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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Antifungal stewardship in solid organ transplantation

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Abstract

Background: Antifungal stewardship (AFS) has emerged as an important component of quality in managing invasive fungal infections (IFIs), and cost-benefit calculations suggest regular training in AFS is well worth the effort.

Methods: This review will discuss the most common IFIs in solid organ transplantation (SOT)-recipients, how to diagnose them, and current recommendations for antifungal treatment and prophylaxis before demonstrating key takeaway points of AFS in this high-risk population.

Results: Effective AFS starts before a patient is admitted for SOT, through education and regular interactions of the interdisciplinary clinical team involved in patient management, considering local factors such as epidemiological data and knowledge of diagnostic options including local turnaround times. Understanding the spectrum of antifungal agents, their efficacy and safety profiles, and pharmacokinetics, as well as duration of therapy is hereby essential.

The most frequent IFIs in SOT recipients are caused by *Candida* species, followed by *Aspergillus* species, both with increasing resistance rates. Diagnosis of IFI can be challenging due to unspecific clinical presentation and difficult interpretation of microbiological findings and biomarkers. Prophylactic strategies, such as those for invasive aspergillosis in lung transplantation or invasive candidiasis (IC) in certain liver transplant settings, as well as the selection of the appropriate therapeutic agents require detailed knowledge on the pharmacokinetics and drug–drug interactions of antifungals.

Conclusions: Here in this review, we address what constitutes good AFS in this heterogeneous field of solid organ transplant recipients.

KEYWORDS
antifungal prophylaxis, antifungal stewardship, appropriate use of antifungals, invasive fungal infection, solid organ transplantation

List of abbreviations: AFS, antifungal stewardship; IA, invasive aspergillosis; IC, invasive candidiasis; ICU, intensive care unit; IFI, invasive fungal infection; RRT, renal replacement therapy; SOT, solid organ transplantation; TDM, therapeutic drug monitoring.

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1 | INTRODUCTION

Successful management of infectious complications remains key for outcomes in solid organ transplant (SOT) recipients. Invasive fungal infections (IFIs) remain important complications after SOT, but the risk varies depending on epidemiologic exposures, type of transplant, and the generated state of the recipient's immune system.[1] While antifungal prophylaxis and empirical therapy are now widely used in SOT recipients, overuse may also have detrimental effects, including adverse events, drug-drug interactions, and increased costs and last but not least may also contribute to antifungal resistance.[2–5]

With a loaded antifungal pipeline and several new drug classes of antifungals now in clinical development, antifungal stewardship (AFS) in the SOT setting will become even more important in the years to come.[6]

In this review, we will shortly discuss the most common IFIs in SOT-recipients, how to diagnose them, and current recommendations for antifungal treatment and prophylaxis before demonstrating key takeaway points of AFS in this high-risk population.

2 | CHARACTERISTICS OF INVASIVE FUNGAL INFECTIONS AMONG SOLID ORGAN TRANSPLANT RECIPIENTS

2.1 | Epidemiology

The overall incidence of IFI is about 4.6%–7.5% in SOT-recipients,[7–10] with the highest rate in small bowel transplantation and the lowest in kidney transplantation. Table 1 shows an overview of causative pathogens of IFI depending on the transplantation type and prevalence is displayed in Figure 1. IFI incidence varies widely between studies, which may be explained by local epidemiology, different diagnostic strategies, as well as differences in antifungal prophylaxis.

