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

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Liver Transplant Recipients

Clinical question A: In liver transplant recipients, what is the optimal anti-*Aspergillus* prophylaxis strategy (universal versus targeted versus no prophylaxis)?

Recommendations

1) In liver transplant recipients, we suggest against using universal anti-*Aspergillus* prophylaxis (*conditional recommendation, low certainty of evidence*).

Comments:

-Universal prophylaxis is defined as the administration of prophylaxis to all liver transplant recipients.
-In the included studies, universal anti-*Aspergillus* prophylaxis (agents examined were anidulafungin, micafungin, itraconazole, and liposomal amphotericin B) was compared with either fluconazole or no antifungal prophylaxis.
-This recommendation places a high value on avoiding adverse events and unnecessary costs, given the lack of clear clinically significant benefits.

2) In liver transplant recipients, we suggest targeted anti-*Aspergillus* prophylaxis for individuals at high risk of invasive aspergillosis (*conditional recommendation, very low certainty of evidence*).

Comments:

-Targeted prophylaxis refers to antifungal prophylaxis given only to patients who are at high risk for invasive aspergillosis. In the evidence reviewed, the most common risk factors for IA included: 1) renal replacement therapy in the peri-transplantation period, 2) re-transplantation, and 3) transplantation for fulminant hepatic failure.
-In the included study, voriconazole was evaluated as a prophylactic agent in both targeted and universal strategies.
-The duration of anti-*Aspergillus* prophylaxis in the included evidence was typically until discharge from the initial transplant hospitalization through 28 days post-transplant.
-This recommendation places a high value on balancing potential benefits while improving stewardship and reducing costs.

Clinical question B: In liver transplant recipients for whom anti-*Aspergillus* prophylaxis is indicated, what is the optimal choice of agents?

Recommendation:

In liver transplant recipients requiring anti-*Aspergillus* prophylaxis, we suggest using an echinocandin or a newer anti-mold triazole (voriconazole, posaconazole or isavuconazole) rather than amphotericin B formulations or itraconazole (*conditional recommendation, very low certainty of evidence*).

Comments:

-This recommendation prioritizes reducing adverse events (e.g. nephrotoxicity and hepatotoxicity), minimizing drug-drug interactions (especially with cyclosporine, tacrolimus, sirolimus and everolimus), and optimizing bioavailability.
-Among the anti-mold triazoles, the available evidence is derived primarily from studies evaluating voriconazole. To date, no peer-reviewed studies have specifically assessed posaconazole or isavuconazole for prophylaxis in liver transplant recipients. Based on indirect evidence from other transplant populations, these anti-mold triazoles (voriconazole, posaconazole and isavuconazole) are expected to provide comparable benefits.

Background

The reported incidence of invasive fungal infections (IFIs) after liver transplant ranges from 7 to 42% [1], *Candida* and *Candida*-like species account for over 80% of IFIs in the peri-transplant period [2, 3]. Although less frequent than invasive candidiasis, invasive aspergillosis (IA) is associated with high rates of dissemination and mortality, especially when occurring early post-transplant [4]. Thus, prevention of IFIs is critical, and many centers implement antifungal prophylaxis in the peri-transplant period [5].

Approaches to prophylaxis vary widely across institutions, reflecting differences in local epidemiology. Some centers do not use antifungal prophylaxis, while others adopt either a universal strategy (defined as prophylaxis administered to all recent transplant recipients) or a targeted strategy (prophylaxis administered to a specific group of recipients considered at risk for fungal infection). The choice of antifungal agent also varies. In some centers, fluconazole, a narrow spectrum triazole with activity limited to yeasts species, is the preferred agent. This preference is based on fluconazole's proven efficacy against yeasts, lower cost, good tolerability, fewer drug-drug interactions compared with broad-spectrum triazoles, and excellent oral availability. Other centers favor echinocandins, which provide activity against *Candida* and *Candida*-like species and are fungistatic against *Aspergillus*, and have minimal drug-drug interactions. A third approach, used in some institutions, applies risk-stratified prophylaxis: no antifungal prophylaxis for those at low risk for IFI, fluconazole for those at risk for *Candida*/yeast infections, and broad-spectrum antifungal (mold-active triazole, echinocandin or amphotericin B products) for those at risk for *Aspergillus* infections [6]. The tiered model is feasible because predisposing factors to *Candida* and *Candida*-like and *Aspergillus* infections after liver transplants are well-established.

This guideline evaluated whether antifungal prophylaxis should be broadened to include *Aspergillus* coverage or initiated in centers that do not routinely use prophylaxis. We sought to address the following questions: 1) is anti-*Aspergillus* prophylaxis beneficial during the peri-transplant period, 2) if beneficial, should prophylaxis be universal or targeted; and 3) if an anti-*Aspergillus* prophylaxis is indicated, which antifungal agent is preferred? In order to make recommendations on universal versus targeted versus no prophylaxis (A), we performed the three following comparisons: A1) universal versus no prophylaxis, A2) targeted versus no prophylaxis and A3) targeted versus universal prophylaxis.

Clinical question A: In liver transplant recipients, what is the optimal anti-*Aspergillus* prophylaxis strategy (universal versus targeted versus no prophylaxis)?

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

Recommendation: In liver transplant recipients, we suggest against using universal anti-*Aspergillus* prophylaxis (*conditional recommendation, low certainty of evidence*).

Comments:

-Universal prophylaxis is defined as the administration of prophylaxis to all liver transplant recipients.

-In the included studies, universal anti-*Aspergillus* prophylaxis (agents examined were anidulafungin, micafungin, itraconazole, and liposomal amphotericin B) was compared with either fluconazole or no antifungal prophylaxis.

-This recommendation places a high value on avoiding adverse events and unnecessary costs, given the lack of clear clinically significant benefits.

Summary of the evidence

Description of the direct evidence

Our systematic review of the literature (spanning from 2000-2025) identified six randomized, controlled trials (RCTs) comparing the use of universal anti-*Aspergillus* prophylaxis (either anidulafungin, micafungin, itraconazole, or liposomal amphotericin B) with not using anti-*Aspergillus* prophylaxis (fluconazole or no antifungal prophylaxis) [7-12].

Studied populations and clinical settings:

Six RCTs enrolled and randomized a total of 828 liver transplant recipients in the early post-transplantation period [7-12]. These studies were conducted between 1999 and 2015 across multiple regions, including North America [8-10, 12], Asia [7] and Europe [11]. All studies enrolled liver transplant recipients; two studies restricted enrollment to patients considered at high risk of IFI (see Supplementary material, Table A1.2 Characteristics of the included studies). In the control arms (no anti-*Aspergillus* prophylaxis), the reported incidence of IA ranged from 0 to 2.0%, and all-cause mortality ranged from 1.1% to 15.8% [7-12].

Studied comparison:

The agents used for universal anti-*Aspergillus* prophylaxis in the intervention groups were heterogenous and included: echinocandins (micafungin and anidulafungin) [7, 8], liposomal amphotericin B [9, 11] or itraconazole [10, 12]. None of the included RCTs evaluated newer mold-active triazoles (voriconazole, posaconazole or isavuconazole) as prophylactic agents. The comparator groups either received fluconazole as an anti-yeast prophylaxis [7-9, 12] or placebo (no antifungal prophylaxis) [10, 11]. The total duration of prophylaxis varied across studies, ranging from 14 days [9] to 10 weeks [12], with the two more recent studies administering prophylaxis for up to 21 days or until hospital discharge, whichever occurred first [7, 8].

