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Table 1. Definitions of the Different Types of Antifungal Prophylaxis in Solid Organ Transplant Recipients

Universal Prophylaxis	The administration of an antifungal agent to all patients in a specific population who are at risk of developing IA before there is any evidence of IA.
Targeted Prophylaxis	The administration of an antifungal agent to specific persons considered at higher risk for developing IA in the absence of any clinical or laboratory evidence of IA. Examples include those with pretransplant colonization, single lung transplantation, cystic fibrosis, or those on augmented immunosuppression.
Preemptive Therapy (specific to lung transplantation)	The administration of antifungal therapy after lung transplantation to patients with culture or biomarker evidence of *Aspergillus* in respiratory tract specimens, without accompanying clinical, bronchoscopic, and/or radiological features of IA [16, 17].
Secondary Prophylaxis	The administration of an antifungal agent to a person with prior IA who remains at risk (e.g., ongoing immunosuppression) to prevent IA recurrence or relapse.

Abbreviations: IA, invasive aspergillosis

Table 2. Summary of Findings: Universal Anti-*Aspergillus* prophylaxis Versus No Anti-*Aspergillus* prophylaxis in Liver Transplant Recipients

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Universal anti-*Aspergillus* prophylaxis**	**Difference**		
Invasive Aspergillosis follow-up: 3 months № of participants: 640 (5 RCTs)[8-12]	**RR 1.11** (0.23 to 5.45)	**Study population**			⊕⊕◯◯ Low[a,b]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 4% in the incidence of IA. Universal anti-*Aspergillus* prophylaxis may result in little to no difference in invasive aspergillosis.
		1.0%	**1.1%** (0.2 to 5.5)	**0.1% more** (0.8 fewer to 4.5 more)		
		Estimated real-life baseline risk**				
		1.9% **(1.4 to 2.6)**	**2.1%** (0.4 to 10.4)	**0.2% more** (1.5 fewer to 8.5 more)		
Mortality (all-cause) № of participants: 828 (6 RCTs) [7-12]	**RR 1.06** (0.67 to 1.69)	8.5%	**9.0%** (5.7 to 14.3)	**0.5% more** (2.8 fewer to 5.8 more)	⊕◯◯◯ Very Low[c,d]	Universal anti-*Aspergillus* prophylaxis may result in little to no difference in mortality (all-cause), but the evidence is very uncertain.
Attributable Mortality № of participants: 827 (6 RCTs) [7-12]	**RR 0.70** (0.18 to 2.72)	1.3%	**0.9%** (0.2 to 3.5)	**0.4% fewer** (1.1 fewer to 2.2 more)	⊕⊕◯◯ Low[b,c]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 2% in the incidence of attributable mortality. Universal anti-*Aspergillus* prophylaxis may result in little to no difference in attributable mortality.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Universal anti-*Aspergillus* prophylaxis**	**Difference**		
Serious Adverse Events № of participants: 825 (6 RCTs) [7-12]	**RR 1.15** (0.40 to 3.30)	1.8%	**2.1%** (0.7 to 6)	**0.3% more** (1.1 fewer to 4.1 more)	⨁⨁◯◯ Low[b,e]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is no more than 4% increase in serious adverse events. Universal anti-*Aspergillus* prophylaxis may result in little to no difference in serious adverse events.
Non-serious Adverse Events № of participants: 757 (5 RCTs) [7, 8, 10-12]	**RR 1.50** (0.96 to 2.35)	13.4%	**20.1%** (12.8 to 31.4)	**6.7% more** (0.5 fewer to 18.1 more)	⨁⨁◯◯ Low[b,c,f]	Universal anti-*Aspergillus* prophylaxis may increase non-serious Adverse Events slightly.
Non-serious Adverse Events (*Echinocandins ONLY*) № of participants: 369 (2 RCTs) [7, 8]	**RR 1.13 (0.62 to 2.06)**	9.7%	**10.9% (6.0 to 19.9)**	**1.3% more (3.7 fewer to 10.3 more)**	⨁⨁◯◯ Low[b,g]	Universal anti-*Aspergillus* prophylaxis with an echinocandin may result in little to no difference in non-serious adverse events.
Graft rejection № of participants: 200 (1 RCT) [8]	**RR 1.50** (0.44 to 5.15)	4.0%	**6.0%** (1.8 to 20.6)	**2.0% more** (2.2 fewer to 16.6 more)	⨁⨁◯◯ Low[h]	Universal anti-*Aspergillus* prophylaxis may result in little to no difference in graft rejection.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Universal anti-*Aspergillus* prophylaxis**	**Difference**		
Graft loss № of participants: 200 (1 RCT) [8]	**RR 0.93** (0.46 to 1.87)	14.0%	**13.0%** (6.4 to 26.2)	**1.0% fewer** (7.6 fewer to 12.2 more)	⨁⨁◯◯ Low[i]	Universal anti-*Aspergillus* prophylaxis may result in little to no difference in graft loss.

