcomes: Incidence of IFI within 100 days post-transplant	High risk for invasive mold infection = criteria for inclusion in the targeted prophylaxis group in the post-intervention phase (defined as re-transplantation, renal failure requiring renal replacement therapy, fulminant hepatic failure as indication for transplant, intraabdominal / thoracic re-exploration within the first month after transplant)	**In the comparator group:** Baseline risk for IA: 0% Baseline risk of mortality: 7.2%	**In patients at high risk of IMI:** Voriconazole 200 mg PO twice daily Duration: until discharge or 28 days (median days received= 11) *Patients at low risk of IMI but high risk of yeast infection received fluconazole prophylaxis, while patients at low risk of IFI did not receive antifungal prophylaxis*	Voriconazole 200 mg PO twice daily Duration: for the immediate post-transplant ICU stay (median days received= 6)	Proven, Probable or Possible IFI according to EORTC/MSG 2008 Total duration: 100 days

Legend:
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
IA: invasive aspergillosis
IFI: invasive fungal infection
IMI: invasive mold infection
NR: not reported

*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
Eschenauer 2015	**Serious**	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. increasing 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).	Intervention status and planned duration clearly defined	No deviation from the intervention reported.	No evidence of missing data.	Diagnosis of IA was based on EORTC/MSG (diagnosis criteria probably not changing with time)	The outcome measurement and analyses are consistent and well described in the Methods.

EORTC/MSG: The European Organization for Research and Treatment of Cancer and the Mycoses Study Group; 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 (at 100 days post-transplant)

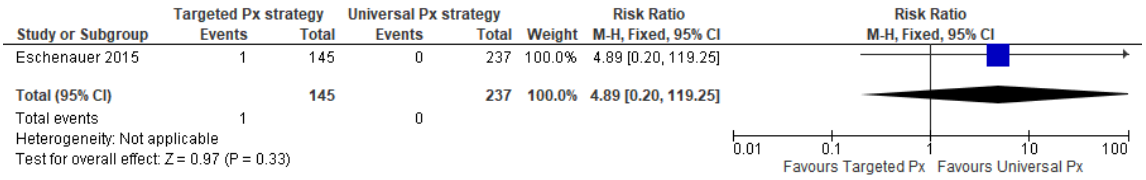


Figure A3.1.b: Mortality (at 100 days post-transplant)

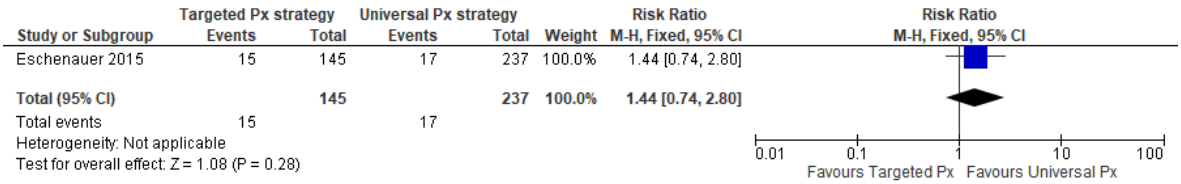


Figure A3.1.c: Attributable mortality (at 100 days post-transplant)

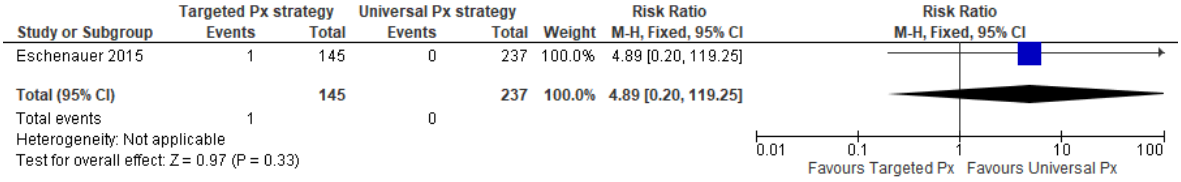
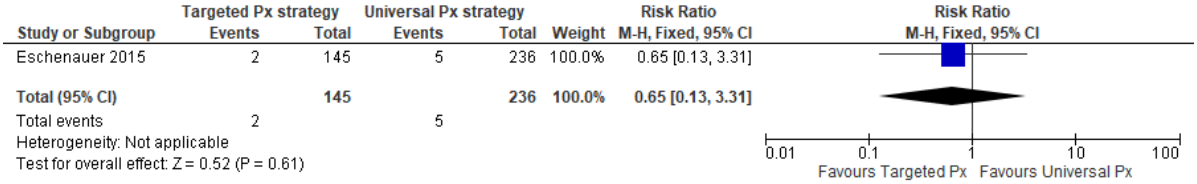


Figure A3.1.d: Serious and non-serious adverse events (at 100 days post-transplant)



SAEs were defined as severe AEs leading to discontinuation.

Supplementary Table A3.4: 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	When comparing targeted anti-*Aspergillus* prophylaxis with universal anti-*Aspergillus* prophylaxis, the desirable consequences of in liver transplant recipients were judged to be a trivial reduction in serious and non-serious adverse events.	The panel underlined that the evidence to support the use of targeted rather than universal prophylaxis is only based on a study using voriconazole as the anti-*Aspergillus* agent in both studied groups.

Undesirable effects

How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ **Trivial** ○ Varies ○ Don't know	When considering the use of targeted anti-*Aspergillus* prophylaxis with universal anti-*Aspergillus* prophylaxis, the undesirable consequences were judged trivial: -no clinically significant increase (i.e. not exceeding the **decision threshold of 4%**) in incidence of invasive aspergillosis and attributable mortality (despite a possible slight increase all-cause mortality).	The panel underlined that the evidence to support the use of targeted rather than universal prophylaxis is based on a study using voriconazole as the anti-*Aspergillus* agent in both studied groups.

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	When considering the use of targeted anti-*Aspergillus* prophylaxis with universal anti-*Aspergillus* prophylaxis, the evidence shows trivial reduction in adverse events, thus not favoring either targeted prophylaxis or universal prophylaxis.	

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	No studies identified. No patient representatives were identified for this section of the guideline.	The panel assumes that patients enrolled for liver transplant recipients would generally support avoiding interventions that are nor providing a clear favorable balance of benefits and harms.

○ **Probably no important uncertainty or variability** ○ 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	No studies included	The panel underlines that restricting the use of anti-*Aspergillus* prophylaxis to liver transplant recipients at high risk of invasive aspergillosis without significantly increasing undesirable events is expected to reduce 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

Daily costs (US$ per day) of fluconazole prophylaxis (AWP versus AC in a single center, US November 2024)

	Daily dose	Cost per day (US$)	
		AWP	AC
Fluconazole	400 mg (PO / IV)	$ 5 to 150 / 0.05 to 1	$ 3 / 8 to 16

The prices presented are AWP for daily dose for generic brand of antifungal except for anidulafungin and isavuconazole which generic formulations are 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.

These direct costs are not including the costs associated with specific therapeutic drug monitoring (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.

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**		

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**	No evidence identified	The real cost-effectiveness was not estimable by the panel due to the lack of available evidence.

Acceptability / Stewardship

Is the intervention acceptable to key stakeholders?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	**Stewardship issues** **1) Mold-active azole prophylaxis:** -There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi, especially non-C. albicans species (especially *Nakaseomyces glabratus (*formerly known as *Candida glabrata*)). The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis in OLT is not clear as only limited studies includes data on antifungal susceptibility in their report. -Anecdotal reports noted breakthrough infection of *Rhizopus* spp. during mold-active azole prophylaxis. **2) Echinocandin prophylaxis:** -Several recent reports raise concerns of emergence of breakthrough *Candida* infection during echinocandin (micafungin) prophylaxis in liver transplant recipients. It should point out that these studies did not link breakthrough *Candida* to echinocandin resistance. This signal was not observed in clinical trials. -In the papers reviewed, there were rare cases of breakthrough *Rhizopus* spp. during echinocandin prophylaxis. -Cryptococcal disease is an uncommon but fatal disease in patients with liver cirrhosis. Echinocandin has no activity against *Cryptococcus*.	**Ease of administration** -most agents used for prophylaxis are administered not more than once or twice daily -some agents have interchangeable route of administration for switching from parenteral to oral (e.g. triazoles) **Management of drug-drug interactions and adverse events** -most drug-drug interactions and adverse events are limited (echinocandins) or easily predictable (e.g. triazoles and hepatotoxicity)

Feasibility

Is the intervention feasible to implement?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	No evidence identified	In most inpatient settings where liver transplantation is performed, avoidance of anti-*Aspergillus* prophylaxis in patient not considered at high risk of invasive aspergillosis is expected to be easily feasible by formally identifying risk factors of invasive aspergillosis during the peri-transplant period.

Equity

What would be the impact on health equity?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased	No evidence identified	Assuming that: 1) anti-*Aspergillus* prophylaxis is administered until discharge or up to 28 days (duration of hospitalization being usually of 10 days in uncomplicated

○ Increased ○ Varies ○ Don't know		vs 21 days in complicated liver transplant recipients), without requirement for prolonged duration of prophylaxis after discharge 2) these agents are usually widely available for inpatient settings (unless limited by local formulary issues), = then, the panel judged that implementing this recommendation should not have any impact on equity.

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**
ACCEPTABILITY / STEWARDSHIP	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
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 liver transplant recipients needing anti-*Aspergillus* prophylaxis, what is the best choice of agent?

Population: Adult liver transplant recipients in early post-transplant period needing anti-*Aspergillus* prophylaxis

Intervention: Anti-*Aspergillus* prophylaxis

= either echinocandins, triazoles, AmB or itraconazole

Comparator: Anti-*Aspergillus* prophylaxis

= either echinocandins, triazoles, AmB or itraconazole

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

Critical

-Reduction in IA (breakthrough)

-Reduction in attributable mortality

-Reduction in SAEs

Important

-Reduction in mortality (all-cause/overall)

-Reduction in non-serious AEs

Removed outcome

-IFIs (not a good surrogate outcome of IA in this population because IFIs were mainly equivalent to invasive Candida infections)

Outcomes not reported:

-Need to change antifungal therapy

-Length of hospital stay, readmission, quality of life

-Graft rejection, graft loss

Literature Search Strategy (same as Clinical Questions A1 & A2)

Eligibility Criteria

Inclusion criteria:

- Patient population: Adults liver transplant patients in early post-transplant period needing anti-*Aspergillus* prophylaxis
- Intervention: Anti-*Aspergillus* prophylaxis
    - -Echinocandins such as caspofungin, micafungin or anidulafungin
    - -Triazoles such as posaconazole, voriconazole or isavuconazole
    - -AmB (IV or inhaled)
    - -Itraconazole (any formulation)
- -Comparator: Anti-*Aspergillus* prophylaxis
    - -Echinocandins such as caspofungin, micafungin or anidulafungin
    - -Triazoles such as posaconazole, voriconazole or isavuconazole
    - -AmB (IV or inhaled)
    - -Itraconazole (any formulation)
- -Outcomes: study reporting on either incidence of IA or/and AEs associated with the use of anti-*Aspergillus* prophylaxis
- Study design: RCTs or Observational studies
- Year: published from 2000 up to present
- Language: English only

Exclusion criteria:

- -Patient population:
    - -Pediatric population
- -Intervention / Comparator
    - -Comparison:
        - -any comparison where the comparator group is not classified at similar risk of aspergillosis (e.g. high risk with targeted anti-*Aspergillus* prophylaxis vs low risk without anti-*Aspergillus* prophylaxis)
        - -any comparison with the same agents with different formulations or doses
- -Study design
    - -One-arm studies (including case series and case reports)
    - -Conference proceedings, abstracts, letters to editor, and comments

PRISMA Flow Diagram of Study Identification and Selection (same as Clinical Questions A1 & A2)

Only studies providing direct comparison between anti-*Aspergillus* agents in liver transplant recipients were comparing echinocandins and AmB.