Studied outcomes:

In the included studies, the primary outcome was the incidence of IFIs during the post-transplant period. Three studies used the standard European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG) [13] definitions to establish the diagnosis of proven or probable IFIs [7-9], while the three earlier studies provided less detail about their diagnostic criteria but were considered broadly comparable to the EORTC/MSG criteria for proven or probable IFI. The EORTC/MSG definitions for IA were updated in 2020 [14] to incorporate positive *Aspergillus* polymerase chain reaction (PCR) results from tissue, bronchoalveolar lavage or blood components in the mycologic evidence section. These updates do not affect the results of our review, as all included studies were performed prior to 2020. All but one study specifically reported on the incidence of IA [7]. Most studies reported mortality (all-cause and/or attributable), serious adverse events (SAE) (generally defined in the studies as events leading to prophylaxis discontinuation), and non-serious AE. Only one study reported outcomes related to graft loss and graft rejection [8]. The follow-up period to assess the outcomes ranged from 30 to 100 days post-transplant.

Study design and risk of bias:

The included trials employed a range of designs, including non-inferiority, superiority or explorative approaches, but generally reported on a relatively small number of patients (varying from 68 to 200 enrolled patients per study). The risk of bias was judged as low for three of the six included studies [8, 9, 11]. The remaining three studies were judged to be at high risk of bias: Kang 2020 [7] and Winston 2002 [12] lacked blinding, while Sharpe 2003 [10] was terminated early as per *a priori* study stopping rules.

Benefits and harms

The use of universal anti-*Aspergillus* prophylaxis in liver transplant recipients may result in comparable outcomes to those observed without anti-*Aspergillus* prophylaxis. Decision thresholds for critical outcomes were prespecified by panel consensus (see Methods), corresponding to minimal important differences of 4% for invasive aspergillosis, 2% for attributable mortality, and 4% for serious adverse events. Based on the panel's pre-determined decision threshold of a 4% reduction in incidence in IA compared with no prophylaxis (see Methods section), the rates of IA appear similar between groups (risk difference [RD]: 0.1%; 95% confidence interval [CI]: -0.8 to 0.2%; low certainty of evidence [CoE]) (Table 1). Similarly, results also appear comparable for attributable mortality (RD: -0.4%; 95% CI: -1.1 to 2.2%; low CoE), all-cause mortality (RD: 0.5%; 95% CI: -2.8 to 5.8%; very low CoE), graft rejection (RD: 2.0%; 95% CI: -2.2 to 16.6%; low CoE), and graft loss (RD: -1.0%; 95% CI: -7.6% to 12.2%; low CoE) (see Supplementary material, Table A1.1 Grading of Recommendations Assessment, Development and Evaluation [GRADE] Evidence Profile). Taken together, this review does not demonstrate a clear benefit of universal anti-*Aspergillus* prophylaxis over no prophylaxis in liver transplant recipients.

With respect to safety, universal anti-*Aspergillus* prophylaxis may result in similar rates of SAE (RD: 0.3%; 95% CI: -1.1 to 4.1%; low CoE) compared with groups without anti-*Aspergillus* prophylaxis. Nevertheless, non-serious AE may be more frequent than among those receiving fluconazole or placebo (RD: 6.7%; 95% -0.5% to 18.1%; low CoE). When stratified by classes of anti-*Aspergillus* agents, echinocandin prophylaxis may result in rates of non-serious AE comparable to those observed in control groups (RD: 1.3%; 95% CI: -3.7% to 10.3%), while itraconazole prophylaxis may result in higher rates of non-serious AE (RD: 12.8%; 95%CI: -1.9% to 41.6%).

Table 1. 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**		
		Study population				
Invasive Aspergillosis follow-up: 3 months № of participants: 640 (5 RCTs)[8-12]	**RR 1.11** (0.23 to 5.45)	1.0%	**1.1%** (0.2 to 5.5)	**0.1% more** (0.8 fewer to 4.5 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. Universal anti-*Aspergillus* prophylaxis may result <u>in little to no difference</u> in invasive aspergillosis.
		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 <u>in little to no difference</u> 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 <u>in little to no difference</u> in attributable mortality.
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 <u>in little to no difference</u> in serious adverse events.

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**		
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.
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 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 40 observational studies and the average and 95%CI was calculated using generalized linear mixed models (commonly referred to as 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.

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.

Other supporting evidence

Incidence of invasive aspergillosis in liver transplant recipients not receiving anti-*Aspergillus* prophylaxis

To better understand the burden of IA in liver transplant, a mapping review of the literature was performed from January 2000 to April 2025 (See Supplemental material, Descriptive question) to determine the incidence of IA in patients not receiving anti-*Aspergillus* prophylaxis.

A total of 40 studies, encompassing 14,385 patients who did not receive anti-*Aspergillus* prophylaxis, were included [8, 11, 12, 15-52]. Most studies (21/40, 52.5%) focused on adult liver transplant populations. Seven studies included a small number of pediatric patients that could not be analyzed separately from the adult cohort. These studies were included as the overall proportion of pediatric patients was low. One study specifically examined adult living donors [37], while another focused on a low-risk population [39]. Most studies were retrospective, observational, and conducted at single centers.

Among these 14,385 patients, 305 developed proven or probable IA. The pooled incidence of IA was 1.9% (95% confidence interval: 1.4% to 2.5%) (See Supplementary material, Figure A1.5 and A1.6). The one-year all-cause mortality among 146 cases with available survival data was 65%.

Estimating the incidence of IA was challenging due to several limitations. Variability between studies likely reflects differences in local epidemiology, ecology and transplant practices, as most studies were from single centers and different continents. Access to antifungal medications may differ by center and publication bias may have influenced estimates. Diagnostic approaches also differed between centers: most relied on histopathology and culture, whereas others, in later years, used galactomannan antigen. Last and most importantly, patient population varied, with some studies including patients at low risk for IA [39], and others included only high-risk cohorts [53]. Notably, most IA cases occurred in patients with established risk factors, including renal replacement therapy (RRT), re-transplantation, or fulminant hepatic failure as the reason for transplantation.

Despite these limitations, the pooled estimated incidence of 1.9% provides important context, demonstrating that the overall risk for IA in unselected liver transplant recipients is relatively low, thereby supporting the conclusion that universal anti-*Aspergillus* prophylaxis is unlikely to provide meaningful benefits.

Rationale for recommendation

The panel agreed that the overall certainty of the evidence for using universal anti-*Aspergillus* prophylaxis in liver transplant recipients is low. Concerns include potential risks of bias and imprecision due to the low number of reported events. In the absence of demonstrable clinical benefits, the panel concluded that the additional harms or drug interactions), together with resource use and cost, weigh against the use of universal anti-*Aspergillus* prophylaxis in liver transplant recipients.

Conclusion

The guideline panel suggested against the use of universal anti-*Aspergillus* prophylaxis for liver transplant recipients following transplantation.

Clinical questions A2 and A3: In liver transplant recipients, should targeted anti-*Aspergillus* prophylaxis in individuals at high risk of invasive aspergillosis be used rather than not using anti-*Aspergillus* prophylaxis, or rather than using universal anti-*Aspergillus* prophylaxis?

Recommendation: In liver transplant recipients, we suggest targeted anti-*Aspergillus* prophylaxis for individuals at high risk of invasive aspergillosis (*conditional recommendation, very low certainty of evidence*).

Comments:

-Targeted prophylaxis refers to antifungal prophylaxis given only to patients who are at high risk for invasive aspergillosis. In the evidence reviewed, the most common risk factors for IA included: 1) renal replacement therapy in the peri-transplantation period, 2) re-transplantation, and 3) transplantation for fulminant hepatic failure.

-In the included study, voriconazole was evaluated as a prophylactic agent in both targeted and universal strategies.

-The duration of anti-*Aspergillus* prophylaxis in the included evidence was typically until discharge from the initial transplant hospitalization through 28 days post-transplant.

-This recommendation places a high value on balancing potential benefits while improving stewardship and reducing costs.

A2) Targeted anti-*Aspergillus* prophylaxis versus no anti-*Aspergillus* prophylaxis in individuals at high risk of invasive aspergillosis

Summary of the evidence

Description of the direct evidence

Our systematic review of the literature (spanning from 2000-2025) identified three non-randomized studies comparing the use of targeted anti-*Aspergillus* prophylaxis (either caspofungin, liposomal amphotericin B, and amphotericin B lipid complex) to not using anti-*Aspergillus* prophylaxis (no antifungal prophylaxis) in individuals at high risk of IA [19, 28, 49].