Invasive candidiasis (IC) is the most common IFI in SOT-recipients, accounting for more than half of the identified IFIs and predominantly affecting patients receiving intra-abdominal transplantation.[7–10] While SOT itself is an independent risk factor for IC, patients often present additional risk factors for IC including central venous catheters, intra-abdominal surgery, admission to intensive care units, and broad-spectrum antibiotic therapy.[11] While *Candida albicans* is the most frequently identified cause of IC, an epidemiological trend toward non-albicans *Candida* species has been recognized in the last years.[7–10,12–14] Furthermore, *Candida auris* has emerged as a human pathogen that increasingly causes intensive care unit (ICU) outbreaks, which may also affect SOT recipients.[15–18]

Aspergillus spp. are the most common invasive mold infections in SOT recipients, and invasive pulmonary aspergillosis is the predominant fungal infection in lung transplant patients as shown in Table 1.[8] Recently, increasing azole resistance in *Aspergillus* spp. has been observed in hematologic patients in Europe, which is a cause for concern and emphasizes the need for cultivation and antifungal susceptibility testing.[19] Other molds like Mucorales or *Fusarium* spp. may also cause fungal infections in SOT recipients.[20]

Additionally, *Pneumocystis jirovecii*, *Cryptococcus* species, and rare yeasts must be considered as well as endemic fungal pathogens.

2.2 | Diagnosis of IFIs

Diagnosis of IFI is difficult to establish. It requires an individual at risk, clinical suspicion, and microbiological evidence. Additionally, radiologically imaging is usually required, especially in lung involvement or deep foci. Despite all difficulties, all efforts should be made to diagnose IFIs early, as time to initiation of therapy affects survival.[21]

The clinical presentation is often unspecific and varies widely from asymptomatic infections to septic shock. While direct detection of fungal pathogens via histology from infected tissue or culture from a normally sterile site (e.g., blood culture for candidemia) remains the gold standard in diagnosis of IFIs, it is often not available or lacks sensitivity. Cultural growth of fungal pathogens from nonsterile sites is sometimes difficult to interpret, as no reliable distinction can be made between colonization and invasive infection. For pulmonary IFIs, it is always recommended to obtain specimens from the lower respiratory tract, that is, bronchioalveolar lavage, as specificity is more limited in respiratory specimens from the upper respiratory tract. Noncultural tests of fungal antigens (e.g. 1,3-beta-D-glucan from serum, galactomannan from BAL or serum, or more recently also antigen detection via *Aspergillus*

TABLE 1 Proportions of fungal pathogens causing invasive fungal infection in solid organ transplant recipients categorized by transplantation type

	Candida spp.	*Aspergillus* spp.	*Cryptococcus* spp.	Pneumocystis	Other
SOT-recipients overall[7–10]	39%-59%	19%-34%	1%-8%	7%-11%	9%-15%
Kidney[7,8,10,63,64]	24%-61%	12%-36%	3%-19%	0%-16%	4%-31%
Liver[7,8,10,65,66]	20%-80%	6%-67%	0%-7%	0%-3%	0%-15%
Lung[7,8,10,67,68]	23%-62%	27%-67%	0%-2%	0%-2%	12%-29%
Heart[7,8,10,11,69]	27%-65%	22%-50%	0%-10%	0%-5%	8%-30%
Pancreas; pancreas–kidney[7,8,10,70]	67%-81%	0%-11%	0%-33%	0%-9%	0%-12%
Small bowel[8]	85%	0%	5%	0%	10%

Abbreviation: SOT, solid organ transplantation.