Include the stratified analysis per classes of agents (echinocandins, AmB and itraconazole only) included in Clinical Question A1 regarding serious and non-serious AEs.

One-arm studies/ reviews on efficacy (breakthrough infection), tolerability (AEs and drug-drug interaction), costs and stewardship will be required to support a formal recommendation.

Supplementary Table B1.1: GRADE evidence profile

Clinical question B1: In liver transplant recipients needing anti-*Aspergillus* prophylaxis, should an echinocandin be used rather than amphotericin B?

P: Adule liver transplant recipients requiring anti-*Aspergillus* prophylaxis

I: Echinocandin

C: Amphotericin B

Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis with an echinocandin	Prophylaxis with amphotericin B	Relative (95% CI)	Absolute (95% CI)		
Invasive Aspergillosis (3 to 12 months)										**MID: at least 40 fewer per 1,000**		
2[1,2]	non-randomized studies	serious[a]	not serious	not serious	very serious[b]	none	6/113 (5.3%)	5/94 (5.3%)	**RR 1.05** (0.27 to 4.07)	**3 more per 1,000** (from 39 fewer to 163 more)	⊕◯◯◯ Very low[a,b]	CRITICAL
Mortality (3 to 12 months)												
2[1,2]	non-randomized studies	serious[a]	not serious	not serious	very serious[c]	none	27/113 (23.9%)	18/94 (19.1%)	**RR 1.24** (0.65 to 2.35)	**46 more per 1,000** (from 67 fewer to 259 more)	⊕◯◯◯ Very low[a,c]	IMPORTANT
Attributable Mortality (3 to 12 months)												
1[1]	non-randomized studies	serious[a]	not serious	not serious	very serious[b]	none	2/95 (2.1%)	1/70 (1.4%)	**RR 1.47** (0.14 to 15.93)	**7 more per 1,000** (from 12 fewer to 213 more)	⊕◯◯◯ Very low[a,b]	CRITICAL
Serious Adverse Events (12 months)												
1[1]	non-randomized studies	serious[a]	not serious	not serious	very serious[d]	none	0/95 (0.0%)	0/70 (0.0%)	not estimable	**0 fewer per 1,000**	⊕◯◯◯ Very low[a,d]	CRITICAL
Non-serious Adverse Events (12 months)												
1[1]	non-randomized studies	serious[a]	not serious	not serious	very serious[e]	none	8/95 (8.4%)	6/70 (8.6%)	**RR 0.98** (0.36 to 2.70)	**2 fewer per 1,000** (from 88 fewer to 85 more)	⊕◯◯◯ Very low[a,e]	IMPORTANT
Graft Rejection (3 months)												
1[2]	non-randomized studies	very serious[a, f]	not serious	not serious	extremely serious[g]	none	3/18 (16.7%)	6/24 (25.0%)	**RR 0.67** (0.19 to 2.31)	**82 fewer per 1,000** (from 328 fewer to 161 more)	⊕◯◯◯ Very low[a,f,g]	IMPORTANT
Graft Loss (3 months)												
1[2]	non-randomized studies	serious[a]	not serious	not serious	very serious[b]	none	2/18 (11.1%)	0/24 (0.0%)	not estimable	**111 more per 1,000** (from 34 fewer to 256 more)	⊕◯◯◯ Very low[a,b]	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Both studies were judged at high risk of bias due to suspected confounding and selection bias not controlled for either by the study design or statistical analysis.
b. The upper boundary of the confidence interval crosses the decision threshold (minimal important difference for recommending or not the prophylaxis) and the confidence interval is very wide, thus providing evidence of serious imprecision around the estimates of effect.
c. Both boundaries of the confidence interval cross the decision threshold (minimal important difference for recommending or not recommending the prophylaxis) and the confidence interval is very wide, thus providing evidence of very serious imprecision around the estimates of effect.
d. No events reported in both groups.
e. The confidence interval is very wide, thus providing evidence of very serious imprecision around the estimates of effect.
f. This outcome is known to be time-dependent (decrease rate of graft rejection with time), thus at high risk of being bias due to the study design (before and after intervention study).
g. The confidence interval is extremely wide, thus providing evidence of extremely serious imprecision around the estimates of effect.

References

1. Rinaldi et al. Breakthrough invasive fungal infection after liver transplantation in patients on targeted antifungal prophylaxis: A prospective multicentre study. Transplant Infectious Disease 2021;23(4):e13608.
2. Singh et al Preemptive prophylaxis with a lipid preparation of amphotericin B for invasive fungal infections in liver transplant recipients requiring renal replacement therapy. Transplantation 2001;71(7):910-913.

Supplementary Table B1.2: 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** *(Echinocandin prophylaxis, total duration)*	**Comparator** *(AmB prophylaxis, total duration)*	**Outcome measurement for IA** *(definition for and diagnostic criteria)* **and duration of follow-up**
Rinaldi 2021 Bologna, Italy Multicentric (3 centers)	Liver transplant recipients (**with stratification for high risk for IC/ IA**) 2015-2018 N= 485 (of which 176 were at high risk of IC/IA and received antifungal prophylaxis) Age (median): 54y in the intervention group vs 53y in the comparator group Exclusion: NR	Prospective cohort study - Subgroup analysis of patients at high risk of IC/IA receiving antifungal prophylaxis Primary outcome: Incidence of b-IFI	Risk stratification: -No risk -Low risk (1 RF for IC) -High risk (>2RF for IC or >1RF for IA) Risk factors for IC (defined as: pre-operative ICU within 90 days, peri-operative *Candida* colonization, choledochojejunostomy, prolonged OT (>8 hours), PRBC >40 units of cellular product, acute renal failure, rejection treated with immunosuppressive agents within 2 weeks, CMV reactivation, prolonged operation) Risk factors for IA (defined as: fulminant hepatic failure, steroids within the last month prior to transplant, multi-visceral transplantation, RRT, rejection requiring ATG, OKT3 or Alemtuzumab, re-transplantation and re-operation) High risk of IA: NR separately but corresponds to at least 39% of the entire cohort (CRRT)	Baseline risk for IA: 4.3% Baseline risk for mortality: 15.7%	Echinocandin (caspofungin or anidulafungin) Duration: suggested for 21 days (median days received= 14)	L-AmB 3mg/kg daily or 10mg/kg weekly Duration: suggested for 21 days (median days received= 9)	Proven or probable IFI defined as per EORTC/MSG 2008 Duration: 12 months
Sun 2013 Pennsylvania, USA Single center	Liver transplant recipients with high risk of IFI Before: 1997-2006 After: 2007-2009 N=42 Age (median): 54y in the intervention group vs 60y in the comparator group Exclusion: NR	Before and after study Descriptive study: efficacy (first episode of IFI) and safety	High risk of IFI (defined as post-transplant dialysis, re-transplantation, re-operation)	Baseline risk for IA: 8.3% Baseline risk for mortality: 29.2%	Micafungin 100mg IV per day Duration: 21 days or until cessation of renal replacement therapy, discharge or death (median days received= 20)	ABLC 5 mg/kg/day Duration: 21 days or until cessation of renal replacement therapy, discharge or death (median days received= 27)	IFI defined as per EORTC/MSG 2002 Duration: 90 days

Legend
ABLC: amphotericin B lipid complex
CRRT: continuous renal replacement therapy
EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group
IA: invasive aspergillosis
IC: invasive candidiasis
IFI: invasive fungal infection,
L-AmB: liposomal amphotericin B
NR: not reported
RF: risk factor

*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 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
Rinaldi 2021	**Critical**	Possible confounding by indication (choice of prophylaxis according to the physician choice) which was not controlled by either the study design or statistical analysis	Difference in duration of prophylaxis received provides evidence of selection bias and was not adjusted for in the analysis.	Intervention status and planned duration clearly defined	Adherence to the protocol is addressed, but only patient receiving the interventions were analyzed.	No evidence of missing data	Diagnosis of IA was based on EORTC/MSG (diagnosis criteria probably not changing with time). Only the first episode of IFI was considered which could have influenced the incidence of IA (unclear if the competing risk was comparable between groups).	The outcome measurement and analyses are consistent with the Methods.
Sun 2013	**Critical**	Possible 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 incidence of IA due to breakthrough/ resistance in the post-intervention period)	Difference in duration of prophylaxis received provides evidence of selection bias and was not adjusted for in the analysis. Selection bias is suspected due to potential changes in enrolled participants over time (i.e. over a 12-year period, participants in the before vs after the intervention may have differed due to unmeasured changes in standard of care). For example, the outcome "Graft rejection", the risk of bias for this domain is judged as "critical' since time dependent (reduction of graft rejection with time).	Intervention status and planned duration clearly defined	Deviations from the interventions occurred in both groups, but their impact on the outcome of interest is not unclear.	Few missing data not likely to have influenced the results	Diagnosis of IA was based on EORTC/MSG (diagnosis criteria might have changed during the 12-year study period).	The outcome measurement and analyses are incompletely described in the Methods.

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

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 (3 to 12 months)

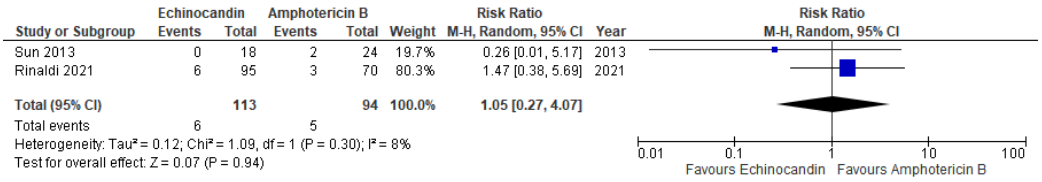


Figure B1.1.b: Mortality (all-cause) (3 to 12 months)

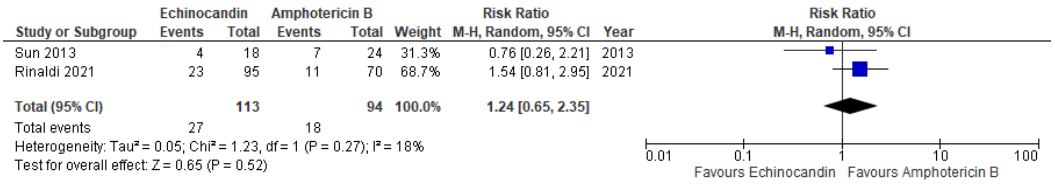


Figure B1.1.c: Attributable mortality (3 to 12 months)

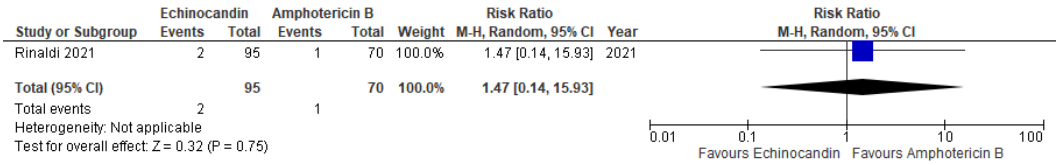


Figure B1.1.d: Serious adverse events (12 months)

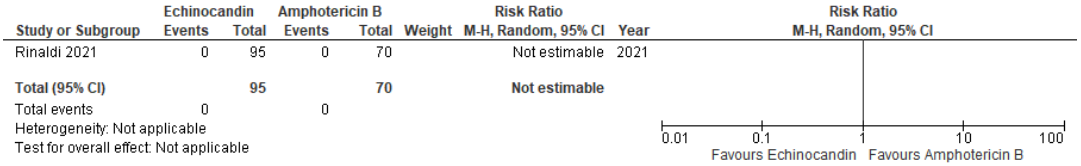


Figure B1.1.e: Non-serious adverse events (12 months)