Studied populations and clinical settings:

The three observational studies reported on a total of 597 patients, of which 145 were considered at high risk of IA [19, 28, 49]. All three studies were retrospective “before-and-after” cohort studies; the “before” periods corresponded to the comparator groups who did not receive antifungal prophylaxis, while the “after” periods corresponded to the intervention groups who did receive targeted anti-*Aspergillus* prophylaxis in individuals at high risk of IA or invasive mold infection (IMI). The timeframe of these studies spanned from 1990 to 2017. Only Chakravarti 2021 reported on a more contemporary cohort (from 2008-2017) [19]. Studies were all performed in North America [19, 28, 49].

All studies only included liver transplant recipients. Two studies stratified liver transplant recipients according to their risk of IA or invasive mold infections (Chakravarti 2021 and Hellinger 2005 respectively). Chakravarti 2021 defined high risk of IA as either: acute liver failure, requirement for RRT within 30 days of transplantation (prior or after orthotopic liver transplant), re-transplantation or colonization with *Aspergillus* prior to transplantation) [19], while Hellinger 2005 defined risk of invasive mold infections as: 1) high risk if on hemodialysis at the time of transplantation, and/or hospital discharge delayed beyond 7 days after transplantation because of allograft or renal insufficiency; 2) intermediate risk if transplanted for fulminant hepatic failure, and/or re-transplantation) [28]. Singh 2001 restricted inclusion to patients requiring RRT [49]. The reported rates of IA among liver transplant participants considered at high risk of IA/IMI and not receiving anti-*Aspergillus* prophylaxis (control groups) ranged from 13.6 to 28.6% (see Supplementary material, Table A2.2 Characteristics of the included studies).

Studied comparisons:

Targeted prophylaxis included caspofungin [19], liposomal amphotericin B or amphotericin B lipid complex [28, 49]. No study evaluated newer anti-mold triazoles (voriconazole, posaconazole, isavuconazole) for prophylaxis. Comparator groups received no antifungal prophylaxis. Prophylaxis duration was until hospital discharge [19, 28, 49], up to 28 days maximum [19], or until discontinuation of RRT or death [49].

Studied outcomes:

For all studies, the primary outcome was post-transplant incidence of IFI. Two studies [19, 28] employed the EORTC/MSG definitions for proven or probable IFI [13, 54], while Singh 2001 relied on histopathology- and culture-based diagnosis [49]. All studies reported IA incidence and attributable mortality; Singh 2001 also assessed all-cause mortality. Serious and non-serious AE were not reported in any of the studies. Follow-up period ranged from 90 days to 12 months.

Study design and risk of bias:

The overall risk of bias for these studies was judged to be serious. The retrospective "before-and-after" design inherently introduced residual confounding and selection bias, including the potential for environmental or practice changes across study periods and differences in the characteristics of enrolled patients. Event numbers were also very small, contributing to the imprecision.

Benefits and harms

Based on the panel's pre-determined decision threshold of a 4% reduction in incidence in IA compared with no prophylaxis (see Methods), targeted anti-*Aspergillus* prophylaxis in liver transplant recipients at high risk for IA or invasive mold infections may reduce the incidence of IA with an estimated risk reduction of -13.7% (95% CI: -15.9 to 5.8%; very low CoE) (Table 2). Targeted prophylaxis may also reduce IA attributable mortality (RD: -11.1%; 95% CI: -13.2 to 0%; very low CoE) (See Supplementary material, Table A2.1 GRADE Evidence Profile). No difference was observed in all-cause mortality (RD: 0%; 95% CI: -26.2 to 51.3%; very low CoE), as compared with those not receiving anti-*Aspergillus* prophylaxis, but the evidence is very uncertain. Serious and non-serious AE were not reported in these studies, but the panel judged that potential harm, including toxicities and drug interactions, were likely similar to those described for universal prophylaxis.

Table 2. 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.
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.

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**		
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.
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 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).

& 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.

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).

Rationale for recommendation

Balance of benefits and harms / Certainty in the evidence

When targeted prophylaxis was compared with no prophylaxis, the panel judged that the balance of benefits and harms favored targeted anti-*Aspergillus* prophylaxis in liver transplant recipients. Specifically, targeted prophylaxis is anticipated to provide a moderate reduction in IA incidence and IA attributable mortality, without evidence of excess harm compared to no prophylaxis although potential harms may vary depending on the antifungal class used. The panel agreed that the overall certainty of the evidence was very low due to risk of bias and imprecision related to small sample size and number of events.

Costs and Resources/ Acceptability

The panel acknowledges that targeted anti-*Aspergillus* would increase direct costs related to drug acquisition, administration, and laboratory monitoring. Although cost-effectiveness could not be determined, the panel judged that the use of targeted anti-*Aspergillus* prophylaxis was acceptable for stakeholders, given its limited duration, ease of administration, and manageable drug-drug interactions.

Patients Values / Equity

The panel assumed that patients would generally value an intervention that offers a favorable balance of benefits and harms, particularly given the high mortality associated with IA. Because prophylaxis is usually provided in the inpatient setting for a limited duration, inequities based on race, socioeconomic status, or geography are unlikely to be significant. Although some centers may not have access to certain antifungal agents, this lack of availability is expected to affect all patients within the institution equally and therefore does not create patient-level inequities.

Conclusion

The guideline panel suggested using targeted anti-*Aspergillus* prophylaxis for liver transplant recipients considered at high risk of IA following transplantation (renal replacement therapy in the peri-transplantation period, re-transplantation, or transplantation for fulminant hepatic failure), rather than no anti-*Aspergillus* prophylaxis. Considerations for implementation are discussed below.

A3) Targeted anti-*Aspergillus* prophylaxis in individuals at high risk of invasive aspergillosis versus Universal anti-*Aspergillus* prophylaxis

Summary of the evidence

Description of the direct evidence

Our systematic review of the literature (spanning from 2000-2025) identified a single non-randomized retrospective study that directly compared targeted anti-*Aspergillus* prophylaxis with universal prophylaxis, in which both groups received voriconazole [23].

Studied populations and clinical settings:

The study, conducted at a single US center, included 382 patients, of whom 78 were classified as high-risk for IA [23]. The study compared a “before” cohort that received universal prophylaxis with voriconazole in the immediate post-transplant intensive care unit (ICU) setting (implemented during an ICU construction-associated outbreak of invasive mold infections) with an “after” cohort that received targeted prophylaxis with voriconazole restricted to patients at high risk of IA. Within the targeted cohort, additional stratification was applied: individuals not at high risk of IA, but at high risk of yeast infection received fluconazole prophylaxis, while those at low risk of IFI received no antifungal prophylaxis.

This study only included liver transplant recipients. High-risk criteria of IA included re-transplantation, renal failure requiring RRT post-transplant, fulminant hepatic failure as the indication for transplantation, and intra-abdominal or thoracic re-exploration within the first month post-transplant. The reported rates of IA and mortality among all liver transplant participants receiving anti-*Aspergillus* prophylaxis (control group) were 0% and 7.2%, respectively (see Supplementary material, Table A3.2 Characteristics of the included study).

Studied comparisons:

Voriconazole was used for both groups. In the universal group, voriconazole prophylaxis was administered during the immediate post-transplant ICU stay, whereas in the targeted group, voriconazole was given only to patients at high risk of IA and continued until hospital discharge or for a maximum of 28 days.

Studied outcomes:

The primary outcome was the incidence of IFI within 100 days after transplant, assessed using the standard EORTC/MSG definitions [13]. Additional outcomes included all-cause mortality, attributable mortality, and the occurrence of serious or non-serious AE, all evaluated within 100 days post-transplant.

Study design and risk of bias:

The risk of bias was judged to be serious, primarily due to retrospective "before-and-after" design. Potential confounding factors included environmental changes and variations in clinical practices across study periods. The very small number of events further contributed to the imprecision.