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

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**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.

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.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Universal anti-*Aspergillus* prophylaxis**	**Difference**		

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 differences 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 differences 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.

Table 3. Summary of Findings: Targeted Anti-*Aspergillus* Prophylaxis Versus No Anti-*Aspergillus* Prophylaxis in Liver Transplant Recipients

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		
Invasive Aspergillosis № of participants: 145 (3 non-randomized studies) [19, 28, 49]	**RR 0.19** (0.06 to 0.66)	16.9%	**3.2%** (1 to 11.2)	**13.7% fewer** (15.9 fewer to 5.8 fewer)	⨁◯◯◯ Very low[a,b,c]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 4% in the incidence of IA. At a high baseline risk of IA, targeted anti-*Aspergillus* prophylaxis may reduce invasive *Aspergillus* Infection, but the evidence is very uncertain.
Invasive Aspergillosis [&] № of participants: 261 (2 RCTs) [8, 9]	**RR 0.20** (0.01 to 4.15)	1.6%	**0.3%** (0 to 6.5)	**1.3% fewer** (1.5 fewer to 4.9 more)	⨁⨁◯◯ Low[d,e]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 4% in the incidence of IA. At a low baseline risk of IA, targeted anti-*Aspergillus* prophylaxis may result in little to no difference in invasive aspergillosis.
Mortality (all-cause) № of participants: 33 (1 non-randomized study) [49]	**RR 1.00** (0.52 to 1.94)	54.5%	**54.5%** (28.4 to 100)	**0.0% fewer** (26.2 fewer to 51.3 more)	⨁◯◯◯ Very low[a,f]	Targeted anti-*Aspergillus* prophylaxis may result in little to no difference in mortality (all-cause) but the evidence is very uncertain.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		
Attributable Mortality № of participants: 145 (3 non-randomized studies) [19, 28, 49]	**RR 0.19** (0.03 to 1.00)	13.6%	**2.6%** (0.4 to 13.6)	**11.1% fewer** (13.2 fewer to 0 more)	⨁◯◯◯ Very low[a,g]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 2% in the incidence of attributable mortality. Targeted anti-*Aspergillus* prophylaxis may reduce attributable mortality, but the evidence is very uncertain.
Serious Adverse Events [£] № of participants: 825 (6 RCTs) [7-12]	**RR 1.15** (0.40 to 3.30)	1.8%	**2.1%** (0.7 to 6)	**0.3% more** (1.1 fewer to 4.1 more)	⨁⨁◯◯ Low[e,h]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is no more than 4% increase in serious adverse events. Targeted anti-*Aspergillus* prophylaxis may result in little to no difference in serious adverse events.
Non-serious Adverse Events [£] № of participants: 757 (5 RCTs) [7, 8, 10-12]	**RR 1.50** (0.96 to 2.35)	13.4%	**20.1%** (12.8 to 31.4)	**6.7% more** (0.5 fewer to 18.1 more)	⨁⨁◯◯ Low[e,i,j]	Targeted anti-*Aspergillus* prophylaxis may increase non-serious adverse events slightly.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		
Non-serious Adverse Events (*Echinocandins ONLY*) **£** № of participants: 369 (2 RCTs) [7, 8]	**RR 1.13 (0.62 to 2.06)**	9.7%	**10.9% (6.0 to 19.9)**	**1.3% more (3.7 fewer to 10.3 more)**	⨁⨁◯◯ Low[e,k]	Targeted anti-*Aspergillus* prophylaxis with an echinocandin may result in little to no difference in non-serious adverse events.

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

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

& 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-randomized 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-randomized studies is not likely to be overestimated.