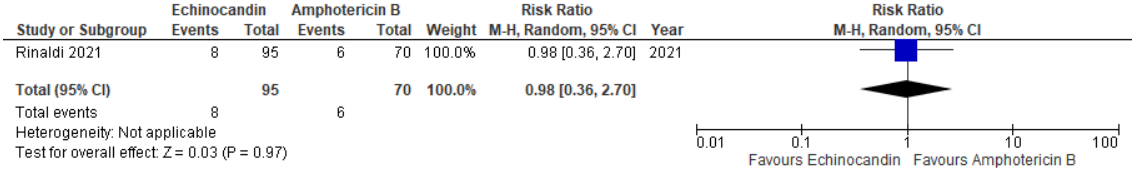


Figure B1.1.f: Graft rejection (3 months)

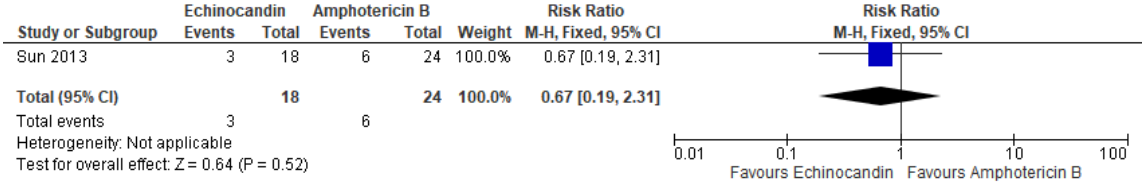
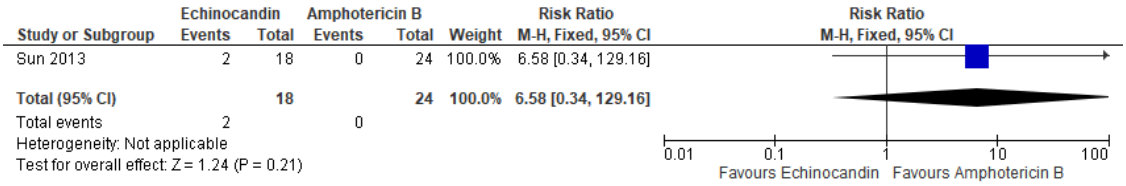


Figure B1.1.g: Graft loss (3 months)



Supplementary Table B1.4: Data on breakthrough infections and adverse events with different antifungal agents

	Risk of breakthrough invasive aspergillosis	Serious adverse events	Severe adverse events (requiring discontinuation)	Hepatotoxicity (Grade and Frequency)	Nephrotoxicity	Non-serious adverse events
Echinocandins						
Caspofungin						
Chakravarti 2021 [5]	0.5% (1/ 210)	NR	NR	None	NR	NR
Doria 2011 [42]	0% (0/16)	NR	NR	13% (2/16)	25% (4/16)	No issues with CNI
Fortún 2009 [43]	0% (0/71)	NR	15% (11/71); liver	8% (6/71)	No issues	No issues with CNI
Fortún 2016 [11]	1% (1/97)	NR	NR	Bilirubin increased	"Improved"	NR
Perrella 2016 [44]	0% (0/26)	NR	NR	No issues	"Slow improvement"	No issues with CNI
Micafungin						
Sun 2013 [45] (high risk cohort)	11% (2/18) Micafungin	NR	NR	None	"Improved"	NR
	8% (2/24) ABLC	NR	NR	None	Cr increased 44% from baseline	NR
Saliba 2015 [46]	1% (2/172)	11.6% (nausea)	6.4% *	4% (GGT)	0%	NR
Kang 2020 [47]	1% (1/86)	28% (24/86)	1% (1/86)	2% (2/85)	0%	Table 5 detail **
Breitkopf 2023 [48]	1.5% (1/67)	None	None	6% (4/67), all mild	None	10% (7/67) (mild; 3 GI, 4 liver)
Anidulafungin						
Winston 2014 [32]	0% (0/98)	NR	1 patient developed prolonged QTc	None	None	NR
Breitkopf 2023 [48]	3% (1/33)	None	None	0%	None	None
Anti-mold triazoles						
Voriconazole						
Balogh 2016 [3]	0% IA 1.1% (2/174) Asp colonization	None	None	Not described	Not described	No described
Eschenauer 2015 [9]	0% (0/327)	None	2.1% (7/327)	3/327	0%	2/327 (1 GI, 1 could not control CNI level)
Isavuconazole						
Marini 2018 [49]	0% (0/48 of high-risk) 0% (0/94 of all liver transplant)	None	2.1% (2/94)	1/94	0%	1/94 (peripheral edema)
Posaconazole						
None						
Itraconazole						
Sharpe 2003 [50]	0%	0%	NR	NR	NR	30%
Biancofiore 2002 [4]	2.4%	NR	NR	NR	NR	NR
Winston 2002 [31]	2.1%	2.1%	2.1%	3.1%	NR	50.5%
Amphotericin B formulations						
Hadley 2009 [51]	0%	2.6% (1/38)	13% (5/38)	NR	7.8% (3/38)	2.6% (1/38)
Castroaudin 2005 [52]	1. (2/21)	0	0	NR	2/219.5% (2/21)	Hypokalemia 9.5% (2/21)
Antunes 2014 [53]	0%	NR	NR	NR	NR	NR
Tollemar 1995 [54]	0%	0%	5% (2/40)		**3.** (1/40)	Back pain 2.5% (1/40)
Lorf 1999 [55] (1mg/kg)	5% (3/58)	NR	NR	NR	NR	NR

Note: ABLC, Amphotericin B Lipid Complex; CNI, calcineurin inhibitor; GGT, gamma-glutamyl transpeptidase enzyme; GI, gastrointestinal; NR, not reported; QTc, QT interval corrected.

Supplementary Table B: 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	When comparing different options of anti-*Aspergillus* antifungal, the benefits (or lack of breakthrough infections) are expected to be comparable. **DIRECT COMPARISONS:** From our systematic review of the literature, the use of echinocandins rather than amphotericin B may result in little to no difference (trivial) in incidence of IA and attributable mortality (evidence is very uncertain). **INDIRECT COMPARISONS:** From Clinical Question 1, our stratified analysis shows that Itraconazole might be associated with more IA than echinocandins (evidence is very uncertain). Echinocandins: The incidence of breakthrough IA has ranged from 0-3% (Chakravarti 2021, Doria 2011, Fortún 2009, Fortún 2016, Perrella 2016). Among echinocandins, micafungin has the highest incidence of breakthrough IA (up to 11% in a high-risk cohort, Pittsburgh), while anidulafungin has the lowest (Winston 2014, Breitkopf 2023). Anti-mold triazoles: Voriconazole is the most studied in liver transplant recipients. In one study, the rate of breakthrough invasive fungal infections in liver transplant recipients was less than 1% (Eschenauer 2015). There is no data on Isavuconazole in liver transplant recipients. In a RCT with 25 patients receiving **itraconazole** versus placebo, no breakthrough IA was reported (Sharpe 2003). In another study 3% (2/97) rate of breakthrough IA was reported (Winston 2014). Amphotericin B formulations: Most data on antifungal prophylaxis in liver transplant recipients involve the deoxycholate formulation of amphotericin B, with reported breakthrough invasive aspergillosis rates ranging from 0-9.5% (Hadley, Castroaudin, Antune, Tollmar, Lorf).	The panel underlined that the evidence to compare the different options of anti-*Aspergillus* prophylaxis is only based on indirect comparisons of breakthrough infections between different populations from studies with small sample size.
Undesirable effects How substantial are the undesirable anticipated effects?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ **Small** ○ Trivial ○ Varies ○ Don't know	When comparing different options of anti-*Aspergillus* antifungal, both Amphotericin B formulations (infusion-related reactions and nephrotoxicity) and Itraconazole (frequent GI side effects) are associated with significant adverse events, while azoles are leading to significant drug interactions. **DIRECT COMPARISONS:** From our systematic review of the literature, the use of echinocandins rather than amphotericin B may result in little to no difference (trivial) in incidence of non-serious	The panel underlined that the evidence to compare the different options of anti-*Aspergillus* prophylaxis is only based on indirect comparisons of adverse events profile between different populations from studies with small sample size.

	adverse events but may increase mortality (evidence is very uncertain). **INDIRECT COMPARIONS:** From Clinical Question 1, our stratified analysis shows that Itraconazole might be associated with more serious and non-serious adverse events than echinocandins (evidence is very uncertain). **Echinocandins:** Harms: Echinocandins, including caspofungin, micafungin, and anidulafungin, are generally well-tolerated, with mild adverse events such as phlebitis, gastrointestinal symptoms, hypokalemia, and abnormal liver function tests. Caspofungin is associated with a higher incidence of liver-related abnormalities and infusion-related pain (Doria 2011) but has minimal interactions with cyclosporine (PMID: 15122312). In liver transplant recipients, severe adverse events leading to discontinuation were reported in 15% of caspofungin users (Fortún 2009), while hepatotoxicity occurred in 8%. Micafungin's adverse effects include nausea (11.6%) and elevated liver enzymes (4%) (Saliba 2014/2015), with nephrotoxicity observed in one study (Sun 2013) where creatinine levels increased by 44%. Breitkopf (2023) reported mild gastrointestinal and liver-related effects in 10% of patients. Anidulafungin showed minimal toxicity, with no reported nephrotoxicity and only one case of prolonged QTc (Winston 2014). Overall, serious adverse events were rare, and calcineurin inhibitors (CNIs) were generally well-tolerated **Anti-mold azoles:** Harms: Adverse effects of anti-mold azoles are dose-dependent and include hepatotoxicity, gastrointestinal symptoms, QT prolongation (notably with voriconazole and posaconazole), and visual disturbances (specific to voriconazole). Drug discontinuation due to adverse events occurred in approximately 2% of cases, with hepatotoxicity being the most common reason. Itraconazole-related adverse events were reported in 30–51% of cases (Sharpe 2003; Winston 2014), with non-serious events occurring in 51–97% of patients. Abnormal liver function tests were observed in 3% of cases, and hepatotoxicity requiring discontinuation was documented in 1.5% of cases. For anti-mold azoles, hepatotoxicity occurred in 2.1% of cases receiving voriconazole (Eschenauer 2014), Gastrointestinal disturbances and challenges with FK level control were also noted. Isavuconazole showed mild adverse events such as peripheral edema (1%) and adverse event documentation was limited for posaconazole. Careful dose adjustments are crucial to minimize risks, particularly in patients with hepatic or renal impairment. Drug-drug interactions: Azoles are potent inhibitors of cytochrome P450 enzymes, particularly CYP3A4, leading to significant interactions with immunosuppressants such as tacrolimus, cyclosporine, and sirolimus. These interactions necessitate close therapeutic drug monitoring and dosage adjustments to prevent toxicity or under-dosing of immunosuppressive agents. **Amphotericin B:** Harms: Amphotericin B has notable side effects, including infusion-related reactions such as fever,	

	chills, and hypotension. Nephrotoxicity (7.8%) remains a significant concern, presenting as hypokalemia, hypomagnesemia, and acute kidney injury. Other non-serious adverse effects included back pain (Tollmar) and liver toxicity (5% in Lorf study at 1 mg/kg dose). Liposomal formulations, such as liposomal amphotericin B, significantly lower these risks and improve tolerability. Severe adverse events leading to drug discontinuation were reported in 5-13% of patients (Hadley, Tollmar), while nephrotoxicity occurred in 2.5-7.8% (Hadley, Castroaudin, Tollmar). Drug-drug interactions: Amphotericin B has minimal direct pharmacokinetic interactions with immunosuppressants but may exacerbate nephrotoxicity when combined with nephrotoxic agents like cyclosporine, tacrolimus, sirolimus or aminoglycosides. Enhanced monitoring of renal function and electrolyte levels is critical to prevent compounded renal toxicity in combination therapy patients.	

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	When comparing different options of anti-*Aspergillus* antifungal, the balance of benefits and harms probably favors the use of either echinocandins or anti-mold azoles (Voriconazole or Posaconazole) as the intervention.	The panel underlined that the evidence to compare the different options of anti-*Aspergillus* prophylaxis is only based on indirect comparisons of adverse events profile between different populations from studies with small sample size.

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 and indirect comparison of balance of benefits and harms.	