Benefits and harms

Based on the panel's decision threshold (see Methods), the use of targeted rather than universal anti-*Aspergillus* prophylaxis may result in comparable rates of serious or non-serious AE (RD: 0.7%; 95% CI: -3.4 to 1.9%; very low CoE), but the certainty of the evidence is very low (Table 3). In liver transplant recipients at high risk of invasive mold infections, targeted prophylaxis may also result in rates of IA (RD: 0.7%; 95% CI: -0.7 to 2.0%; low CoE) and attributable mortality (RD: 0.7%; 95% CI: -0.7 to 2.0%; low CoE) that are comparable to those observed with universal prophylaxis (See Supplementary material, Table A3.1 GRADE Evidence Profile). However, targeted prophylaxis may be associated with an increase in all-cause mortality (RD: 3.2%; 95% CI: -2.8 to 9.1%; very low CoE) when compared to universal anti-*Aspergillus,* but the evidence is very uncertain.

Table 3. 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
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.

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**		

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.

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.

Rationale for recommendation

Balance of benefits and harms / Certainty in the evidence

The panel judged that the balance of benefits and harms does not clearly favor either strategy. Specifically, the evidence showed that targeted prophylaxis was anticipated to provide trivial undesirable effects (small to no increase in IA and attributable mortality) with trivial desirable effects (small to no reduction in AE) as compared to universal prophylaxis. The panel agreed that the certainty in the evidence was very low due to the risk of bias associated with the study design as well as the imprecision.

Acceptability / Stewardship issues

The panel judged that restricting anti-*Aspergillus* prophylaxis to a targeted group of individuals was acceptable to stakeholders, largely because of stewardship benefits.

Costs and Resources / Patients Values / Equity

The panel acknowledged that restricting anti-*Aspergillus* prophylaxis to target individuals at high risk of invasive disease would reduce drug-drug interactions, toxicities, and selective pressure for resistance, while also lowering direct drug acquisition and monitoring costs. Cost-effectiveness was not formally evaluated, but targeted prophylaxis was expected to be more resource-efficient than universal use. Patients are likely to value avoiding unnecessary antifungal exposure while still receiving protection when the risk is elevated. Restricting prophylaxis to high-risk groups was not expected to introduce inequity, as all patients meeting defined criteria would remain eligible. The panel also recognized that some centers may have local protocols for yeast prophylaxis that overlap with anti-*Aspergillus* prophylaxis, suggesting that the latter may not always represent a major incremental cost or use of additional resources. Overall, the panel assumed that most patients would support this targeted approach, though some variability in how stewardship considerations would be valued may exist.

Conclusion

The guideline panel suggested using targeted anti-*Aspergillus* prophylaxis in liver transplant recipients at high risk of IA following transplantation (renal replacement therapy in the peri-transplantation period, re-transplantation, or transplantation for fulminant hepatic failure), rather than universal prophylaxis in all liver transplant recipients.

Considerations for Implementation of the recommendation

Universal antifungal prophylaxis has the potential to prevent IA, but carries risks of toxicities, including hepatotoxicity, and drug interactions with immunosuppressive agents. A targeted approach allows antifungal use to be reserved for those most likely to benefit, while sparing lower risk patients unnecessary complications. Identifying appropriate candidates for prophylaxis requires careful risk stratification based on local epidemiology and individual patient characteristics.

Individual risk factors of invasive aspergillosis

Liver transplant recipients face a heightened risk of IA due to various predisposing factors. Well-recognized risk factors include post-transplant RRT, reoperation, and fulminant hepatic failure. These factors contribute to a cumulative state of increased immunosuppression, increasing susceptibility to fungal infections. While re-transplantation has been historically linked to a higher IA risk, its significance in this context remains uncertain due to variability across studies [55]. In a multicenter case-control study of 184 recipients [56], reoperation (adjusted odds ratio [aOR] 5.99; 95% CI 1.45-24.7) and systemic antibiotic use (aOR 5.03; 95% CI, 1.09-23.2) were independent risk factors for early IA. Unexpectedly, anti-mold prophylaxis (aOR 11.9; ; 95% CI, 1.45-97.6) was also associated with IA, likely reflecting confounding-by-indication, as prophylaxis was given to patients judged at high risk using heterogeneous criteria. Effectiveness may have been limited by the short median time to onset (11 days) and variable prophylaxis regimens (voriconazole, liposomal amphotericin B at varying doses, or echinocandins). Renal failure and RRT, established risk factors in prior studies, were not independently associated with IA, possibly due to collinearity with other risk factors, variability in definitions, and small sample size [56].

Because patient risk status can change over time, targeted prophylaxis requires active reassessment, typically until discharge from the initial transplant hospitalization or up to 28 days. The need for RRT and reoperation may emerge days to weeks after transplantation, warranting initiation of prophylaxis at that stage. Graft rejection as an outcome was assessed in only one study [8]. Importantly, the role of anti-*Aspergillus* prophylaxis in the setting of acute or chronic rejection in liver transplant has not been studied.

Combining individual risk factors of invasive aspergillosis

Although individual studies have identified several risk factors for IA, no study has systematically examined the cumulative effect of multiple risk factors.

Observational studies such as Chakravarti 2021, Hellinger 2005, and Singh 2001 highlighted re-transplantation, RRT, and severe preoperative conditions as contributors to IA risk [19, 28, 49]. While Hellinger 2005 stratified patients by risk levels, the study did not assess how the accumulation of multiple risk factors influenced IA incidence [28]. Therefore, while the presence of individual risk factors appears to increase the risk, the additive effect of combining several factors remains uncertain.

Local incidence rate of invasive aspergillosis in individuals at high risk and not receiving anti-Aspergillus prophylaxis

Overall, the available evidence suggests that the incidence of IA in liver transplant recipients at high risk of IA averaged at 16.9% (ranging between 13.6 to 28.6%) when no anti-*Aspergillus* prophylaxis was given. These estimates, however, vary considerably across centers.

Based on the panel's pre-determined decision threshold of a 4% reduction in incidence in IA compared with no prophylaxis, this sensitivity analysis presented in Table 4 indicates that a reasonable cut-off for offering targeted prophylaxis is an expected baseline IA incidence of **5% or greater.** At this incidence level, prophylaxis can reduce the IA risk to **0.9%**, approximating the incidence observed in low-risk liver transplant recipients. Accordingly, the panel concludes that, in liver transplant recipients with a baseline IA incidence of **5% or higher**, the use of targeted anti-*Aspergillus* prophylaxis may be justified.

Table 4. Modeling the effect of targeted anti-*Aspergillus* prophylaxis in liver transplant recipients with different baseline incidences of invasive aspergillosis

Incidence of IA in individuals at high risk and not receiving anti-*Aspergillus* prophylaxis	Risk Difference with 95% confidence interval	Expected incidence of IA in individuals at high risk receiving anti-*Aspergillus* prophylaxis	Number needed to treat
15%	-12.2% (-14.1 to -5.1%)	2.8% (0.9 to 9.9%)	8
10%	-8.1% (-9.4% to -3.4%)	1.9% (0.6 to 6.6%)	12
5%	-4.1% (-4.7% to -1.7%)	0.9% (0.3 to 3.3%)	24
2.5%	-2.0% (-2.4% to -0.8%)	0.5% (0.1 to 1.7%)	50
IA: Invasive aspergillosis			
Assumption: RR 0.19, 95%CI (0.06 to 0.66), derived from pooled analysis of three observational studies comparing targeted vs no anti-*Aspergillus* prophylaxis [19, 28, 49].			

Duration of anti-*Aspergillus* prophylaxis

Among the randomized trials, the duration of prophylaxis varied from 14 days [9] to a maximum of 10 weeks [12]. The two more recent studies reported a prophylaxis duration of up to 21 days or until hospital discharge, whichever occurred first [7, 8]. In observational studies, prophylaxis was administered until hospital discharge [19, 28, 49], until death or discontinuation of RRT [49]. Chakravarti 2021 additionally capped prophylaxis at a maximum of 28 days [19].