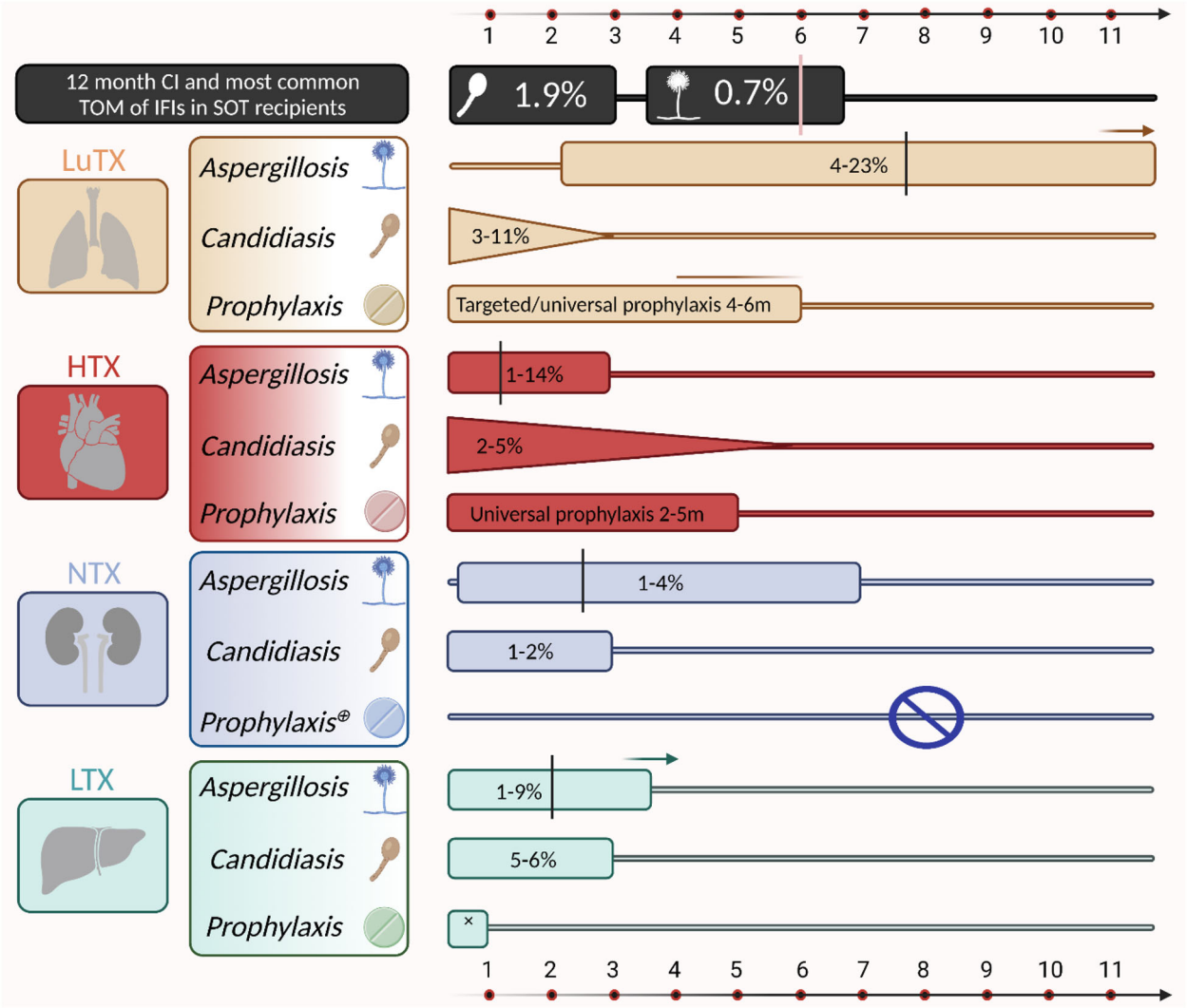

FIGURE 1 Summary of IFI prevalence and timing when those fungal infections normally occur as well as prophylaxis recommendations for selected organ transplantations and fungal pathogens.
The most common timeframe of IFI occurrence and recommended duration of prophylaxis are displayed in months. Vertical bars indicate the mean onset of invasive aspergillosis. Detailed information on prophylactic management is represented in Table 2. General prophylaxis is not recommended. x Targeted prophylaxis 2–4 weeks. CI, cumulative incidence; HTX,[69,77] heart transplantation; IFI, invasive fungal infection; LTX,[8,79] liver transplantation; LuTX,[28,75,76] lung transplantation; NTX,[8,78] kidney transplantation; SOT, solid organ transplantation; TOM, time of manifestation.

