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Review article

Fungal infections in solid organ transplantation: An update on diagnosis and treatment

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ABSTRACT

Invasive fungal infections constitute an important cause of morbidity and mortality in solid organ transplantation recipients. Since solid organ transplantation is an effective therapy for many patients with end-stage organ failure, prevention and treatment of fungal infections are of vital importance. Diagnosis and management of these infections, however, remain difficult due to the variety of clinical symptoms in addition to the lack of accurate diagnostic methods. The use of fungal biomarkers can lead to an increased diagnostic accuracy, resulting in improved clinical outcomes. The evidence for optimal prophylactic approaches remains inconclusive, which results in considerable variation in the administration of prophylaxis. The implementation of a standard protocol for prophylaxis remains difficult as previous treatment regimens, which can alter the distribution of different pathogens, affect the outcome of antifungal susceptibility testing. Furthermore, the increasing use of antifungals also contributes to incremental costs and the risk of development of drug resistance. This review will highlight risk factors, clinical manifestations and timing of fungal infections and will focus predominately on the current evidence for diagnosis and management of fungal infections.

Contents

Abbreviations: AP, aerosolized pentamidine; BAL, bronchoalveolar lavage; BDG, (1,3,)-β-d-Glucan; BID, twice daily; EORTC, European Organisation for Research and Treatment of Cancer; G6PD, glucose-6-phosphatase dehydrogenase; GM, galactomannan; GMS, Grocott methenamine silver; HR, hazard ratio; IA, invasive aspergillosis; IDSA, Infectious disease society of America; IFI, invasive fungal infection; IF/Mab, immunofluorescent staining with monoclonal antibodies; L-AmB, lipid formulation of amphotericin B; LTx, lung transplantation; MHb, methemoglobinemia; MSG, Infectious Diseases Mycoses Study Group; PJP, pneumocystis jiroveci pneumonia; PPV, positive predictive value; QD, once daily; SOT, solid organ transplantation; TDM, therapeutic drug monitoring; TMP-SMX, trimethoprim–sulphamethoxazole.

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1. Introduction

Invasive fungal infections (IFI) constitute an important cause of morbidity and mortality among solid organ transplantation patients. These infections often result in graft failure and death, while early diagnosis and management is still challenging. Since solid organ transplantation (SOT) is an effective therapy for many patients with end-stage organ failure, prevention and treatment of fungal infections remain a major point of attention. The one-year cumulative incidences of the first IFI in SOT patients range from 1.3–11.6% [1]. Data from the Transplant-Associated Infection Surveillance Network (TRANSNET) demonstrated that the most frequent IFIs were invasive candidiasis (53%), invasive aspergillosis (19%), cryptococcosis (8%), non-Aspergillus molds (8%) and endemic fungi (5%) [1].

Although recent improvements have been made, the diagnosis of IFI is often still difficult due to symptoms of IFIs mimicking those of other infections and noninfectious illnesses and the lack of accurate diagnostic methods. As the median time to onset of candidiasis, aspergillosis and cryptococcosis is 103, 184 and 575 days after transplantation respectively, a permanent low threshold of suspicion is needed in these patients because of the use of potent immunosuppression [2]. The optimal way of detection and management of fungal infections is not always clear in clinical practice. As SOT patients are at risk for a variety of opportunistic infections, prophylaxis is of major importance to reduce the incidence and impact of these infections.

There currently exists considerable variation between different centers in the choice of prophylactic agent, reflecting the need for a proper assessment of possible strategies. Drug-related adverse events like acute kidney injury, gastrointestinal symptoms and leukopenia however frequently arise in SOT recipients as a consequence of prophylaxis [3].

Multiple new tests have been developed to facilitate the diagnosis of IFI. The current approach often consists of culture and microscopy, while serum or fluid biomarkers can be advantageous for starting empiric therapy or ruling out invasive infection. Conventional blood cultures may fail to diagnose candidiasis in up to 25–50% of cases [4]. Other diagnostic methods, like the detection of 1,3,B-d-Glucan (BDG) associated with *Candida* colonization, can be a promising tool for diagnosing or ruling out IFI. These newer diagnostic tests are nonetheless not routinely used, in part because their diagnostic accuracy is not clear yet and in part because treatment modality as well as prophylactic strategies often vary among transplant centers.