Clinical question B: In liver transplant recipients for whom anti-*Aspergillus* prophylaxis is indicated, what is the optimal choice of agent(s)?

Recommendation: In liver transplant recipients requiring anti-*Aspergillus* prophylaxis, we suggest using an echinocandin or a newer anti-mold triazole (voriconazole, posaconazole or isavuconazole) rather than amphotericin B formulations or itraconazole (*conditional recommendation, very low certainty of evidence*).

Comments:

-This recommendation prioritizes reducing adverse events (e.g. nephrotoxicity and hepatotoxicity), minimizing drug-drug interactions (especially with cyclosporine, tacrolimus, sirolimus and everolimus), and optimizing bioavailability.

-Among the anti-mold triazoles, the available evidence is derived primarily from studies evaluating voriconazole. To date, no peer-reviewed studies have specifically assessed posaconazole or isavuconazole for prophylaxis in liver transplant recipients. Based on indirect evidence from other transplant populations, these anti-mold triazoles (voriconazole, posaconazole and isavuconazole) are expected to provide comparable benefits.

Summary of the evidence

Description of the direct evidence

Our systematic review of the literature (spanning from 2000-2025) identified two network meta-analysis reporting on the efficacy of universal antifungal prophylaxis for the prevention of IFIs [57, 58], although neither assessed

differences in safety among antifungal agents. No RCTs comparing different antifungal agents used for targeted prophylaxis were identified.

Our systematic review identified two non-randomized studies reporting on the use of either echinocandins or amphotericin B formulations as targeted prophylaxis in liver transplant recipients considered at high risk of IFIs [44, 59].

Studied populations and clinical settings:

The two observational studies reported on a total of 527 patients, of which 218 were considered at high risk of IFIs [44, 59].The most recent study was performed in Europe between 2015 to 2018 [44], while the older study occurred in North America between 1997 to 2009 [59].

Studied comparison:

Rinaldi 2021 was a prospective cohort study where the choice of prophylaxis was left to the attending physician [44], while Sun 2013 was a retrospective "before-and-after" cohort study (in "before" period patients received amphotericin B formulations, while in "after" period patients received an echinocandin) [59]. The targeted prophylaxis was planned for a total duration of 21 days [44, 59] or until cessation of RRT, hospital discharge or death [59].

Rinaldi 2021 included patients at high risk for invasive candidiasis or IA, and defined high risk of IA as the presence of fulminant hepatic failure, corticosteroids within the month prior to transplant, multi-visceral transplantation, RRT, rejection requiring anti-thymocyte globulin, exposure to orthoclone-muromonab-CD3 (OKT3) or alemtuzumab, re-transplantation or reoperation [44]. In contrast, Sun 2013 defined high risk for IFI as patients requiring post-transplant dialysis, undergoing re-transplantation, or requiring reoperation (See Supplementary material, Table B1.2 Characteristics of the included studies) [59].

Studied outcomes:

The primary outcome was the incidence of IFI during the post-transplantation period, defined according to EORTC/MSG criteria. Rinaldi 2021 reported IFI at 12 months using the 2008 EORTC/MSG definitions [13], while Sun 2013 reported IFI at 90 days using the 2002 EORTC/MSG definitions [54]. All-cause mortality was reported in both studies, but attributable mortality, AE (either serious or non-serious), and graft loss / rejection were inconsistently reported.

Study design and risk of bias:

The risk of bias was judged serious, mainly due to potential confounding-by-indication with evidence of selection bias, differences in prophylaxis duration (5-7 days difference in total duration of prophylaxis between groups), and variation in outcome assessment timepoints (90 days versus 12 months). All studies had small sample size and reported a very small number of events for most of the outcomes.

Benefits and harms

The use of echinocandins for targeted prophylaxis may result in similar rates of IA (RD: 0.3%; 95% CI: -3.9 to 16.3%; very low CoE) and attributable mortality (RD: 0.7%; 95% CI: -1.2 to 21.3%; very low CoE) compared with amphotericin B formulations. The use of echinocandins may result in a higher all-cause mortality (RD: 4.6%; 95% CI: -6.7 to 25.9%, very low CoE). No serious AE were reported in Rinaldi 2021. Non-serious AEs may be comparable between groups (RD: -0.2%; 95% CI: -8.8 to 8.5%; very low CoE). Overall, the evidence is very uncertain (See Supplementary material, Table B1.1 GRADE Evidence Profile).

Other supporting evidence

Our systematic review of the literature comparing universal versus no anti-*Aspergillus* prophylaxis (either fluconazole or no antifungal prophylaxis) in liver transplant recipients (see Clinical Question A1) provides indirect comparisons between echinocandins, amphotericin B formulations and itraconazole.

Breakthrough IA was absent in one echinocandins study (0% with anidulafungin [8] but occurred in 1.9% of itraconazole recipients [10-12]). When stratifying our meta-analysis per class of antifungal agents (See Supplementary material, Figure A1.3.a), the subgroup analysis showed that echinocandins (versus fluconazole) may lower the risk of breakthrough IA, with a RR of 0.20, 95%CI (0.01 to 4.15) [8], whereas itraconazole (versus fluconazole or placebo) may increase risk, with a pooled RR of 2.13, 95%CI (0.33 to 13.83) [10-12].

AE profiles also varied. SAE occurred in 0.9% of itraconazole recipients [10-12], 1.1% of echinocandin recipients (micafungin or anidulafungin) [7, 8], and 13.2% of amphotericin B recipients (liposomal AmB) [9]. When stratifying our meta-analysis per class of antifungal agents (See Supplementary material, Figure A1.3.d), the subgroup analysis showed that echinocandins (versus fluconazole) was associated with a pooled RR of 0.65, 95%CI (0.06 to 7.08) [7, 8], while liposomal amphotericin B (versus fluconazole) was associated with a RR 1.32 (0.34 to 5.07) [9], and itraconazole (versus fluconazole or placebo) with a pooled RR of 4.69, 95%CI (0.23 to 96.47) [10-12]. Non-serious AE were more frequent with itraconazole (24.3%) [10-12] than with echinocandins (10.9%) [7, 8]. Similarly, the subgroup analysis by class of agents showed that echinocandins (versus fluconazole) were associated with a pooled RR of 1.13, 95%CI (0.62 to 2.06) [7, 8], while itraconazole (versus fluconazole or placebo) was associated with a pooled RR of 1.74, 95%CI (0.89 to 3.40) [10-12].

Overall, relative efficacy and AEs profile of these agents remain uncertain due to absence of direct comparative data.

Other considerations

Summary by antifungal class: benefits, harms, drug-drug interactions and stewardship considerations
A more detailed description of adverse events is provided in the Pharmacology Tables (See Appendix).

Echinocandins

Benefits: Across studies, breakthrough IA ranged from 0% to 3% [19, 25, 60-62]. There is a lack of robust comparative data favoring one echinocandin over another. Micafungin was associated with the highest breakthrough IA rates (11 % in a high-risk cohort) [59], while anidulafungin had the lowest (0-3%) [8, 63]. Caspofungin in general showed no breakthrough IA, though small series reported rates of 0.5 to 1% [19, 25].

Harms: Echinocandin prophylaxis appears to be generally safe in high-risk liver transplant recipients. In a prospective trial of caspofungin (71 patients), grade IV laboratory abnormalities occurred in ~30%, but were attributed to early post-transplant changes rather than drug toxicity; discontinuation for AE was infrequent (8%) [61]. A smaller retrospective study found similar transient lab changes without clinical toxicity [60]. Micafungin was evaluated in a large, randomized trial (344 patients), showing low rates of hepatic and renal events and no excess risk of rejection [64]. A smaller cohort study (18 micafungin; 24 ABLC) reported comparable hepatic and renal outcomes, with slightly less early renal dysfunction in micafungin recipients [65]. In a randomized trial, anidulafungin was well tolerated with no significant toxicity versus fluconazole; only 1% discontinued therapy for QTc prolongation [8]. Overall, serious toxicity is uncommon, and most laboratory abnormalities likely reflect post-transplant physiology rather than intrinsic drug effects.