specific lateral flow device assays from BAL[22,23]) are now widely used and may provide additional evidence of an IFI. However, mycological tests must always be interpreted in conjunction with other clinical and radiological evidence of IFI. It has to be emphasized though, that, for example, radiological evidence of invasive pulmonary aspergillosis may solely consist of unspecific infiltrates or consolidations.[24,25]

2.3 | Antifungal therapy

If IFI is suspected, prompt initiation of empiric or early pre-emptive therapy should be considered, since a delay may result in worse clinical outcomes. For IC, most guidelines favor an echinocandine as initial therapy.[26,27] For invasive aspergillosis, voriconazole is the antifungal of choice, always necessitating therapeutic drug monitoring (TDM) due to its small therapeutic spectrum, while isavuconazole and liposomal Amphotericin B are considered alternatives.[28,29] In a recent trial posaconazole showed noninferiority to voriconazole while being better tolerated and showing fewer drug-drug interactions.[30] However, in general drug–drug interactions with commonly used immunosuppressants represent a major problem of all mold active azoles, requiring not only TDM of the azoles (with the exception of isavuconazole) but often also a priori dose adjustments of immunosuppressants like cyclosporin A, sirolimus, and tacrolimus, with subsequent monitoring of drug levels.[31] If fungal culture is available, treatment should be adapted according to susceptibility testing.[28,29]

2.4 | Antifungal prophylaxis

Antifungal prophylaxis has been shown to reduce the prevalence of invasive fungal diseases, while also reducing empiric antifungal treatment and potentially obstructive bronchiolitis following lung transplant.[28,32,33] While generally effective, antifungal prophylaxis may also reduce the diversity of the human mycobiome. Where breakthrough infections occur, they are often caused by resistant and difficult to treat fungal pathogens, like *Mucorales*, non-albicans *Candida*, or rare molds or rare yeasts.[34,35] Furthermore, diagnostic tests for IFIs are generally less sensitive in the presence of antifungal prophylaxis.[36]

In the absence of worldwide accepted consensus recommendations, transplant centers have often established their own individual prophylactic strategies.[32,33,37–39]

Recommendations for antifungal prophylaxis by transplant type are outlined in Tables 2 and 3 as well as Figure 1. *Candida* infections are predominant in liver and pancreas transplant recipients, and antifungal prophylaxis is recommended for those with certain risk factors (Table 2).[32,33,37–39] Recommended antifungal agents in these settings are usually fluconazole or echinocandins; particularly Micafungin 100 mg/day has been reported to be very effective and safe compared to azoles.[40] For lung transplant recipients, mold active prophylaxis is generally recommended (Table 3).[28,33] To date, there are no consensus recommendations for prophylaxis in heart transplant recipients. However, taking into account local epidemiology, it is now common practice to use antifungal prophylaxis heart transplant recipients in the majority of centers.[41]

Pneumonia caused by the ubiquitous fungus *Pneumocystis jirovecii* often occurs early after transplantation and may occur in all transplant recipients. Here, prophylaxis with trimethoprim-sulfamethoxazole is a well-established standard,[42] although sometimes associated with poor tolerability.[43] Importantly, echinocandins may also show some activity against *Pneumocystis*.[44]

An attractive option in prophylaxis for the future, for example, after liver transplantation, may be rezafungin, a new echinocandin that due to its pharmacological properties can be administered once weekly during clinic visits and covers *Candida* spp., *Aspergillus* spp. as well as *Pneumocystis jirovecii*, thus avoiding multidrug regimens and significantly reducing the risk of drug-drug interactions that are rarely a problem with echinocandins but may occur with azoles.[5] Inhaled antifungals, like opelconazole, which is currently evaluated in a phase III trial, may be future options for prophylaxis in lung transplant recipients.