2. Methods

We searched for relevant articles published until August 2018 in the following databases: Medline and Embase. This search included randomized controlled trials, cohort studies, retrospective studies, reviews and guidelines. Search terms in Medline included: 'kidney transplantation aspergillus', 'kidney transplantation fungal infections', 'kidney transplantation pneumocystis', 'transplantation fungal infection, review', ' histoplasmosis transplantation', 'cryptococcosis transplantation', 'phaeohyphomycosis transplantation', 'pneumocystis transplantation', 'echinocandin transplantation', 'voriconazole transplantation', 'posaconazole transplantation', 'amphotericin b transplantation', 'trimethoprim-sulfamethoxazole transplantation', 'galactomannan transplantation', 'β-D-glucan transplantation', 'voriconazole genetics', 'voriconazole tdm'. Relevant articles published in the last 5 years were searched for. Mesh terms included: "Kidney Transplantation" AND "Aspergillosis"; "Transplantation" AND "Aspergillosis"; "Transplantation" AND "Invasive Pulmonary Aspergillosis"; "Transplantation" AND "Candidiasis", filtered for articles published in the last 5 years; "Invasive Fungal Infections" AND "Transplantation", filtered for articles published in the last 10 years. Search terms in Embase included: 'Transplantation and mycosis', with 2017–2013 and systematic review as filters. Public guidelines of the Infectious Disease Society of America were accessed and screened for information on 24/04/17. Public guidelines of The European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society Joint Clinical Guidelines were accessed and screened for information on 30/08/18.

References were qualitatively evaluated. Only studies in English qualified for inclusion, abstracts or conference papers were excluded. Studies were eligible if they reported epidemiology, diagnosis or treatment of fungal infections and data regarding these variables were analyzed. Using the search strategy described, we identified 3160 references. These underwent screening by reading the abstract. Studies were excluded because of irrelevance, overlap or study design. This yielded 81 potential studies for inclusion. After reading full text articles, 41 studies were included in this review. Four secondary articles found in the references from the primary search were also included.

3. Results

3.1. Aspergillosis

3.1.1. Clinical presentation and risk factors

Invasive aspergillosis (IA) is one of the most relevant fungal infections in SOT recipients. It occurs in 1–15% of the SOT patients and currently reported mortality rates of invasive aspergillosis are approximately 22% despite novel treatment modalities [5]. In lung transplant recipients, invasive pulmonary disease has an even higher mortality rate of 67–82% [5].

Although no specific symptoms exist, the typical presentation is fever, cough and expectoration, with multilobar nodular involvement on CT scan. It should be noted that 18% of kidney transplant recipients had no fever, nor expectorations or pleuritic chest pain while being infected with *Aspergillus* [6]. Furthermore, the presence of cavitation or the halo sign is reported in only 33% and 25% of patients, respectively [6]. Primary skin infection with *Aspergillus* may occur as a result of trauma or infected catheters, with erythematous papules and plaques as the typical skin lesions. Secondary infection usually results from hematogenous spread or direct spread from other foci and is associated with a high probability of mortality. Cerebral aspergillosis will often be diagnosed under the form of a single large brain abscess [7].

As there is a high mortality rate of IA in lung transplant recipients with invasive fungal disease, awareness of the risk factors in this population is of vital importance.

Single lung transplant, CMV infection, early airway ischemia, hypogammaglobulinemia and colonization with *Aspergillus* all augment the risk of developing IA. While retransplantation and renal failure are important risk factors for IA in liver transplant recipients, other risk factors exist for kidney transplant recipients [5]: Risk factors for early-onset infection, occurring within the first 3 months post-transplant, are a prolonged period of renal replacement therapy pre-transplant and leukopenia, whereas donor cytomegalovirus seropositivity is a risk factor for late-onset IA [8]. Prolonged steroid administration and graft failure requiring dialysis also augment the probability of the development of IA in kidney transplant recipients [5].