Stewardship considerations with prophylaxis: Several recent reports have raised concerns about the emergence of breakthrough *Candida* and *Candida*-like infection particularly with *C. parapsilosis* [44] and the development of secondary echinocandin resistance in *Nakaseomyces glabratus (*formerly known as *Candida glabrata)* during echinocandin prophylaxis in liver transplant recipients [63]. Most reports involved micafungin, but these findings are assumed to be generally applicable to all echinocandin agents. Importantly, none of these studies established a direct causal link between breakthrough *Candida* and *Candida*-like infections and echinocandin resistance, and this signal was not observed in clinical trials. Rare cases of breakthrough *Rhizopus* spp. infections were also reported during echinocandin prophylaxis. Additionally, echinocandins have no activity against *Cryptococcus* and *Rhizopus spp*., and cryptococcal disease remains an uncommon but potentially fatal complication in patients with liver cirrhosis. Clinical echinocandin resistance in *Aspergillus* species is uncommon, and although echinocandin-resistant *Aspergillus fumigatus* has been described during echinocandin therapy [66], such reports are rare. To our knowledge, there are no reported cases of *Aspergillus* infection occurring during echinocandin prophylaxis in liver transplant recipients to date.

Anti-Mold Triazoles

Among the mold-active triazoles, voriconazole is the most studied in liver transplant recipients.

Benefits: Breakthrough IFIs in liver transplant recipients receiving mold-active triazoles are uncommon, generally below 3%. One study reported a breakthrough infection rate of less than 1% in patients receiving voriconazole [23]. RCTs comparing itraconazole with placebo reported no breakthrough IA cases [10], while Winston 2002 documented a 3% (2/97) breakthrough IA rate [12]. No mold infections were reported with

isavuconazole through 100 days post-transplant [67]. No published data on posaconazole breakthrough IA rates in liver transplant recipients are available.

Harms: AEs of anti-mold triazoles include hepatotoxicity, gastrointestinal symptoms, QTc prolongation (notably with voriconazole and posaconazole), skin reactions and photo carcinogenesis [68] and visual disturbances (specific to voriconazole). Drug discontinuation due to AE occurred in approximately 2% of cases, with hepatotoxicity being the most common reason. Itraconazole-related AE were reported in 30–51% of cases [8, 10], 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 voriconazole, hepatotoxicity occurred in 2.1% of patients [23], alongside gastrointestinal disturbances and challenges with maintaining adequate tacrolimus levels. Isavuconazole was associated with mild AE such as peripheral edema (1%). AE data for posaconazole in liver transplant recipients remain limited. Careful dose adjustments are crucial to minimize risks, particularly in patients with hepatic or renal impairment (See Pharmacology Tables: Tables 5a, b and c).

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 underdosing of immunosuppressive agents.

Stewardship considerations with prophylaxis: The use of mold-active triazoles may contribute to colonization and/or infection with triazole-resistant fungi, especially non-*Candida albicans* species (e.g. *N. glabratus*). However, the clinical burden of triazole-resistant *Candida* and related yeasts associated with mold-active triazole prophylaxis in liver transplant recipients remains poorly defined, as few studies reported antifungal susceptibility data in this context. Prolonged exposure to mold-active triazoles can also select for triazole-resistant *A. fumigatus* and *A. flavus*; however, the risk of such resistance has not been specifically documented in liver transplant recipients receiving prophylaxis. This likely reflects the low incidence of IA in this population, the relatively short duration of prophylaxis compared with patients with chronic pulmonary aspergillosis, and the lack of systematic antifungal susceptibility testing and reporting. Importantly, triazole resistance may also arise from environmental exposure to agricultural azole fungicides [69], suggesting that both clinical antifungal use and environmental selection pressure contribute to the overall risk. Anecdotal reports note breakthrough infection of *Rhizopus spp*. during mold-active triazole prophylaxis. Although these events may not necessarily be directly attributable to drug selection pressure.

Amphotericin B

Overall, amphotericin B is less commonly used for prophylaxis in liver transplant recipients, but if administered, lipid formulations (liposomal amphotericin B or amphotericin B lipid complex) are preferred due to their improved therapeutic index, which reduces nephrotoxicity while maintaining efficacy.

Benefits: Most data on antifungal prophylaxis in liver transplant recipients involve the deoxycholate formulation of amphotericin B, with reported breakthrough IA rates ranging from 0-9.5% [9, 70-73].

Harms: Amphotericin B has notable side effects, including infusion-related reactions such as fever, chills, and hypotension. It has notable nephrotoxic potential, which manifests as azotemia and tubular effects, such as hypokalemia, hypomagnesemia, and renal tubular acidosis. Tubular effects occur even with short-term use and are largely independent of cumulative dose. Other reported non-serious AE include back pain [71] and liver toxicity (5% at 1 mg/kg dose [72]). In the setting of early post-liver transplant, liposomal amphotericin B-driven increases in total bilirubin and mixed transaminases and cholestatic enzymes (albeit often mild-to-moderate) may be a source of concern leading to premature discontinuance. Liposomal formulations, such as liposomal amphotericin B, has significantly lowered these risks and improved tolerability, but remain associated with nephrotoxicity in 2.5-7.8% of patients [9, 70, 71], and SAE leading to discontinuation in 5-13% [9, 71].

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, vancomycin or aminoglycosides. Enhanced monitoring of renal function and electrolyte levels is critical.

Stewardship considerations with prophylaxis:
There is no cross resistance between amphotericin B and triazoles or echinocandins. Amphotericin B also has a low propensity for acquired resistance among *Candida*, *Candida*-like species and *Aspergillus* [74], making short-term prophylaxis generally low risk from a resistance standpoint. Its use is primarily limited by

formulation-specific toxicities, particularly nephrotoxicity and electrolyte disturbances, which are mitigated but not eliminated by lipid formulations [75]. In addition, use may be constrained by higher cost and the need for intravenous administration. Breakthrough infections during amphotericin prophylaxis typically reflect intrinsic resistance or gaps in antifungal coverage (e.g., *A. terreus*, *Lomentospora prolificans*, *Scedosporium*, *Fusarium*) rather than drug-induced selection. To date, no significant emergence of resistance has been reported in liver transplant patients receiving amphotericin B prophylaxis. Ongoing antifungal susceptibility surveillance and careful consideration of sequential antifungal exposures remain important stewardship principles, particularly with prolonged or repeated use.

Rationale for recommendation

Balance of benefits and harms / Certainty in the evidence

When comparing anti-*Aspergillus* prophylaxis options in liver transplant recipients, the panel judged that the balance of benefits and harms generally favored echinocandins and the newer anti-mold triazoles (voriconazole, posaconazole and isavuconazole), primarily due to their more favorable side effect profile as compared to amphotericin B formulations (infusion-related reaction and nephrotoxicity) and itraconazole (gastrointestinal side effects and variable absorption). However, direct evidence in liver transplant recipients remains limited. To date, posaconazole has not been formally studied for prophylaxis in this population. Although isavuconazole use has been reported in a study that included liver transplant recipients, data specific to its effectiveness for prophylaxis have not yet been published. As a result, recommendations regarding posaconazole and isavuconazole are extrapolated from trial data in other transplant populations.

Overall, the certainty in the evidence remains very low due to the paucity of head-to-head comparative studies and the small sample size of available cohort studies.

Other considerations

The panel judged that either voriconazole, posaconazole, isavuconazole or echinocandins are preferred for antifungal prophylaxis. Itraconazole is limited by unreliable absorption and significant drug-drug interactions. Voriconazole and posaconazole also have notable interactions, requiring careful monitoring. Amphotericin B formulations have limited tolerability at optimal dosing, are only available intravenously, and carry increased costs. Stewardship considerations may influence agent selection and differ across antifungal classes.