3 | ANTIFUNGAL STEWARDSHIP IN THE SOLID ORGAN TRANSPLANT SETTING

AFS differs from antimicrobial stewardship, which conceptually encompasses fungi but primarily addresses bacteria, although research in this field indicates that structured AFS programs are highly needed and show improvement of antifungal therapy.[45,46] There is a particular need for AFS in the SOT setting, where surveys across treating centers in Europe have highlighted potential knowledge gaps and have revealed opportunities for improvement in terms of adequate therapy selection, dosing, duration, and potential drug-drug interactions.[45,47] Some recent studies have shown the potential benefits of AFS in this setting.[48–50]

At first AFS must be implemented into hospital policies to ensure enough resources needed for high quality AFS that ultimately results in improvements in IFI management and outcomes (Figure 2). Also, clear goals should be defined and routinely evaluated (e.g., initial diagnostic approach, choice of antifungal, duration of antifungal therapy) to implement adequate use of antifungals.[51] Additionally, with better management, AFS will hopefully improve outcomes and eventually promote itself, further increasing its acceptance among the departments involved. As secondary goal, AFS programs usually result in cost savings by reducing unnecessary or prolonged use of antifungal agents, posing as an additional stimulus for hospital managers to support establishing a local AFS program.[46,51–53]

Required human resources for AFS have been defined before and should include infectious specialists, clinical microbiologists, pharmacists, and specialists in involved departments and do not differ in the addressed patient population.[51,52] Optimally, each specialized SOT division should have at least one responsible physician with experience in managing IFI, who is integrated in the AFS program.[51,52] In the pretransplant phase and the early stages, after transplant, the AFS team would need to involve ICU physicians and the transplant surgeons, in the follow-up period also infectious diseases physicians, pulmonologists, nephrologists, cardiologists, and hepatologists.[45] For a structural approach also clearly defined dashboards at given times are needed (e.g., once a week) to identify patients at high risk and elaborate strategies to minimize those risks.[51] Clinical recommendations should be based as much as possible on published evidence and follow international guidelines. As such the One World One Guideline initiative gives detailed guidance on management of mucormycosis,[54] rare molds,[55] rare yeasts,[56] and endemic mycoses,[57] which can be adapted to local availability of antifungals. Further, detailed guidance for the SOT setting is also available from the American Society of Transplantation Infectious Diseases Community of Practice.[3,4,28,58] EQUAL scores are now available for management of the most important fungal infections that implements a variety of guidelines and current best practises into simple score cards, which have been translated into multiple languages.[59–61] In addition, these international guidelines could be translated into local guidelines that can be implemented for a standardized approach when IFI is suspected and should always take into account the organ transplanted.[52,57]

As mentioned above IFIs are complex infections, which require a lot of expertise on different aspects such as interpretation of diagnostic tests and selection of appropriate antifungal agents.[28,52] Therefore, after standardized work up of a suspected fungal infection, the AFS members need to evaluate the initial testing, interpret results, and may adapt therapy according to the specific requirements of the individual situation.[46,51,62] It should be noted that AFS members as supervisors provide their expertise as recommendations to improve the acceptance of the program, leading to better cooperation between

TABLE 2 Risk factors and prophylaxis regimens for invasive candidiasis and aspergillosis related to lung, heart, liver, kidney, and pancreas transplantations

	Candida RISK FACTORS	*Candida* PROPHY-LAXIS	DURATION	*Aspergillus* RISK FACTORS	BROAD SPECTRUM MOLD ACTIVE PROPHYLAXIS	DURATION	PNEUMOCYSTIS RISK FACTORS	PROPHYLAXIS	DURATION
LUNG[28,71,72]				Single-lung transplantation Early airway ischemia Rejection and augmented immunosuppression within the last 3 months, particularly in cystic fibrosis (CF) patients Pre-/Posttransplant *Aspergillus* colonization within a year of transplant Positive intraoperative *Aspergillus* culture in CF patients CMV infection Hypogammaglobulinemia (acquired)	Voriconazole Isavuconazole Liposomal Amphotericin B		Low total and CD4+ lymphocyte counts Patient age Cytomegalovirus infection (CMV) Hypogammaglobulinemia Graft rejection	Trimethoprim-sulfamethoxazole 80 mg/400 mg po or 160/800 mg poDaily or three times weekly	6–12 months prolonged up to lifelong in some settings
HEART [28,71,72]				Reoperation CMV infection Posttransplantation hemodialysis presence of another patient with IA in the transplant program 2 months before or after the procedure rejection admission to the ICU mechanical ventilation and extracorporeal membrane oxygenation (ECMO)	Itraconazole Voriconazole Or Echinocandin	Azoles 50-150 days, Echinocandins up to 120 days	See above	See above	6–12 months prolonged up to lifelong in some settings