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 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 liver transplant recipients would generally support avoiding interventions that are nor providing a clear favorable balance of benefits and harms.

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	No studies included.	Daily costs (US$ per day) of anti-*Aspergillus* agents (average wholesale prices (AWP) versus acquisition costs (AC) in a single center, US November 2024)

Echinocandins	Daily dose	Cost per day (US$)	
		AWP	AC
Micafungin	100 mg (IV)	$58 to 224	$59
Caspofungin	50 mg (IV)	$83 to 405	$53
Anidulafungin	100 mg (IV)	$229	$211

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

Amphotericin B	Daily dose (for 70 kg)	Cost per day (US$)	
		AWP	AC
Liposomal Amphotericin B	3 mg/kg or 210mg (IV)	$1,285 to 1,558	$257
Amphotericin lipid complex	5mg/kg or 350mg (IV)	$441	$240
Amphotericin deoxycholate	0.5 to 1 mg/kg or 35 to 70 mg (IV)	$42 to 84	$36

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

The prices presented are AWP for daily dose for generic brand of antifungal except for anidulafungin and isavuconazole which generic formulations are 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.

These direct costs are not including the costs associated with specific therapeutic drug monitoring (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.

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**		

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**	No evidence identified	The real cost-effectiveness was not estimable by the panel due to the lack of available evidence.

Acceptability / Stewardship

Is the intervention acceptable to key stakeholders?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	**Stewardship issues** **1) Mold-active azole prophylaxis:** -There is a concern that utilization of triazoles might increase the risk for colonization and/or infection by azole-resistant fungi, especially non-*C. albicans* species (especially *Nakaseomyces glabratus (*formerly known as *Candida glabrata*)). The burden of azole-resistant *Candida* spp. associated with mold-active azole prophylaxis in OLT is not clear as only limited studies includes data on antifungal susceptibility in their report. -Anecdotal reports noted breakthrough infection of *Rhizopus* spp. during mold-active azole prophylaxis. **2) Echinocandin prophylaxis:** -Several recent reports raise concerns of emergence of breakthrough *Candida* infection during echinocandin (micafungin) prophylaxis in liver transplant recipients. It should point out that these studies did not link breakthrough *Candida* to echinocandin resistance. This signal was not observed in clinical trials. -In the papers reviewed, there were rare cases of breakthrough *Rhizopus* spp. during echinocandin prophylaxis. -Cryptococcal disease is an uncommon but fatal disease in patients with liver cirrhosis. Echinocandin has no activity against *Cryptococcus*. **3) Amphotericin B prophylaxis** -Likely more frequent / more variability than other agents due to lower doses, even if not frequent with short term prophylaxis -Resistance with longer use, difficult to quantitatively measure (e.g., *Aspergillus terreus* or *Aspergillus flavus*)	**Ease of administration** -most agents used for prophylaxis are administered not more than once or twice daily -some agents have interchangeable route of administration for switching from parenteral to oral (e.g. triazoles) **Management of drug-drug interactions and adverse events** -most drug-drug interactions and adverse events are limited (echinocandins) or easily predictable (e.g. triazoles and hepatotoxicity)

Feasibility

Is the intervention feasible to implement?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	No evidence identified	In most inpatient settings where liver transplantation is performed, the panel does not expect any feasibility issues between the different agents.

Equity

What would be the impact on health equity?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	No evidence identified	In most inpatient settings where liver transplantation is performed, the panel does not expect any equity issues between the different agents.

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**
ACCEPTABILITY / STEWARDSHIP	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know

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 ○

Kidney Transplant Recipients

Table of Contents

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

Background

Kidney transplant procedures are classed as clean surgeries. They involve the anastomosis of two sterile vascular structures (artery to artery, and vein to vein) and implantation of the donor's ureter into the dome of the bladder. Peri-operative yeast and mold infections are uncommon. As a result, peri-operative antifungal prophylaxis is often limited to topical mucosal agents, such as nystatin, to prevent thrush. Prolonged renal replacement therapy before transplant is known to increase the risk of IA in the first 3 months after transplant [56, 57].

Literature Review

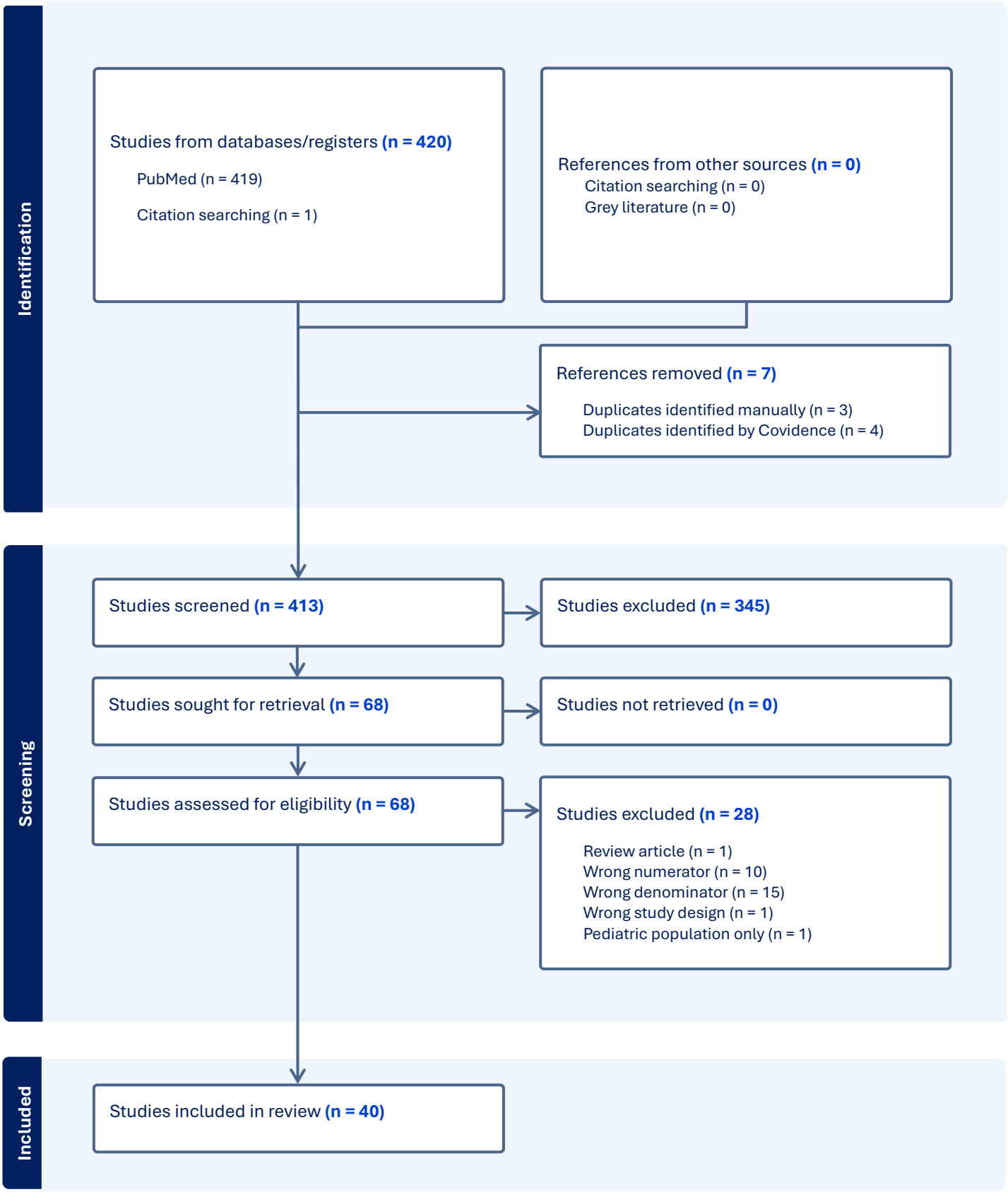
To understand the true burden of IA in kidney transplant, a mapping review across 34 observational studies was performed to determine the incidence of IA in kidney transplant recipients not receiving anti-*Aspergillus* prophylaxis. Articles with restrictive kidney transplant patient populations, such as intensive care unit admissions only, were excluded. Kidney transplant recipient populations that were combined with a second transplanted organ such as pancreas or liver transplant were also excluded when possible. Articles were examined for duplicate population coverage; articles with the most detail were retained (Supplementary Table 1).

Literature Search Strategy (last updated on April 2nd, 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 ("Kidney Transplantation"[Mesh] OR "kidney transplant*" OR "renal 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 2nd, 2025

Supplementary Figure 1: PRISMA Flow diagram of study identification and selection (last updated on April 2nd, 2025)



Among 420 articles identified, most (345) were excluded by review of the title and abstract. Reasons for exclusion of 28 further articles after full text review are included on the PRISMA flow diagram (Supplementary Figure 1). Among 40 articles that underwent data extraction, 34 contributed to the pooled incidence of IA [16, 19, 58-89], with separate review of two registry studies [90, 91] and four studies of infection derived after commercial transplantation [92-95].

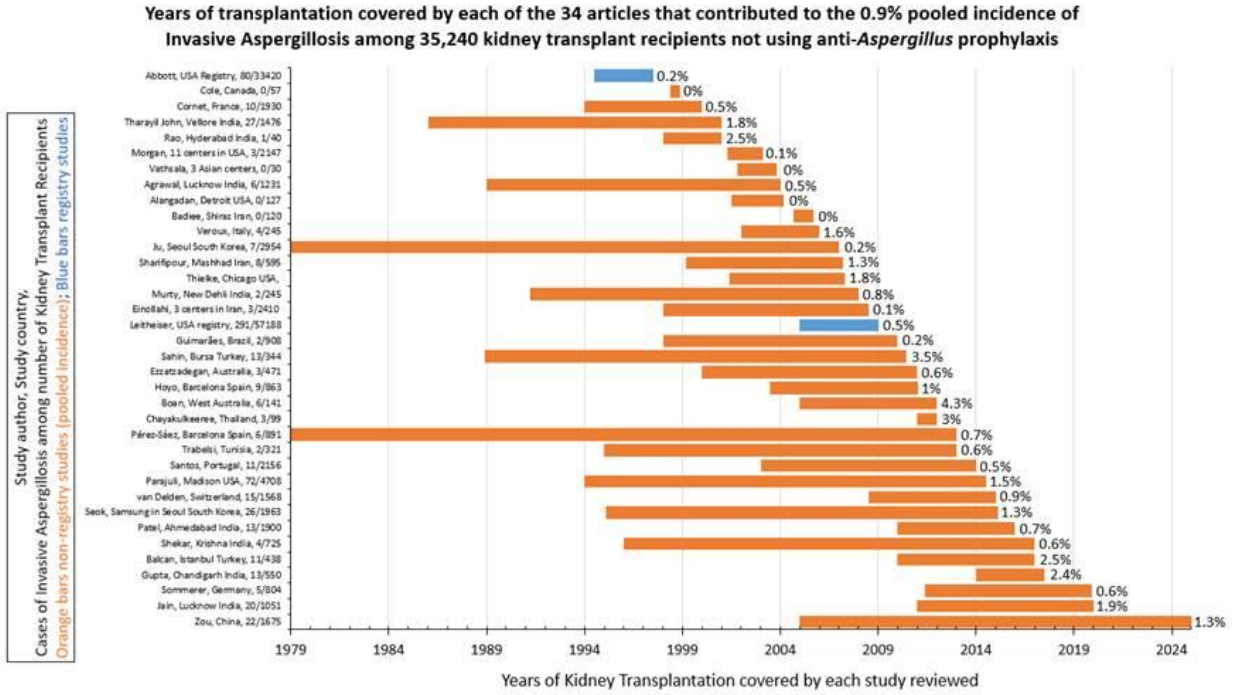
Supplementary Table 1. Source of definitions of proven or probable invasive aspergillosis