£ Adverse Events were not reported in the 3 non-randomized 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.

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.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		No anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		

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 or not the prophylaxis) and likely include 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 (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.

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).

Table 4. Summary of Findings: Targeted Anti-*Aspergillus* Prophylaxis Versus Universal Anti-*Aspergillus* Prophylaxis in Liver Transplant Recipients

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty of Evidence	What happens
		Universal anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		
Invasive Aspergillosis № of participants: 382 (1 non-randomized study) [23]	not estimable	0%	**0.7%** (0.02 to 3.8)	**0.7% more** (0.7 fewer to 2.0 more)	⨁⨁◯◯ Low[a,b]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 4% in the incidence of IA. Targeted anti-*Aspergillus* prophylaxis may result in little to no difference in invasive aspergillosis.
Mortality (all-cause) № of participants: 382 (1 non-randomized study) [23]	**RR 1.44** (0.74 to 2.80)	7.2%	**10.3%** (5.3 to 20.1)	**3.2% more** (2.8 fewer to 9.1 more)	⨁◯◯◯ Very low[a,c]	Targeted anti-*Aspergillus* prophylaxis may increase mortality (all-cause) slightly, but this estimate is very uncertain.
Attributable mortality № of participants: 382 (1 non-randomized study) [23]	not estimable	0%	**0.7%** (0.02 to 3.8)	**0.7% more** (0.7 fewer to 2.0 more)	⨁⨁◯◯ Low[a,b]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is a reduction of at least 2% in the incidence of attributable mortality. Targeted anti-*Aspergillus* prophylaxis may result in little to no difference in attributable mortality

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of Evidence	What happens
		Universal anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		
Serious and Non-Serious Adverse Events № of participants: 382 (1 non-randomized study) [23]	**RR 0.65** (0.13 to 3.33)	2.1%	**1.4%** (0.3 to 7)	**0.7% fewer** (3.4 fewer to 1.9 more)	⨁◯◯◯ Very low[d]	The panel judged that the clinical decision threshold between recommending and not recommending prophylaxis is no more than 4% increase in serious adverse events. Targeted anti-*Aspergillus* prophylaxis may result in little to no difference in serious and non-serious Adverse Events, but this estimate is very uncertain.

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

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty of Evidence	What happens
		Universal anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis**	**Difference**		
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.						

Table 5. Summary of findings: Universal anti-*Aspergillus* prophylaxis versus No anti-*Aspergillus* prophylaxis in lung transplant recipients

Outcome (N of participants, N studies)†	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of evidence
		No anti-*Aspergillus* prophylaxis	**Universal anti-*Aspergillus* prophylaxis**	**Difference**	
Invasive Aspergillosis at 14 to 56 months (637 participants, 4 non-randomized studies) [15-18]	**RR 0.66** (0.31-1.45)	**Study population**			⨁◯◯◯ Very low
		25.6%	16.9% (7.9-37.1)	**8.7% fewer** (17.6 fewer to 11.5 more)	
		Critical concern about clinical and statistical heterogeneity makes these estimates unreliable			
		Estimated real-life baseline risk**			
		19.0%**	12.5% (5.9-27.5)	**6.5% fewer** (13.1 fewer to 8.5 more)	
		Critical concern about clinical and statistical heterogeneity makes these estimates unreliable			
Aspergillus colonization (413 participants, 2 non-randomized studies) [15,18]	**RR 0.75** (0.46-1.22)	16.1%	12.0% (7.4-19.6)	**4.0% fewer** (8.7 fewer to 3.5 more)	⨁◯◯◯ Very low
Mortality (all cause) (412 participants, 2 non-randomized studies) [15,18]	**RR 0.62** (0.10-3.75)	17.5%	10.9% (1.8-65.7)	**6.7% fewer** (15.8 fewer to 48.2 more)	⨁◯◯◯ Very low
Serious Adverse Events (55 participants, 1 non-randomized study) [17]	**RR 0.80** (0.03-18.42)	0.0%	0.0%	**0.0% fewer** (0 fewer to 0 more)	⨁◯◯◯ Very low

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

† The number of participants and studies for which each specific outcome are reported.

***** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

****** Estimated real-life baseline risk was based on a separate mapping review of the literature including 6 observational studies and the average and 95%CI was calculated using generalized linear mixed models (commonly referred to as GLMM).