(Continues)

TABLE 2 (Continued)

	Candida RISK FACTORS	*Candida* PROPHYLAXIS	DURATION	*Aspergillus* RISK FACTORS	BROAD SPECTRUM MOLD ACTIVE PROPHYLAXIS	DURATION	PNEUMOCYSTIS RISK FACTORS	PROPHYLAXIS	DURATION
LIVER [58] [71,72]	Surgical revision or prolonged surgery Retransplantation Renal failure with dialysis High transfusion requirement Choledochojejunostomy *Candida* colonization perioperatively	Fluconazole 400 mg daily	1-4 weeks while risk factors are present	Retransplantation Renal failure with dialysis up to 7 days of transplant Reoperation involving thoracic or intra-abdominal cavity	Echinocandin or Voriconazole	For 14–21 days	See above	See above	6–12 months
KIDNEY [33,72,73]				Vascular amin use >24h after surgery ICU re-admission >1 bacterial infection High corticosteroid dosage	No general prophylaxis recommendation (incidence <5%) Insufficient data No general recommendations		See above	See above	See above
PANCREAS [28,58,72–74]	Enteric drainage Vascular thrombosis Postperfusion pancreatitis RRT	Fluconazole 400 mg daily		Acute graft rejection Initial graft dysfunction Re-laparotomy CMV RRT	Insufficient data		See above	See above	See above

Abbreviations: ICU, intensive care unit; RRT, renal replacement therapy.

TABLE 3 Targeted antifungal prophylaxis for SOT-recipients of liver, lung, and heart transplants. Recommendations of the American Society of Transplantation Infectious Diseases Community of Practice ([28,58]): 1 - strong recommendation, 2 - weak recommendation; A - high quality of evidence, B - moderate quality of evidence, C - low quality of evidence

	Liver transplant[a]	Lung transplant	Heart transplant
Inhaled Ampb	-	2C	-
Lip AmpB	2B	-	-
Posaconazole/Isavuconazole	-	2C	-
Voriconazole	2C[b]/1A[c]	1C	1C
Fluconazole	1B	-	-
Itraconazole	-	1C	1C
Echinocandine	2C[b]/1A[c]	-	1C

[a]Recommendations for following high-risk factors: re-transplant, renal replacement therapy, reoperation.
[b]Recommendation for invasive candidiasis.
[c]Recommendation for invasive aspergillosis.