Conclusion

The guideline panel suggested using an echinocandin or a newer anti-mold triazole (voriconazole, posaconazole or isavuconazole) rather than amphotericin B formulations or itraconazole for targeted anti-*Aspergillus* prophylaxis for liver transplant recipients at high risk of IA in the post-transplantation period.

Considerations for Implementation of the recommendation

When selecting a preferred agent for antifungal prophylaxis, the panel suggested considering the following drug characteristics: 1) efficacy; 2) side effect profile and tolerability; 3) potential for drug-drug interactions with commonly used transplant medications; 4) oral bioavailability; 5) need for therapeutic drug or laboratory monitoring; 5) cost; and 6) broader ecological impact from an antimicrobial stewardship perspective. Given the improved oral availability and tolerability of newer anti-*Aspergillus* triazoles, itraconazole, with its variable gastrointestinal absorption and significant interpatient pharmacokinetic variability, is now infrequently used as a first-line prophylactic agent and is generally reserved for specific situations where alternative agents are unsuitable.

At present, no data clearly support either an echinocandin or an *Aspergillus*-active triazole as the preferred agent for prophylaxis. Echinocandins offer several advantages, including excellent activity against *Candida* and *Candida*-like spp., including triazole-resistant species which is the most common fungal infection in liver transplant recipients, a favorable toxicity profile and minimal interactions with calcineurin inhibitors. Their limitations include the intravenous only administration, uncertain efficacy against *Aspergillus*, lack of activity against *Cryptococcus* and *Rhizopus*, and occasional breakthrough *Candida* and *Candida*-like infections.

Mold-active triazole (especially posaconazole and isavuconazole) provide strong activity against *Aspergillus*, *Cryptococcus* and some *Rhizopus spp*., but carry drawbacks including breakthrough *Candida* and *Candida*-like infections (with potential for triazole-resistant), significant drug-drug interactions with immunosuppressive therapies,

and substantial interpatient pharmacokinetic variability. Current data on the use of posaconazole or isavuconazole specifically for prophylaxis in liver transplant recipients are lacking. However, based on their established efficacy in other immunocompromised populations and their favorable pharmacologic profiles, extrapolation to this setting may be reasonable, but further clinical data is preferable.

Amphotericin B is generally reserved for cases where triazoles are contraindicated, or broad-spectrum antifungal coverage is essential.

Ultimately, the choice of prophylactic anti-*Aspergillu*s agent should be guided by local epidemiology and center-specific experience, including rates of IA and prevalence of triazole-resistant *Candida* and Candida-like species in addition to benefits, risk, drug-drug interactions and stewardship considerations.

Research gaps /needs

Despite existing studies on anti-*Aspergillus* prophylaxis in liver transplant recipients, several critical gaps remain. First, there are no studies systematically evaluating newer *Aspergillus*-active triazoles, such as posaconazole or isavuconazole, long-acting echinocandins (e.g. rezafungin), or other emerging antifungal classes (See Pharmacology Tables, Table 1c) in this population. Most randomized trials and observational studies primarily assessed older agents, including amphotericin B formulations and itraconazole, which are now largely replaced in clinical practice due to concerns over efficacy, toxicity, and pharmacokinetics. Prospective studies are needed to clarify the role of these newer agents, considering their apparent improved oral bioavailability, broader antifungal spectrum, and potentially better tolerability.

Second, echinocandins are fungistatic against *Aspergillus*, and breakthrough aspergillosis has been documented in other immunocompromised populations, such as patients with hematologic malignancy. Existing liver transplant studies did not demonstrate breakthrough IA when prophylactic echinocandins were used during the peri-transplant period. The incidence of IA after liver transplant is relatively low, and the sample size and event rates in existing studies might not have adequate power to detect a clinically meaningful increase in risk.

Third, liver transplantation practices, immunosuppressive regimens and antifungal stewardship principles have evolved substantially over the past decade. For example, the incidence of triazole-resistant *Aspergillus* species has increased, and several novel antifungal agents are in development that may offer new options for prophylaxis and treatment. Additionally, eligibility criteria for liver transplantation have also evolved (e.g., severe alcoholic hepatitis on high-dose corticosteroids) and risk factors for IA continue to change. Current prophylaxis data are largely limited to the immediate post-transplant period, leaving gaps regarding the optimal duration of prophylaxis. Defining an optimal duration is critical to minimize unnecessary antifungal exposure while providing adequate duration of protection for the period of highest risk, including periods of augmented immunosuppression or complications later post-transplant.

Taken together, these issues raise questions about the applicability of older data to contemporary clinical practice. Prospective data are needed, ideally through large, multicenter observational cohorts or international registries using target trial emulation methods, to define modern risk-adapted prophylaxis strategies.

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leading the panel in accordance with the GRADE process, developing the manuscript and curating the supplementary material.

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The following panelists have reported relationships **unrelated** to the topic of fungal infections/antifungal therapies since 2021–2025, when the guideline work began, with the indicated companies. **M.H.N.** received research grants from bioMérieux (target NGS for fungal diagnosis direct from samples) and Melinta (Rezafungin clinical trial). **J.H.Y.** received research funding for subject enrollment on clinical trials from AlloVir (adoptive T cells) and Ansun (DAS-181 for viral infections); served as Editor-in-Chief for *Clinical Microbiology Reviews*; serves as an Associate Editor for *Transplantation and Cellular Therapy;* receives research funding for subject enrollment on clinical trials from AiCuris (HSV infection), GSK (RSV vaccination), Lumen (C diff infection), Pulmotect (respiratory viral infections), SNIPR (phage therapy), Shire/Takeda (CMV infection), and Vedanta (C diff infection). **S.M.H.** received educational grants and served in advisory roles with Takeda, Xedition, Kamada, Knight Therapeutic, Sanofi, and GSK for unrelated topics; served in editorial roles with the *Journal of Heart and Lung Transplantation and Transplant Infectious Diseases*. **N.P.** served in past advisory/consulting roles with ClearView and Alcimed (unrelated); held editorial roles with *Medical Mycology* and the *Journal of Heart and Lung Transplantation Open*. **D.R.A.** served in advisory roles for Roche, Basilea, Cidara, Astellas, Mundipharma, F2G, Amplyx, and Elion; owned stock in Symbiotica; served on the editorial board for *Clinical Infectious Diseases*/*Journal of Infectious Diseases* (CID/JID) as editor for *Antimicrobial Agents and Chemotherapy* (AAC), *Journal of Infectious Diseases*, mBio, and PLoS Pathogens; served as a member for the Clinical and Laboratory Standards Institute (CLSI). **M.S.** received funding from the Public Health Agency of Canada for initiatives related to antimicrobial stewardship. **M.I.A.** served as a consultant for Karius (application of Karius for fungal diagnostics in immunocompromised children); Miravista (evaluating fungal diagnostics in children with research support paid to institution); received travel reimbursement from St. Jude Children's Research Hospital (participation in infectious disease research conferences); serves as an editorial board member for *Transplant Infectious Disease* and the *Journal of the Pediatric Infectious Diseases Society*; serves on the American Academy of Pediatrics (AAP) Committee on Infectious Diseases). **E.J.B.** served in advisory roles for Avir Pharma and GSK; participates as a guidelines panel member for the American Society of Clinical Oncology and Infectious Diseases Society of America (neutropenic fevers); received honoraria as Section Editor, Up-to-Date. **P.H.C.** participated in a speakers bureau for Astellas (isavuconazole); received research funding from Aicuris (recruited patients for HSV