3.1.2. Diagnosis

The cornerstones of diagnosing IA have been culture and microscopic examination [9]]. Tissue from patients with a suspected invasive fungal infection should be stained, with potassium hydroxide wet mount smear being the most sensitive screening test for rapid detection [2]. However, this can be time-consuming and cultures from a respiratory specimen only have a moderate sensitivity [10]. *Aspergillus* is rarely isolated from respiratory tract samples in liver transplant recipients, but detection of the pathogen then has a moderately high positive predictive value (PPV) for developing invasive aspergillosis (41% to 72%). The PPV of *Aspergillus* culture in heart transplant recipients is approximately 60% [5].

Adequate risk assessment is needed for selecting diagnostic methods and interpreting the results. Serum galactomannan is a possible test for diagnosing IA, but the sensitivity varies according to the index cutoff and pre-test risk.

Serum GM had a specificity of 98.5% in liver transplant recipients, whereas this was 95% in lung transplant recipients [5]. The galactomannan assay showed an overall sensitivity and specificity in SOT recipients of 22% and 84%, respectively. In BAL of lung transplant recipients, GM demonstrated a sensitivity of 81.8% and a specificity of 95.8% for the detection of *Aspergillus*. It should be noted that false positive tests of galactomannan were seen in 13–20% of the cases [5].

BDG testing displays mediocre specificity and reproducibility in BAL. For the diagnosis of IA, BAL BDG had inferior specificity compared to GM (67% versus 94%, respectively) and results were often inconsistent with retesting [11]. BDG was more specific (92%) in serum than in BAL but had a similar sensitivity (55%) for diagnosing IFI [11]. Diagnosis of invasive fungal infections with BDG had a positive and negative predictive value of 69.2% and 83.1% in serum, while this was 27.6% and 86.3% in BAL. Possible causes of the high false positive rate of BDG are among others concomitant bacterial infection, colonization with *Candida* and the type of hemodialysis membranes when dialysis is used [12, 13].

Another possible diagnostic test can be polymerase chain reactions (PCR), which has a high sensitivity for detecting fungal pathogens. However, due to variations in extraction techniques, molecular targets, amplification methods and protocols, there is not yet a standard diagnostic assay that has been widely accepted. PCR is therefore not included in the EORTC/MSG consensus definitions as a reliable biomarker [10].

Table 1 provides an overview of non-culture-based assays for diagnosing invasive aspergillosis in SOT recipients.

3.1.3. Treatment

For the treatment of IA, voriconazole (Vfend, Pfizer, New York, New York) is recommended as the first-line agent. Loading dosage of voriconazole in adults is 6 mg/kg IV infusion every 12 h for 1 day followed by 4 mg/kg IV every 12 h, with oral dosage being 200 mg every 12 h [5]. Transient visual disorders are a notable side effect, with reversible disturbance of vision occurring in around 30% of patients. As an elevation of liver enzymes is another common side effect, liver function tests should be measured prior to therapy and then every 2–4 weeks during therapy. Furthermore, cutaneous squamous cell carcinoma, the most common malignancy after SOT, is associated with prolonged voriconazole usage and fluoride accumulation from voriconazole use is also being linked to painful periostitis in SOT recipients [14].

The concurrent administration of voriconazole and cyclosporine (Neoral, Novartis, Switzerland) and tacrolimus (Prograf, Astellas Pharma, Northbrook, Illinois) (Rapamune, Pfizer) should be done with caution; the co-administration of sirolimus is contra-indicated. In a study by Vanhove et al., tacrolimus dose-corrected trough concentrations increased by a factor 5.0 when voriconazole was administered [15]. CYP3A5 genotype and several clinical variables modulate the tacrolimus–azole interaction, however, it is not yet possible to determine the individual reduction for tacrolimus when voriconazole is initiated. For optimal therapeutic effects, monitoring of tacrolimus trough concentrations is recommended. Therapeutic drug monitoring (TDM) and consequent dosage adjustment of voriconazole can be recommended for patients not responding to therapy or for those where toxic effects are likely [16].

TDM of voriconazole, regardless from clinical response, is recommended by the IDSA and can also result in patient-specific dosing recommendations [17]. Of note, patients are advised to avoid ingesting voriconazole with fatty meals as they can decrease the bioavailability of voriconazole.