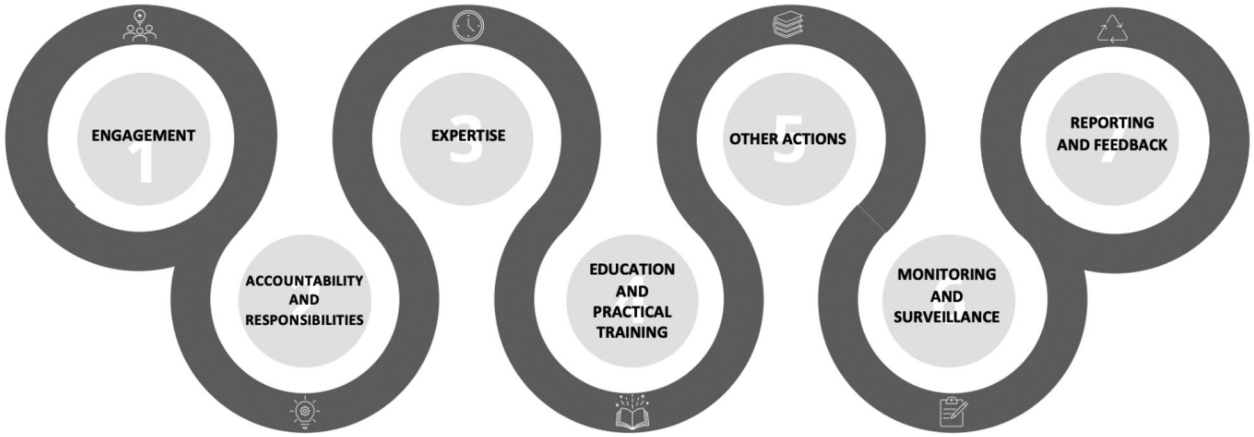

FIGURE 2 Key elements in antifungal stewardship (AFS) as recently defined by the Infectious Diseases Society of America (IDSA).[51]

the specialized departments and the AFS experts. In SOT-recipients, important considerations lie in the drug–drug interactions of antifungal agents, especially azoles and the required immunosuppressive therapy needed in this population as well as the safety in the presence of organ dysfunction.[52,62] Furthermore, patients often have a history of multiple antifungal therapies, particularly after lung transplantation, which increases the risk of different, more resistant fungi species.

Since both the initial approach and therapy surveillance are crucial in suspected IFI, targeted educational programs play an important role in AFS programs. In addition to filling knowledge gaps in terms of IFI, again better understanding in this matter could also lead to a better exchange.[46,51,53]

Finally, criteria must be defined measuring the effectiveness of AFS before the program starts. Surrogate parameters for different interventions need to be clearly defined at the beginning to minimize the risk of bias. These may include incidence of IFI for prevention strategies (e.g., targeted prophylaxis, hygienic procedures), measures of overall antifungal drug use for appropriate prescription, or, most importantly, mortality and length of ICU-stay for patient outcome for SOT-recipients with diagnosed IFI (59, 61).

Assessed data will provide the basis for evolution of IFI- management. It is crucial to evaluate obtained data to reveal shortcomings, design strategies going forward, and enable a successful feedback-loop including antifungal specialists as well as physicians at the main describing departments. Set measures need to be revised periodically to assure continuous improvement of the AFS (59,61,62).

4 | SUMMARY AND CONCLUSIONS

SOT-recipients are at risk for developing IFIs, which are associated with high morbidity and mortality. IFIs are heterogenous and unspecific in early clinical presentation, therefore awareness of the physician is needed to initiate adequate diagnostic steps, and optimally early treatment, which is essential for survival. Treating physicians need to be aware of local epidemiology, risk profiles of their patients, and adequate time points for initiation of antifungals, as well as standardized diagnostics and prophylaxis/treatment algorithms. Knowledge of antifungal agents including efficacy profiles and duration of therapy is vital, for which regular training is essential.

To achieve these goals, AFS can contribute the expertise of its members in a structured manner. Additionally, periodical educational programs and the constant discourse with the AFS team will lead to increased awareness among members throughout the departments involved. Established feedback mechanisms will monitor outcomes and interventions, to identify potential shortcomings and secure constant adaption. Hopefully, this ultimately will result in improved management of IFIs in SOT-recipients, which again is crucial for outcome in this high- risk population.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Lisa Kriegl and Johannes Boyer designed the structure of the review, performed literature search, and wrote the first draft of the manuscript. Matthias Egger participated in the designing the review, created figures, critically reviewed, and revised the manuscript. Martin Hoenigl co-designed the review structure, oversaw writing of the review and the drafting of the Figures, critically reviewed, and revised the manuscript.

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