Outcome (N of participants, N studies) [†]	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of evidence
		No anti-*Aspergillus* prophylaxis	**Universal anti-*Aspergillus* prophylaxis**	**Difference**	
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.					

Table 6. Summary of Findings: Universal Anti-*Aspergillus* prophylaxis Versus Targeted Anti-*Aspergillus* Prophylaxis or Preemptive Therapy in Lung Transplant Recipients

Outcome (N of participants, N studies) †	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of evidence
		Universal anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy**	**Difference**	
Invasive Aspergillosis at 12 to 18 months (495 participants, 3 non-randomized studies) [25, 28, 46]	**RR 2.38** (0.72-7.84)	10.4%	24.8% (7.5-81.6)	**14.4% more** (2.9 fewer to 71.2 more)	⨁◯◯◯ Very low
		Critical concern about clinical and statistical heterogeneity makes these estimates unreliable			
Breakthrough Invasive Aspergillosis at 12 to 18 months (495 participants, 3 non-randomized studies) [25, 28, 46]	**RR 0.88** (0.11-6.81)	2.5%	2.2% (0.3-17.2)	**0.3% fewer** (2.2 fewer to 14.7 more)	⨁◯◯◯ Very low
Post-transplant Aspergillus colonization at 12 months to 18 months (390 participants, 2 non-randomized studies) [28, 46]	**RR 1.06** (0.62-1.81)	12.8%	13.6% (7.9-23.2)	**0.8% more** (4.9 fewer to 10.4 more)	⨁◯◯◯ Very low
Mortality (all cause) (200 participants, 2 non-randomized studies) [25, 28]	**RR 1.54** (0.14-16.48)	8.1%	12.4% (1.1-100)	**4.4% more** (6.9 fewer to 100.0 more)	⨁◯◯◯ Very low
Serious Adverse Events (390 participants, 2 non-randomized studies) [28, 47]	**RR 0.13** (0.01-2.22)	47.7%	6.2% (0.5-100)	**41.5% fewer** (47.2 fewer to 58.2 more)	⨁◯◯◯ Very low
Non-Serious Adverse Events (92 participants, 1 non-randomized study) [28]	**RR 0.33** (0.13-0.85)	44.6%	14.7% (5.8-37.9)	**29.9% fewer** (38.8 fewer to 6.7 fewer)	⨁◯◯◯ Very low

Outcome (N of participants, N studies) †	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of evidence
		Universal anti-*Aspergillus* prophylaxis	**Targeted anti-*Aspergillus* prophylaxis or pre-emptive therapy**	**Difference**	
Graft rejection (295 participants, 1 non-randomized study) [47]	**RR 0.34** (0.20-0.57)	40.4%	13.7% (8.1-23.0)	**26.7% fewer** (32.3 fewer to 17.4 fewer)	⨁◯◯◯ Very low

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

† The number of participants and studies for which each specific outcome are reported.

***** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 7. Comparative Antifungal Prophylaxis Strategies in Lung Transplantation

Strategy	Advantages	Limitations
Universal Prophylaxis	- Aimed at preventing IA for all patients - Standardized, so easier to implement - May reduce IA incidence and mortality during high-risk periods	- Increased antifungal exposure - Higher risk of toxicity and resistance - Higher cost of antifungal agents - Potential overtreatment
Targeted Prophylaxis	- Limits antifungal exposure to high-risk recipients - Potentially lowers toxicity and cost	- Requires accurate risk stratification - Risk of missing early IA among patients not meeting criteria
Preemptive Therapy	- Antifungal use based on early microbiologic or biomarker detection - Avoids unnecessary treatment	- Relies on frequent bronchoscopies and reliable surveillance testing - Risk of delayed therapy - Operational complexity and higher diagnostic cost
No prophylaxis and No Preemptive Therapy	- Avoid antifungal drug exposure, drug costs, and associated adverse events - Operational simplicity - May reduce selection pressure for antifungal resistance - Avoids concerns about false negative diagnostic tests for IA	- Higher risk of IA during the early post-transplant period, especially among patients with established risk factors - Potential for increased IA-associated morbidity and mortality - Higher downstream costs related to treatment of established infection

Table 8. Summary Table for Selecting Antifungal Prophylaxis Strategies

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