Second line therapy for IA can be amphotericin B lipid complex (Abelcet, Leadiant Biosciences, United Kingdom) 5 mg/kg/day IV, liposomal amphotericin B (AmBisome, Astellas Pharma) 3–5 mg/kg/day IV, micafungin (Mycamine, Astellas Pharma) 100–150 mg/day IV, caspofungin (Cancidas, Merck, Kenilworth, New Jersey) 50 mg/day IV or isavuconazole (Cresemba, Astellas Pharma) 200 mg/day [5,18]. Compared to voriconazole, isavuconazole displays similar efficacy but with significantly less hepatobiliairy adverse events and fewer clinically important drug-drug interactions. Isavuconazole is only a moderate CYP3A4 inhibitor and, unlike voriconazole, does not inhibit CYP2C9 and CYP2C19. The current US and EU prescribing information states that the concomitant administration of isavuconazole and ciclosporin, tacrolimus or sirolimus results in an increased exposure of these agents but does not recommend dose adjustment up-front. However, close monitoring of the drug concentrations of the immunosuppressive agents with dose adjustments as needed is advised. Table 2 displays the antifungals which are frequently used to treat invasive aspergillosis.

The optimal duration of therapy for IA is not established, treatment is generally administered for 6–12 weeks. Evaluation of GM and cultures of *Aspergillus* can be of help to guide the decision to discontinue therapy.

Knowledge of the local resistance rate is necessary to guide the choice of therapy, due to the increasing rate of azole resistance in *Aspergillus* species. The use of combination therapy of voriconazole and a echinocandin like caspofungin can best be reserved for salvage therapy [5]. Surgery can be an option as part of the secondary prophylactic approach for patients with a history of IA who currently have resectable foci of *Aspergillus* disease [19].

3.1.4. Prophylaxis

Prophylactic strategies for IA widely vary among institutions. The recommended agents used for prophylaxis in different transplant types are outlined in Table 3. For liver transplantation, *Aspergillus* prophylaxis can best be administered under the form of lipid formulation of amphotericin B (L-AmB) 3–5 mg/kg/day or an echinocandin [5]. The choice of drug can be based upon host factors and co-administration of other drugs. Current IDSA recommendations regarding liposomal amphotericin B as *Aspergillus* prophylaxis are a dosage of 1–2 mg/kg daily [20]. In heart transplant recipients, routine use of prophylaxis for IA is not recommended [21]. Use of universal prophylactic itraconazole (Sporanox, Johnson and Johnson, New Brunswick, New Jersey) 400 mg per day reduced the risk of IA, with a calculated relative risk of 0.2 (CI 95% 0.07–0.9). Another strategy consisted of targeted prophylaxis with an echinocandin (caspofungin 50 mg/day, micafungin 100 mg/day or anidulafungin (Eraxis, Pfizer) 100 mg/day) which

Table 1
Clinically validated non-culture-based assays for diagnosing invasive aspergillosis in SOT recipients.