	Source of definitions	Year of publication	Author	Country
Non-registry studies	EORTC/MSG (De Pauw 2008 or Segal 2008 or Donnelly 2020)	2012 2017 2014 “ 2015 2015 2018 2016 2020 2020 2022 2025	Ezzatzadagen Boan Hoyo Pérez-Sáez Santos Sahin Balcan Guimarães Seok van Delden Sommerer Zou	Australia “ Spain “ Portugal Turkey “ Brazil South Korea Switzerland Germany China
	EORTC/MSG initial version (Ascioglu 2002)	2002 2005 2018 2009	Cornet Morgan Parajuli Ju	France United States “ South Korea
	Altiparmak 2002, Castaldo 1991, or Horvath 1991	2005 2008	Badiee Einollahi	Iran “
	Clinical with no red flags to indicate inclusion of possible IA	2001 2002 2003 2005 2009 2017 2019 2020 2022 2007 2009 2006 2009 2013 2014 2005	Cole Rao Tharayil John Agrawal Murty Patel Shekar Gupta Jain Veroux Sharifipour Alangaden Thielke Trabelsi Chayakulkeeree Vathsala	Canada India ” “ ” “ “ “ “ Italy Iran United States “ Tunisia Thailand Singapore, Philippines, and Malaysia
Registry studies	ICD-9 codes	2001 2020	Abbott Leitheiser	United States “
Commercial transplant (i.e., transplant tourism)	Castaldo 1991	2002	Altiparmak	Turkey
	Clinical with no red flags to indicate inclusion of possible IA	2001 2005 2018	Sever Kennedy Al Salmi	Turkey Australia Oman

EORTC/MSG: The European Organization for Research and Treatment of Cancer and the Mycoses Study Group; IA: invasive aspergillosis; ICD-9: International Classification of Diseases, Ninth Revision

Although the studies were published after 2000, the lookback period was as long as 34 years, so patients transplanted as early as 1979 were included (Supplementary Figure 2). None of the included studies reported incidence stratified by transplant year; therefore year of transplantation was not analyzed as a risk factor in any study.

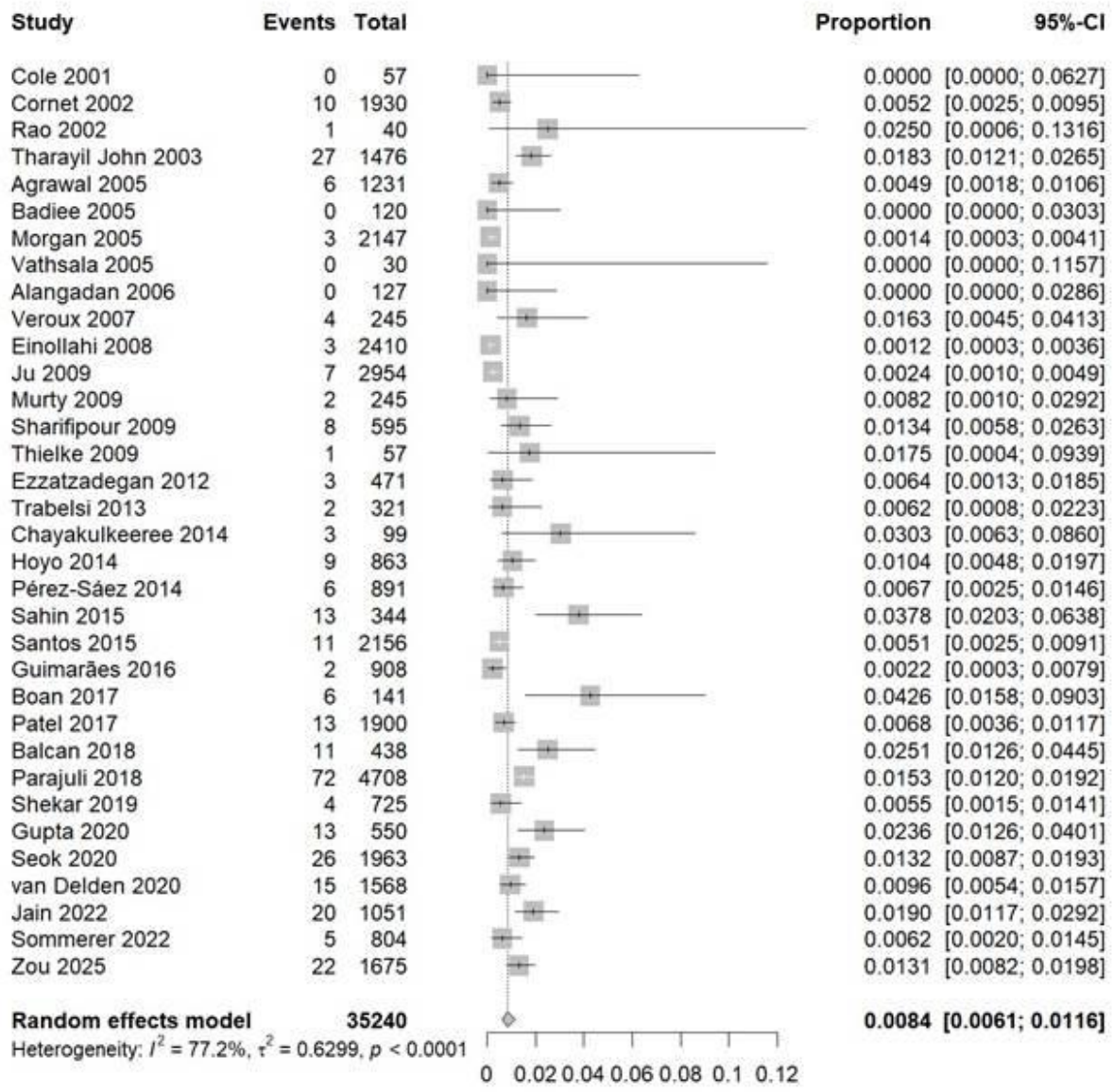
Supplementary Figure 2: Incidence of invasive aspergillosis by years of transplantation covered by each included study



Among 35,332 patients included in 34 studies, 92 patients were removed from the denominator when calculating the incidence of IA. Among these, 44 had received anti-*Aspergillus* prophylaxis and were not included in the incidence estimate [86]. If clearly stated by the authors, other reasons to be removed could have included multiple organ transplantations and incomplete case data to determine infection [77, 89]. There were instances where patients from the included studies had combined organ transplants could not be separated out [82]. Also, studies may have included patients who were not receiving their first renal transplant, which might have affected incidence calculation.

Among 35,240 kidney transplant recipients who were included, 328 cases of proven or probable IA were identified (using EORTC/MSG criteria or a similar definition, Supplementary Table 1) [93, 96-98].
The pooled incidence for IA was 0.8% 95% confidence interval (CI) 0.6 to 1.2%) using a generalized linear mixed-effects model (Supplementary Figure 3).

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



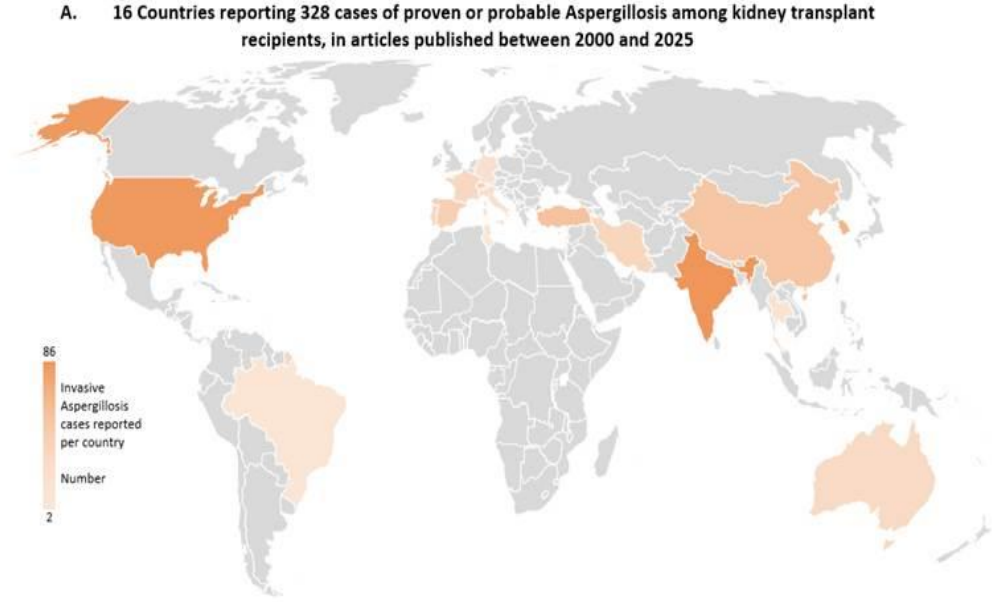
One-year all-cause mortality in individuals with IA was 45% for the 124 cases in which survival outcomes were recorded. While most studies had a single center contribution to a country's incidence, studies did not overlap in time or location so there was no potential to duplicate cases (Supplementary Table 2). India had eight studies, Iran and the United States had three studies each, two studies were each reported from Australia, South Korea, Spain, and Turkey.

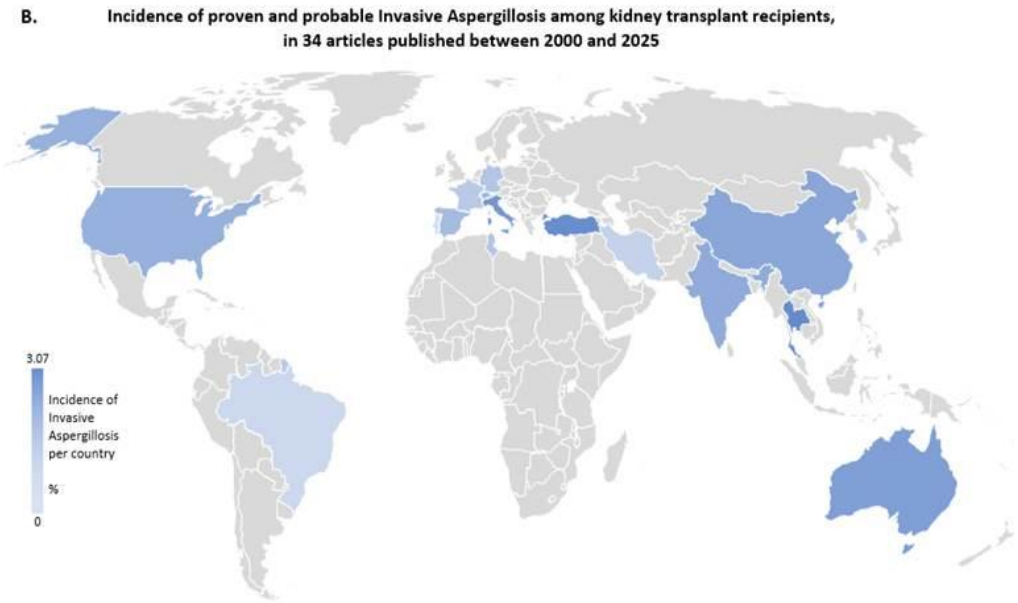
Supplementary Table 2: Lack of potential overlap between non-registry studies from the same country

	Study	Region	Cohort year	Pub year	Overlap?
Australia	Boan	West	1/2005 – 12/2011	2017	No
	Ezzatzadegan	East (Sydney)	1/2000 – 12/2010	2012	"
India	Agrawal	Lucknow	1/1989 – 12/2003	2005	No
	Jain	"	1/2011 – 12/2019	2022	"
	Gupta	Chandigarh	1/2014 – 6/2017	2020	"
	Murty	New Dehli	2/1991 – 2007	2009	"
	Patel	Ahmedabad	2010 – 2015	2017	"
	Rao	Hyderabad	1/1998 – 12/2000	2002	"
	Shekar	Gannavaram	1996 – 2016	2019	"
	Tharayil John	Vellore	1/1986 – 12/2000	2003	"
Iran	Badiee	Shiraz	9/2004 - 8/2005	2005	No
	Einollahi	Theran	1/1998 – 6/2008	2008	"
	Sharifipour	Mashhad	2/1999 – 2/2007	2009	"
South Korea	Ju	Seoul (Yonsei Univ)	1/1979-12/2007	2009	No
	Seok	" (Samsung Med Ctr)	2/1995 – 3/2015	2020	"
Spain	Hoyo	Barcelona (University)	6/2003 – 12/2010	2014	No
	Pérez-Sáez	" (Hospital del Mar)	1/1979 – 12/2012	2014	"
Turkey	Sahin	Bursa	12/1998 – 6/2010	2015	No
	Balcan	Istanbul	2010 - 2016		"
United States	Parajuli	Wisconsin	1/1994 – 6/2014	2018	No
	Morgan	11 centers	3/2001 – 12/2002	2005	"
	Alangaden	Detroit	7/2001 – 2/2004	2006	"
	Thielke	Illinois	1/1986 – 12/2000	2003	"

Among 16 countries that did report cases of proven or probable IA among kidney transplant recipients, the number ranged from 2 to 86 cases per country (Supplementary Figure 4, Panel A). The incidence ranged from 0 to 3.2% per country (Supplementary Figure 4, Panel B). Three studies involving five countries reported no cases of IA in their cohorts.