Pritelevir study); received other remuneration from Pfizer (data review on Aztreonam-Avibactam study); served as president at Michigan State Infectious Diseases Society; serves as editor at the *British Journal of Antimicrobial Agents and Chemotherapy*. **S.C-A.C.** received organizational benefits from MSD Australia (untied educational grants); served as Pathology editor for the *Journal of Clinical Microbiology*, editor for *Microbiology*, editor-in-chief for *Medical Mycology*, and as a board member for the Mycoses Study Group Education and Research Consortium (MSGERC). **S.P.H.** served in past advisory and consulting roles with Pfizer (advisory roles regarding infections associated with BCMA bispecific antibodies and myeloma therapies), Roche (advisory board regarding infectious complications of therapies for multiple myeloma), Treeline Biosciences (consulting regarding infectious complications of novel targets therapies for lymphoma) and Seres Therapeutics (consulting regarding infectious complications of leukemia therapy and use of live spore products in hematologic malignancy patients); received research funding from GlaxoSmithKline (GSK) for a study of sotrovimab prophylaxis against COVID-19 infection in immunocompromised individuals; serves in an advisory role (scientific) with Takeda (infection adjudication committee for a clinical trial). **S.A.K.** reported family relationships (spouse consulting roles or employment) with Boston Scientific, Janssen, Novartis, Myovant, Blue Earth Diagnostics, MDx Health, AIQ, Reversal Therapeutics, Stratagen Bio, and Nanocan; received research funding from GlaxoSmithKline (GSK); serves in an advisory role with Vertex Pharmaceuticals (member of a safety adjudication committee for a clinical trial; unrelated). **G.R.T.** served in advisory as a consultant for Cidara (clinical trial design). **M.G.S.** served as associate editor for Annals of Internal Medicine (American College of Physicians). **V.L.** received funding from Centre de Recherche du Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'île-de-Montréal (CIUSSS_NIM).

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

Kidney Transplant Recipients

Kidney transplant procedures are generally classified as clean surgeries, connecting two sterile vascular structures (artery to artery, and vein to vein) and implanting the donor ureter into the dome of the urinary bladder. Peri-operative yeast and mold infections are uncommon. Peri-operative antifungal prophylaxis is often limited to topical mucosal agents, such as nystatin, to prevent thrush. IA infections are uncommon. Prolonged RRT before transplant is known to increase the risk of IA [76, 77].

Incidence of invasive aspergillosis in kidney transplant recipients not receiving anti-*Aspergillus* prophylaxis

To understand the true burden of IA in kidney transplant recipients, a mapping review across 34 observational studies published from 2000 to 2025 was performed to determine the incidence of IA in kidney transplant recipients not receiving anti-*Aspergillus* prophylaxis (See Supplementary material for details) [30, 34, 78-109]. Among 35,240 kidney transplant recipients from the 34 studies, 328 cases of proven or probable IA were identified based on EORTC/MSG criteria [13, 14, 54] or comparable definitions [110-113]. The pooled incidence of IA was 0.8% (95% confidence interval 0.6 to 1.2%). The one-year all-cause mortality among 124 cases with available survival data was 45%.

Incidence of invasive aspergillosis in kidney transplant recipients from registry studies

Two large United States database registry studies that used billing codes to detect cases of IA included a total of 90,608 patients [114, 115]. These registry studies were of similar duration (3.5 and 4 years respectively) but from different periods; (1994-1997 and 2005-2008, respectively). The pooled incidence for IA 0.4% (95% CI: 0.2% to 0.6%).

Additional factors for consideration

Factors associated with increase IA risk include low volume transplant centers, older age, preceding bacterial pneumonia, Candida colonization (which may be a surrogate marker for severe immunosuppression), diabetes, chronic lung or heart disease, and leukopenia [80, 115]. Other factors that may increase risk include delayed graft function, acute rejection, and RRT [86, 89].

Limitations

Estimating the incidence of IA was challenging due to several limitations. Kidney transplant recipients are generally not considered at high risk for IA; thus, anti-mold prophylaxis is generally not used. reporting of prophylaxis use was inconsistent, potentially leading to misclassification. Definitions of proven and probable IA varied across studies and over the long time frame of patient enrollment. Although EORTC/MSG criteria or similar definitions were followed to include cases of only proven or probable IA, cases of possible IA may have been included, particularly during earlier years. Most studies were retrospective, observational, and single center, and diagnostic modalities for IA varied between centers. For the six studies that only reported pulmonary IA, non-pulmonary infection site(s) may have been missed and could have contributed to an underestimate of the incidence of IA. Not all studies included the ages of patients, and pediatric patients were mixed with adults in some of the studies. The two large registry studies used diagnoses from billing codes which may be unreliable, and for many of these patients only the first hospitalization was included. Finally, factors that increase the risk for IA in individual patients could not be well defined.

Conclusions

Given the low pooled incidence of IA (0.4%), the use of universal anti-*Aspergillus* prophylaxis is expected to provide limited benefits and thus a less favorable balance of benefits and harms. The current available evidence does not support the use of universal IA prophylaxis in kidney transplant recipients.

Research gaps

Factors that may increase the risk for IA in individual patients need to be better defined particularly: re-transplantation, augmented immunosuppression (e.g., reinduction immunosuppression, donor organs with high panel of reactive antigens). The issue of commercial kidney transplantation involving high risk for infection is one that needs

to be more fully evaluated, as the role of local environmental exposure in the era of transplant tourism may be an additional risk factor [111, 116-118]. Finally, no studies reported on donor-derived infections.

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Pancreas Transplant Recipients

Pancreas transplant recipients are susceptible to infections, most commonly peri-operative wound or intraabdominal bacterial or yeast infections. As the pancreatic duct is fragile, at the time of transplant surgery 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 for 1-2 weeks. The risk and epidemiology of IA following pancreas transplant, either related to surgical procedure or to subsequent immunosuppression, are not well described.

Incidence of invasive aspergillosis in pancreas transplant recipients not receiving anti-*Aspergillus* prophylaxis

To understand the true burden of IA in pancreas transplant recipients, a mapping review across observational studies published from 2000 to 2025 was performed to determine the incidence of IA in patients who did not receive anti-*Aspergillus* prophylaxis (See Supplemental material, Descriptive question for details). Among 1,234 pancreas transplant recipients from 11 studies [26, 87, 119-127], 10 cases of proven or probable IA were identified using EORTC/MSG criteria or comparable definitions [13, 14, 54, 110]. The pooled incidence of IA was 0.8% (95% confidence interval 0.3% to 1.7%). The one-year all-cause mortality was 70%, although only three deaths were clearly attributable to IA. Timing of IA onset was reported in four cases, ranging from approximately 90 to 340 days post-transplant, with infections predominantly involving the lungs and paranasal sinuses.

Limitations

Estimating the incidence of IA was challenging due to several methodological limitations. Definitions of proven and probable IA varied over the long timeframe of patient enrollment, since most studies were published prior to the 2008 EORTC/MSG criteria. The small number of IA cases and limited reporting of patient- and donor-level risk factors precluded robust statistical assessment of risk factors. Although some reports suggest a higher incidence of IA among patients receiving lymphocyte-depleting agents such as alemtuzumab, available data are insufficient to confirm this association [120, 123, 125].

The overall quality of the evidence is low, reflecting several potential sources of bias. Most studies were retrospective and single center, which may introduce selection and reporting biases. Key clinical variables, such as donor and recipient comorbidities, peri-operative management, and prior *Aspergillus* colonization, were inconsistently reported, 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 transplant populations.

Conclusions

Given the low pooled incidence of IA (0.8%), the use of universal anti-*Aspergillus* prophylaxis is expected to provide limited benefits and thus a less favorable balance of benefits and harms. The current available evidence does not support the use of universal IA prophylaxis in pancreas transplant recipients.

Research gaps

The use of pancreas transplant to control diabetes has declined since its peak in 2004, due to improved medical therapies and better overall management of diabetes. Transplant centers and patients have explored islet cell transplantation as an alternative, though it is not yet a standard treatment. The decline in procedure volume has led to fewer surgeons trained in pancreas procurement and transplantation, which may impact their skill level. Despite lower volumes, outcomes for pancreas transplants have consistently improved, with high graft and patient survival. Given these trends, further publications on the incidence of IA in pancreas transplant recipients are unlikely. Multi-center studies using systematic transplant registry data would be valuable to define IA risk and guide prophylaxis strategies.

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