Assay		Species	Specimen(s)	Comments
Detection of galactomannan	Platelia™ Aspergillus antigen assay (Bio-Rad Laboratories) Commercially available CE-marked and FDA released for serum and BAL fluid testing Immunoenzymatic sandwich microplate assay using the same rat monoclonal antibody EBA-2 as detector and capture antibody Manual test that can easily be semi-automated Reported as an optical density index (sample divided by control)	Mainly Aspergillus species but other genera of fungi such as Talaromyces (Penicillium), Alternaria Paecilomyces, Geotrichum, Fusarium and Histoplasma have shown reactivity with the monoclonal antibodies	Serum	Strongly recommended for screening (twice weekly) high-risk neutropenic patients not receiving mould-active antifungals. A positive sample is defined by either two consecutive samples with an OD value >0.5 or a single assay >0.7. Use of mould-active agents dramatically reduces the sensitivity and the positive predictive value of the test as a screening tool, although the performance remains good to excellent when used as a diagnostic test in patients with suspected features on imaging. Marginally recommended for use as a screening tool in non-neutropenic patients [e.g. most solid organ transplant recipients] as its performance is far less accurate.
			Broncho-alveolar lavage fluid	Strongly recommended for use, irrespective of neutrophil count. An OD value >1 is considered positive. However, an OD value <0.5 virtually excludes invasive pulmonary aspergillosis whereas a value >3.0 confirms the diagnosis in an at-risk patient with (suspected) CT scan abnormalities. Mould-active drugs reduce the sensitivity. The test can be false-negative in BALf samples pre-treated with mucolytic agents.
			Cerebrospinal fluid	Moderately recommended as an aid to diagnose cerebral aspergillosis: experience is limited and the OD index cut-off value to define positivity is unclear (certainly >1.0).
			Other specimens	Although anecdotally tested on urine, pleural fluid, ascites, sputum, fluid from abscesses, and other body fluid samples, the use of this assay has not been validated for any of these specimens; hence, the use of the GM assay cannot be recommended in these settings.
			Causes of false-positivity to be considered	• Galactofuranose has been demonstrated in various foods, particularly cereals, cereal products and cream desserts. Dietary factors must therefore be considered when assessing the course of antigenemia in patients with altered intestinal barriers. • Initial reports of false-positive test results in patients receiving piperacillin-tazobactam (Tazobactam®) have not been confirmed more recently. However, generic products and other semi-synthetic ß-lactam antibiotics may still cause false-positivity • There have been reports of positive reactions for galactomannan in serum and bronchoal-veolar lavage fluid associated with PLASMA-LYTE™.
Detection of (1 → 3)-β-D-glucan	Fungitell® (Associates of Cape Cod) Commercially available CE-marked and FDA-cleared for serum samples Colorimetric assay	"Panfungal ": Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., *Sporothrix schenckii*, *Saccharomyces cerevisiae*, and Pneumocystis jirovecii. Assay does not detect Mucorales (Zygomycetes)	Serum	Moderately recommended as an aid to diagnose invasive fungal disease (moderate sensitivity and lack of species identification). Excellent negative predictive value permits reduction of inappropriate systemic antifungal therapy (though mainly studied in ICU patients). Interpretation: negative = <60 pg/mL; indeterminate = 60 to 79 pg/mL; positive = greater than or equal to 80 pg/mL. Lipemic, icteric, or hemolyzed specimens cannot reliably be analyzed. Of note, other assays, some of which are CE-approved (e.g. Wako), use different cut-off values!! (Usually high serum values) additionally support a presumed diagnosis of Pneumocystis jiroveci pneumonia in patients with positive PCR for Pneumocystis on BALf.

Table 1 (*continued*)

Assay		Species	Specimen(s)	Comments
			Other body fluids	The use of this assay has not been validated for other body fluids (including BALf); hence, the use of the BDG assay cannot be recommended in these settings.
			Causes of false-positivity to be considered	• (Gram positive) bacteremia • Hemodialysis utilizing cellulose membranes • Blood and platelet transfusions • Fractionated blood products such as albumin and immunoglobulins • Surgical exposure to BDG-containing sponges and gauze • Patients whose gastro-intestinal tract is colonized with Candida species and have mucositis
Detection of fungal DNA by polymerase chain reaction	In-house developed assays Several commercially available assays	Panfungal or Aspergillus specific	Blood	Moderately to strongly recommended for use: depends on type of assay and centre experience: test has a good negative predictive value whereas two positive PCR results should be considered highly indicative of an active Aspergillus infection. Sensitivity of Aspergillus PCR using plasma is superior to that using serum.
			Broncho-alveolar lavage fluid	Strongly recommended for use to diagnose invasive aspergillosis.
Detection of fungal DNA plus resistance by PCR	AsperGenius® (PathoNostics) Commercially available Multiplex real time PCR CE-marked	Aspergillus species	Broncho-alveolar lavage fluid	Detection of Aspergillus fumigatus, Aspergillus terreus, and Aspergillus species and identification of 4 azole resistance markers (L98H, tandem repeat 34, T289A, and Y121F) in Aspergillus fumigatus. At present insufficient data in solid organ transplant recipients.
Detection of mannoproteins	AspLFD (Olm Diagnostics) Aspergillus GM LFA (IMMY) Immunochromatographic assays Commercially available CE-marked for BALf and serum	Aspergillus species	Broncho-alveolar lavage fluid	The AspLFD can be used as a true point-of-care test in non-bloody, non-sticky BALf samples. The Aspergillus GM LFA always needs pre-treatment. The non-commercial prototype test demonstrated good sensitivity (90–100%) in SOT recipients; data on the performance of the recently released commercial assays are still pending. The sensitivity of the prototype assay was negatively impacted by mould-active drugs.
			Serum	The non-commercial prototype test demonstrated poor sensitivity (around 40%) in serum samples; data on the performance of the recently released commercial assays are still pending. At present, the assay cannot be recommended for testing serum samples.
Combination of assays (e.g. GM or LFD and PCR)			Blood Broncho-alveolar lavage fluid	Strongly recommended for use.