Supplementary Figures 4: Panel A. Countries reporting cases of proven or probable aspergillosis among kidney transplant recipients. **Panel B.** Mean incidence of cases of proven or probable aspergillosis among kidney transplant recipients reported by country.





Studies focused on adult kidney transplant populations. Nine studies restricted their study population to adults only, accounting for 3,036 patients (8.6%) [58, 59, 62, 64, 77, 82, 84, 87, 88]. Twenty-one studies did not indicate a fully adult age range in the denominator, accounting for 30,238 patients (85.8%) [16, 19, 61, 63, 65-68, 70, 73-76, 78-81, 85, 86, 89]. In these studies, the denominator age was reported as a standard deviation [73] or interquartile range [79, 86], or only the ages of patients with IA were provided [16, 61, 63, 66-68, 75, 76, 80, 85, 89] Four studies specifically listed the age range to include children as young as 4 years [60, 69, 71, 72].

The definitions of proven and probable IA varied across studies, reflecting the wide publication span from 2000 to 2025 (Supplementary Table 1). In cases where there were no references to a specific paper regarding published definitions, the methods section was reviewed to determine if clinical criteria used by the authors were analogous to

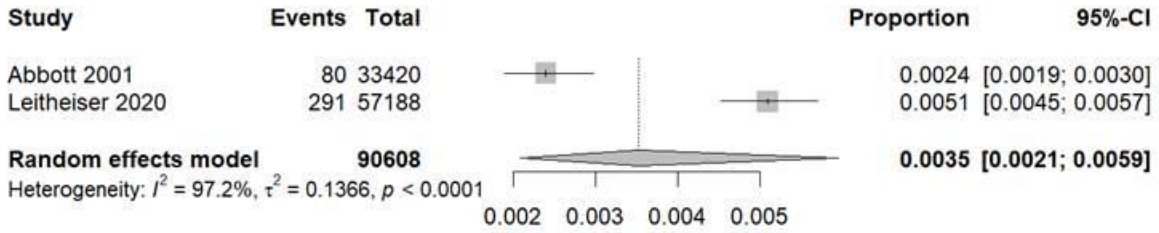
definitions provided by De Pauw/Segal et al in 2008 [96, 99] and updated by Donnelly et al in 2020 [100], and to examine whether the authors included cases of possible IA that should have been excluded.

Most studies were retrospective and observational. Patients from 26 single-center studies accounted for 28,526 (81%) of the cohort [16, 58-63, 67-72, 74-81, 83-85, 88, 89]. Two studies reported prospective collection of infection outcomes among their collective 3,044 transplant recipients in India and Switzerland [83, 86].

Registry Studies based on Diagnosis and Billing Codes

Two large registry studies were not included in the denominator used for calculating the pooled incidence of IA among patients not receiving anti-*Aspergillus* prophylaxis [73, 91]. These United States database registry studies totaled 90,608 patients, covering 3.5 years (1994-1997) and 4 years (2005-2008). The pooled incidence for IA was 0.4% using a generalized linear mixed model (95% CI 0.2, 0.6) (Supplementary Figure 5).

Supplementary Figure 5: Forest plot of incidence of invasive aspergillosis in kidney transplant recipients among 2 large United States registry studies



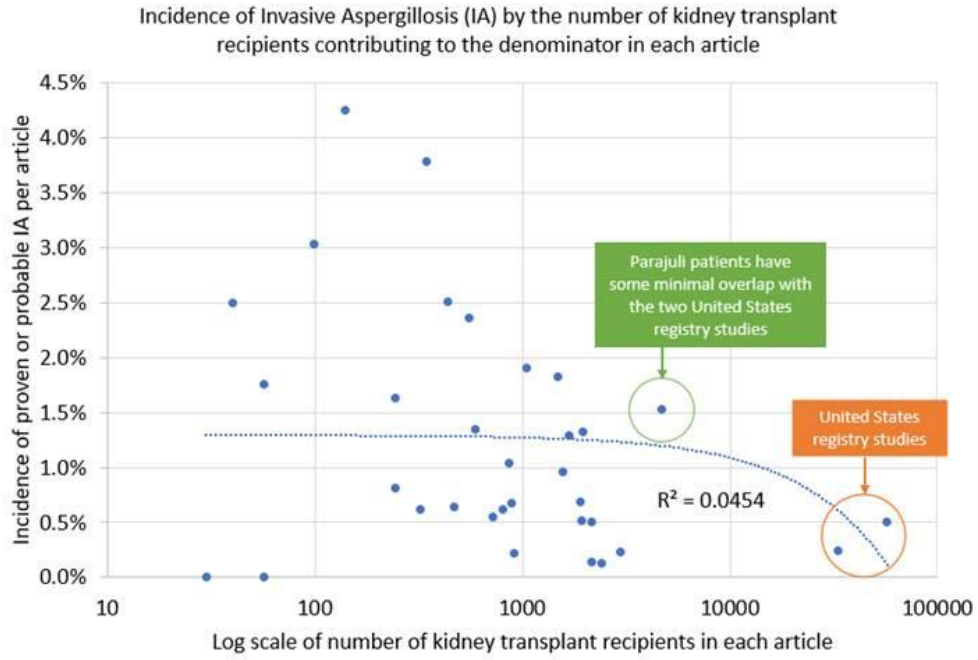
There was probably some overlap among IA patients identified in the 20.5-year Wisconsin retrospective cohort study of 4708 transplant recipients [73] with both registry studies. These two large registry studies with 371 cases of proven or probable IA likely underestimate incidence. Abbott et al identified cases using ICD-9 codes (all 117.3x International Classification of Diseases 9th Modification Diagnosis hospital codes) for IA, so uncoded and/or un-hospitalized patients could have been missed. Since registry studies in general infer diagnoses from billing codes rather than the results of actual medical documentation, they are dependent on the quality of the coding processes. Also, data become unreliable as patients live longer than 3 years after transplant because United States Medicare reporting is not required 3 years after transplant [90]. Another potential contributing factor to underestimation was counting only the first hospitalization for any fungal infection after renal transplant for a given individual transplanted [90]. Additionally, the Abbott and Leitheiser studies might underestimate incidence as the patient population used in the denominator in the Wisconsin study was scrutinized for IA infection among both hospitalized and outpatient patients using different local databases [73, 91].

Using these large databases, the authors performed logistic regression to evaluate risk factors among IA patients. In one model (Abbott), IA was associated with both increased patient mortality and duration of hospitalization (16.7 +/- 12.8 days, p=0.001). In the other model, age > 65 years (relative risk (RR) 2.05, 95%CI 1.57,2.67), Candida colonization (RR 5.41, 95%CI 3.41,8.58), diabetes (RR 3.40, 95%CI 2.70,4.29), hepatitis C (RR 3.16, 95%CI 2.00,5.00), leukopenia (RR 3.71, 95%CI 2.77,4.96), and bacterial pneumonia prior to IA (RR 6.11, 95%CI 4.68,7.97) were the major risk factors (Leitheiser). The authors speculated that some bacterial pneumonias could later have been reclassified as invasive pulmonary aspergillosis (IPA) based on cultures or other diagnostic information, but the coding for bacterial pneumonia still remained. They also speculated that candida colonization, diabetes, and hepatitis C could have been surrogate markers for an immunosuppressed state.

Additional Findings

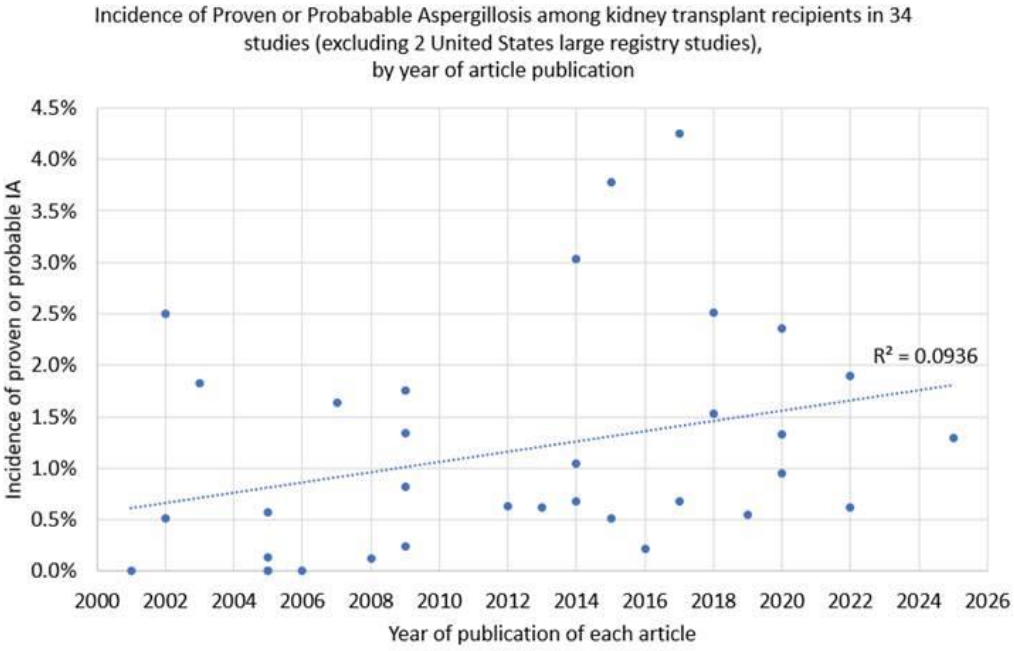
We plotted the incidence of IA against the number kidney transplant recipients forming the denominator of examined patients on a logarithmic scale, incorporating both registry studies (Supplementary Figure 6). The dispersion of incidence around 100 patients is very wide, and this tightens appreciably around 1,000 patients. There is a conglomeration of studies at around 1,000 transplant recipients that matches well with the pooled incidence. A downward trend appears for studies including more than 10,000, suggesting fewer reported infections; however, the correlation is weak (R-squared = 0.0454). An R-squared value closer to 1 represents better fit. The ability to put 10,000 or more patients in a single study relies on a large database, which inherently carries limitations that can lead to underestimation of incidence.

Supplementary Figure 6: Incidence of invasive aspergillosis by number of kidney transplant procedures per included study



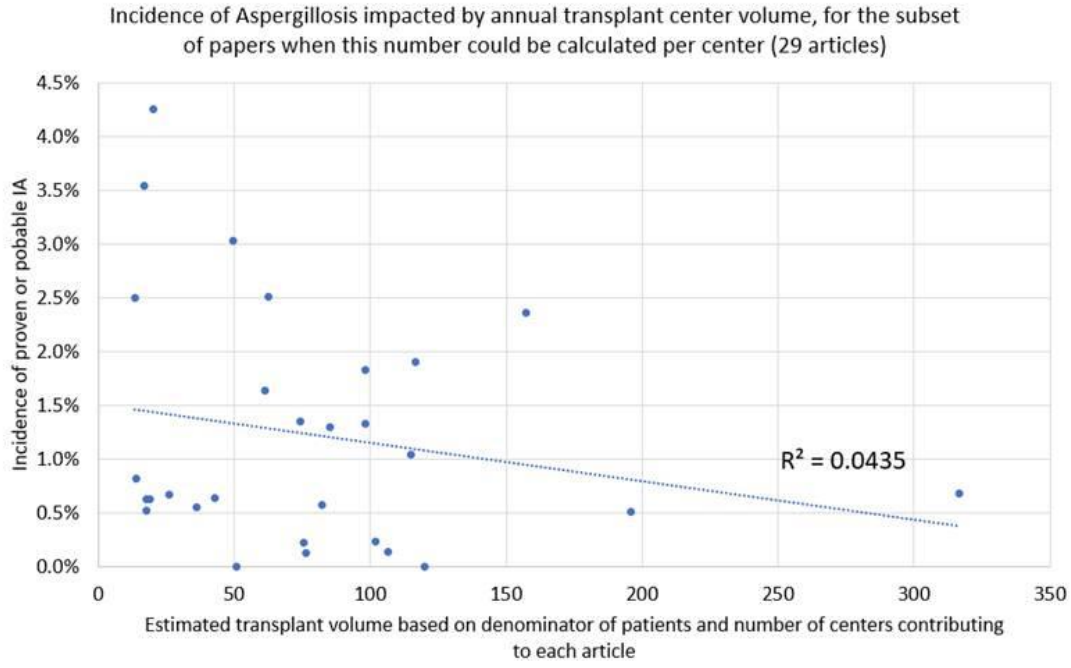
There appeared to be a slight apparent upward trend between the incidence of IA and the year of publication (excluding registry studies) (Supplementary Figure7); however, the correlation was very weak (R-squared = 0.0936), indicating no meaningful association.

Supplementary Figure 7: Incidence of invasive aspergillosis by year of publication



Twenty-nine studies included adequate information that allowed for an approximate calculation of annual transplant volumes at the reporting centers. A slight inverse trend was observed, with centers performing fewer transplants had a higher IA incidence (Supplementary Figure 8). The correlation however was weak (R-squared =0.0435), indicating no meaningful association between transplant center volume and IA incidence, as an R-squared value closer to 1 represents a better fit.

Supplementary Figure 8: Incidence of invasive aspergillosis by annual volume of kidney transplant procedures



Risk Factors for Invasive Aspergillosis

The largest of the two registry studies developed a set of risk factors specific to IA among kidney transplant recipients [91]. The major risk was recipient age older than 64 years (adjusted risk ratio [aRR] = 1.58), possibly reflecting immune senescence, and uncaptured co-morbidities or concomitant medications. Bacterial pneumonia preceding the IA diagnosis (aRR = 3.4) was also significant; the authors surmised that documentation of bacterial pneumonia may either represent true bacterial infection or pneumonia that was later reclassified as pulmonary aspergillosis. Candida colonization (aRR = 2.3) was also significant for the development of IA because it may be a surrogate marker for severe immunosuppression. Clinical co-morbidities that could increase IA risk included diabetes (aRR = 2.2), co-infection with hepatitis C, and leukopenia [91].

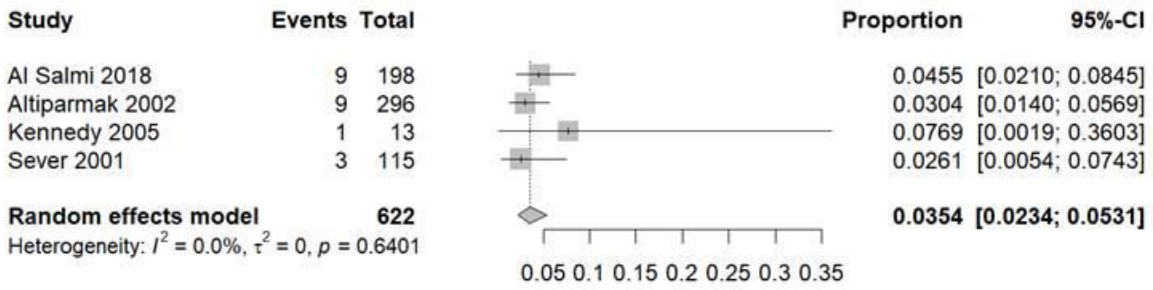
In a case-control study of 26 cases of IPA, multivariate analysis identified delayed graft function (odds ratio [OR] 10.6, 95% CI 1.1–106.8, p= 0.045) to be associated with IPA [79]. In subgroup analyses (time to diagnosis), diabetes (OR 6.6, 95% CI 1.3–34.3, p= 0.026) was associated with IPA within 6 months post-transplant, while acute rejection (OR 15.0, 95% CI 2.8– 81.4, p= 0.002) was associated with IPA later than 6 months from transplant [79]. In a study examining patients with IPA who died versus those who survived [89], receipt of continuous renal replacement therapy was associated with a higher risk of death (3 of 7 who died) vs 1/15 surviving IPA patients. All seven who died developed “complications during treatment”, vs 1/15 who survived. There were no comparisons with the denominator.

In a study comparing IA among solid organ transplant (SOT) recipients, renal transplant patients frequently had co-morbid conditions, with a statistically significant association between IA in renal recipients and chronic lung disease (44% vs. 6%, P = 0.030), and a trend toward a higher prevalence of chronic heart failure (33% vs. 6%, P = 0.09) [70].

Commercial Transplant

The incidence of IA is higher for recipients of commercial transplants, which can be described as a profit-motivated process involving the procurement and distribution of human organs for transplant. IA could result from exposure to infected donors or from breaches in aseptic technique during organ procurement, transport, or implantation, or from local environmental factors. In our review, four studies occurred in the setting of commercial transplant, or “transplant tourism”, and were examined separately from the retrospective studies and the two large registry studies [92-95]. Sever and Altiparmak, published in 2001 and 2002 respectively from Istanbul, Turkey, appear to have potential patient overlap between 1992 and 1999 [92, 93]. In Altiparmak, 9/296 transplanted patients had IA (3%), but it is not clear which IA pts were transplanted locally, in India, or in Russia [93]. In Sever, all three of the IA patients (3/115, 2.6%) had received their transplant in an outside country. In Kennedy, 1 of 13 Australian patients who travelled for renal transplant developed IA (7.7%) [92]. In Al Salmi, 9 of 198 (162 had travelled for transplant) patients in a national registry from Oman had proven IA (4.5%) [95]. The pooled incidence for IA was 3.5% using a generalized linear mixed model (95% CI 2.3, 5.3) (Supplementary Figure 8). Due to the potential for patient overlap and the inability to know which patients in the numerator had travelled to a different country for transplant, the accuracy of this higher incidence rate is not clear.

Supplementary Figure 9: Forest plot of incidence of invasive aspergillosis in kidney transplant recipients among 4 studies of recipients of commercial kidney transplant



Donor-derived transmission

We found no centers reporting the incidence of contamination of preservation fluid as a source of donor-derived transmission [101], although isolated case reports of contaminated preservation fluid have been described [102, 103].

Limitations

Estimating the incidence of IA in kidney transplant recipients was challenging due to several limitations. Kidney transplant recipients are generally not considered at high risk for IA; thus, the general default is to not use anti-mold prophylaxis. Hence, either use or non-use of prophylaxis was rarely reported and might have led to misclassification of the intervention. The incidence of IA among renal transplant recipients should be easier to calculate than for other SOT populations, because most centers do not use mold-active anti-*Aspergillus* prophylaxis when the underlying incidence is low at $\leq$ 1%. This analysis, however, struggled to find studies that reported their individual patient's use of mold-active prophylaxis. In the end, only 44 patients were excluded based on text in a table from a single article listing the use of fungal prophylaxis [86].

Six of the 33 studies examined IPA infections only [16, 61, 71, 79, 80, 89], accounting for 26% of the denominator. Some IA infections having a non-pulmonary site at the time of review may have been missed and are thus contributing to an underestimate of the incidence of IA from these reporting centers.

The wide range of incidence might be attributed to variations in institutional environment and transplant practice as most studies were from single centers on various continents. Moreover, the methods used for the diagnosis of IA also differed between centers: most relied on histopathology and culture, whereas others used galactomannan antigen.

Conclusions

The incidence of IA in kidney transplant recipients is very low, with a pooled incidence of approximately 0.8% (95% CI 0.6 to 1.2%), likely overestimated due to reliance on single-center studies focused on fungal infections. Mortality associated with IA is high but difficult to attribute solely to IA because of the absence of appropriate comparative controls and confounding factors. Overall, the current available evidence does not support the use of universal IA prophylaxis in kidney transplant recipients.

Research Gaps

This analysis struggled to find papers with reported application of good definitions for proven and probable IA. Some studies that relied on clinical definitions directly reported that they were excluding possible (or colonizing) cases of IA, but most did not. With a good historical trend in the development and improvement of definitions as new diagnostic testing for *Aspergillus* became available, Ascioglu in 2002 [104] progressing to De Pauw or Segal in 2008 [96, 99], then to Donnelly in 2020 [100], future studies should list & follow established definitions in the methods sections of their papers.

As the field of transplant surgery evolves, and patients go on to receive second, third, or even fourth kidney transplants, the incidence of IA is unknown during retransplant situations (e.g., reinduction immunosuppression, donor organs with high panel of reactive antigens). Transplant patients may live longer yet develop transplant-related malignancies that require chemotherapy treatments that would change their level of immunosuppression, so future looks at the incidence of aspergillosis among this population would be helpful [105].

The higher incidence of IA reported among recipients of commercial kidney transplantation ("transplant tourism") suggests this group may face increased risk. This issue requires more thorough investigation to understand the underlying factors and to guide prevention strategies.

Lastly, the role and impact of anti-*Aspergillus* prophylaxis in kidney transplant recipients, particularly among high-risk subgroups, remain unclear due to limited data on prophylaxis use and patient outcomes. Well-designed prospective studies are needed to clarify when and for whom prophylaxis may be beneficial.

Pancreas Transplant Recipients

Table of Contents

Descriptive question: In pancreas transplant recipients, what is the baseline risk of invasive aspergillosis among patients not receiving anti-*Aspergillus* prophylaxis, and which factors are associated with an increased risk of IA?

Background

Pancreas transplant recipients are at risk for fungal infection, particularly peri-operative bacterial wound or intraabdominal yeast infections. The pancreatic duct is fragile, so a duodenal cuff is prepared from the donor small bowel and anastomosed to the recipient's bladder (bladder-drained, historically common) or small bowel (enteric-drained, common in recent years). Since yeast are part of small bowel flora, peri-operative yeast prophylaxis with fluconazole is often administered perioperatively for 1-2 weeks. The risk for IA in this population is less clear.

Literature Review

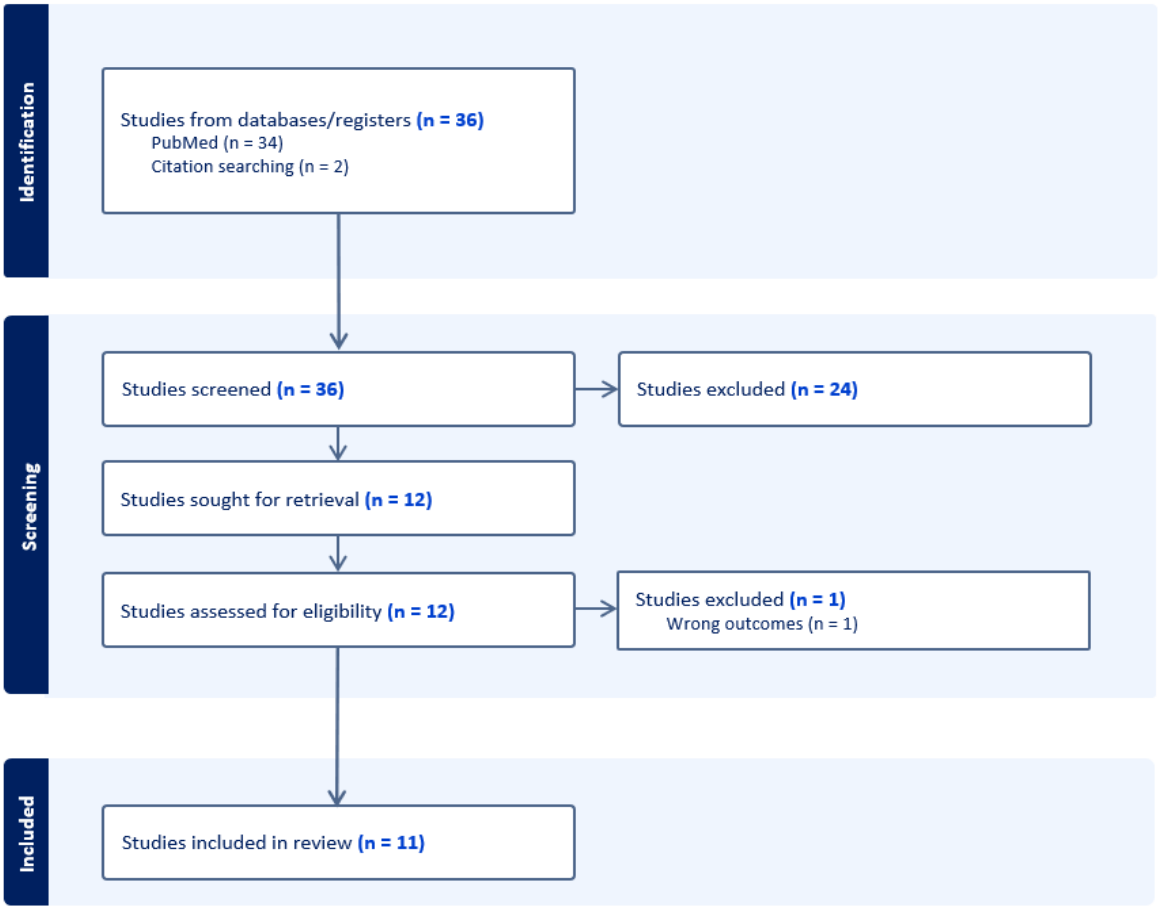
PubMed was searched from January 2000 to April 2025 (see Search strategy below) for studies reporting infectious outcomes among pancreas transplant recipients not receiving anti-*Aspergillus* prophylaxis. Studies were retained if they reported IA among the outcomes of the patients in their examined cohort, even if no IA was specifically found, to minimize overestimation of IA incidence. All types of pancreas transplant were included: simultaneous pancreas kidney transplant (SPK), pancreas after kidney transplant (PAK), pancreas transplant alone (PTA), and "kidney pancreas" (KP).

Literature Search Strategy (last updated on April 2nd, 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 (("Pancreas Transplantation"[Mesh] OR "pancreas transplant*" OR "pancreatic 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 2nd, 2025

Supplementary Figure 1: PRISMA flow diagram of study identification and selection (last updated on 2nd April 2025)



Among 36 articles identified, most (24) were excluded by review of the title and abstract. After one article was excluded due to wrong outcomes, 11 articles had data extracted.

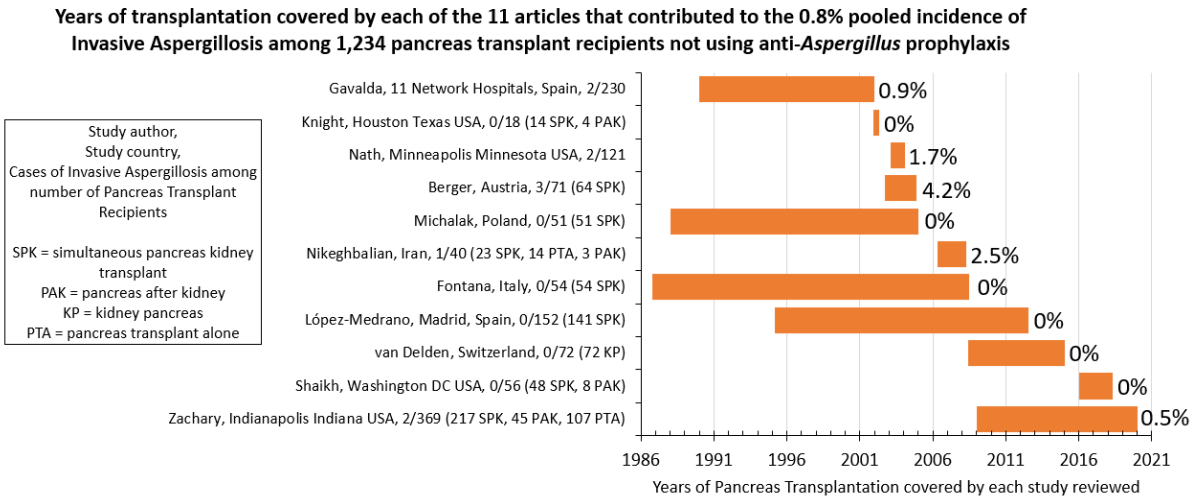
The analysis assembled 11 studies in which the methods section provided sufficient detail to allow identification of IA cases [12, 86, 106-114]. Among 1,234 pancreas transplant recipients with or without kidney transplant (sometimes simultaneous, other pancreas after kidney), 10 cases of proven or probable 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)	2022	López-Medrano	Spain
		2023	Zachary	Indianapolis, USA
	Clinical with no red flags to indicate inclusion of possible IA	2003	Knight	Houston, USA
		2005	Michalak	Poland
		2005	Nath	Minneapolis, USA
		2005	Nikeghbalian	Iran
		2006	Berger	Austria
		2009	Fontana	Italy
		2019	Shaikh	Washington DC, USA
Multiple center studies	EORTC/MSG (De Pauw 2008 or Segal 2008 or Donnelly 2020)	2020	van Delden	Switzerland
	EORTC/MSG initial version (Ascioglu 2002)	2005	Gavalda	Spain

Although the studies were published after 2000, the lookback period was as long as 22 years, so patients transplanted as early as 1986 were included.

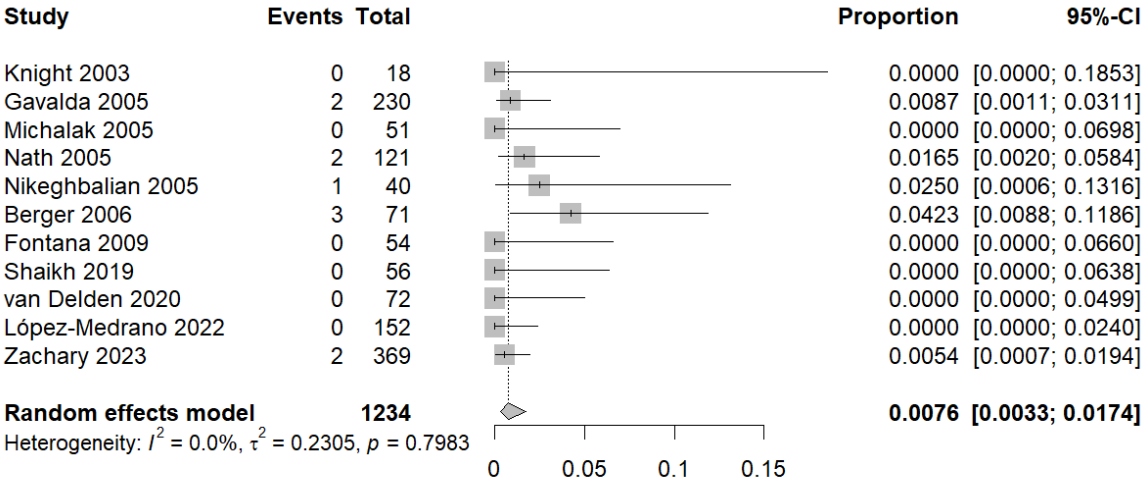
Supplementary Figure 2: Incidence of invasive aspergillosis by years of transplantation covered by each included study



Among patients not receiving anti-*Aspergillus* prophylaxis, any fungal prophylaxis administered consisted of either fluconazole or nystatin.

The pooled incidence for IA was 0.8% (95% confidence interval (CI) 0.3 to 1.7%) using a generalized linear mixed model. One-year all-cause mortality among IA cases was 70%, although only three deaths were clearly attributable to IA.

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



The timing of IA onset was reported in four cases, ranging from approximately 90 to 340 days post-transplant, with infections affecting the lungs and sinuses.

Nuances of These Studies

Nine of 11 studies were retrospective, observational single-center studies [106-114], while two studies reviewed patients from groups of hospitals within their country (Spain and Switzerland) [12, 86]. One

retrospective study reported on two eras of fungal prophylaxis (fluconazole and micafungin); only the fluconazole era was assessed for IA incidence [109]. One study assessed fungal outcomes during a prospective assignment of immunosuppressive regimens [108].

The small number of IA cases and limited reporting of patient- and donor-level risk factors precluded formal statistical analysis of risk factors. Some observations suggest IA may be more common among patients receiving lymphocyte-depleting immunosuppressants such as alemtuzumab, but the data are insufficient to draw firm conclusions [106, 111, 114]. The peak year for pancreas transplantation in the United States was 2004, and this was a time when centers were using lymphocyte-depleting medications for induction and/or maintenance immunosuppression. The three single-center studies with an IA incidence of 1.5% or greater were published with patients transplanted during this era. Nath and colleagues specifically reported that their cohort was all pancreas transplant recipients who received alemtuzumab for induction or maintenance immunosuppression [111]. Another study reported using alemtuzumab solely for induction and observed no no cases [113].

No study included a multivariate analysis. We were not able to identify specific risk factors for IA in the pooled analysis, nor were we able to identify any of the established risk factors observed in other organ transplant populations among the 10 cases of IA reported. Information about surgery after the transplant procedure was minimal, with one successfully treated IA case at ~ day 90 requiring a re-exploration in the first week after transplant [112]. One patient who died with and of IA was a retransplant [106]. Two cases were listed as having concomitant cytomegalovirus infection [106, 112]. Body site of IA involvement was clear for four cases: three pulmonary and one sinusitis [106, 111, 114]. No information was available regarding respiratory tract colonization with *Aspergillus* prior to transplant or post-transplant dialysis.

Limitations

The overall quality of evidence is limited, reflecting several potential sources of bias. Most studies were retrospective and observational, which may introduce selection and reporting biases. Data on donor and recipient co-morbidities, peri-operative management, and prior *Aspergillus* colonization were sparse, limiting adjustment for confounders. Additionally, heterogeneous definitions and follow-up durations across studies may have led to underestimation or overestimation of IA incidence. The low number of events further limits the ability to identify risk factors or generalize findings to contemporary populations. Despite these limitations, the available evidence suggests that IA incidence in pancreas transplant recipients is very low.

Conclusion

The pooled incidence of IA derived from this mapping review of 11 observational studies is 0.8% (95% CI 0.3 to 1.7). Overall, this represents a very low incidence, although it is based on limited data. Current evidence does not support routine universal IA prophylaxis in pancreas transplant recipients, whether for pancreas alone or multi-organ transplants.

Research Gaps

The use of pancreas transplant to control diabetes has declined since its peak in 2004, likely reflecting advances in medical therapies and better overall management of diabetes care and transplant practice. Islet cell transplantation has been explored as an alternative in selected centers, though it is not yet a standard treatment. The decline in procedure volume raises concerns about maintaining surgical expertise, even as outcomes after pancreas transplantation have consistently improved, with high graft and patient survival. Given these trends, single-center reports of IA in pancreas transplant recipients are likely to be limited. Multi-center studies using systematic transplant registry data would therefore be valuable to define IA risk and guide prophylaxis strategies.

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