Legend: BALf, bronco-alveolar lavage fluid; BDG, 1,3-B-d-Glucan; GM, galactomannan; OD, optical density; PCR, polymerase chain reaction.

resulted in an incidence of IA of 2.25% [21]. Other possible regimens in heart transplant recipients are voriconazole 200 mg or itraconazole 200 mg twice daily for 50–150 days [5].

There is evidence for a beneficial effect of prophylaxis, but since a systematic review did not yield a single randomized controlled trial, there are no official guidelines yet for this SOT type.

In lung transplant recipients, universal voriconazole prophylaxis 200 mg twice daily resulted in a lower incidence of IFI than pre-emptive prophylaxis using itraconazole 200 mg twice daily at 1 year post-LTx [22]. However, in a meta-analysis by Bhaskaran et al., there was not a significant reduction in IA with universal anti-*Aspergillus* prophylaxis versus no prophylaxis (RR: 0.36, CI: 0.05–2.62) [23]. Other data showed that prophylaxis for IA in lung transplant has a number needed to treat of 6.8, but this meta-analysis also noted the heterogeneity of studies and the lack of randomized controlled trials (RCTs) [24]. Inhaled amphotericin B 25 mg/day, inhaled AmB lipid complex 50 mg, voriconazole 200 mg twice daily and itraconazole twice daily for 4 months are used as other prophylactic regimens [5]. Possible disadvantages of itraconazole however are the potential of multiple drug interactions and the risk of usage in patients with ventricular dysfunction. The evidence for employing posaconazole (Noxafil, Merck) in first-line prophylaxis remains limited [22]. Currently, there is no evidence for the administration of prophylactic agents in other solid organ transplant types.

A prophylactic regimen with L-AmB or an echinocandin for 4 weeks can be expensive compared to the use of an azole. Therefore, voriconazole or itraconazole can sometimes be preferred over L-AmB as the option of choice based on a cost-effectiveness analysis.

Table 2
Optimal treatment for invasive aspergillosis in SOT recipients.

Drug	Dosage	Comments
First-line agent		Treatment is generally continued for 6–12 weeks.
Voriconazole	Loading dosage: 6 mg/kg IV infusion every 12 h for 1 day, succeeded by 4 mg/kg IV every 12 h. Oral dosage: 200 mg/12 h.	
Second-line agents		Treatment is generally continued for 6–12 weeks.
Amphotericin B Lipid Complex	5 mg/kg/day IV.	
Liposomal Amphotericin B	3–5/mg/kg/day IV	
Isavuconazole	200 mg/day.	The combination of voriconazole and an echinocandin can be used as salvage therapy.
Micafungin	100–150 mg IV qd.	
Caspofungin	70 mg IV day 1, followed by 50 mg IV daily.	

Legend: IV, intravenously; IA, invasive aspergillosis; qd, once-daily.

Furthermore, the cost of prophylaxis can be reduced if necessary by using alternative regimens like high-dose weekly L-AmB, wich proved to be a safe prophylactic strategy for high-risk liver transplant recipients and more cost-effective than daily L-AmB 3-5-mg/kg [25].

3.2. Pneumocystosis

3.2.1. Clinical presentation and risk factors

Because of the frequent use of prophylaxis, *Pneumocystis Jirovecii* pneumonia (PJP) occurs typically >180 days after transplantation, with most cases being diagnosed within one year after the discontinuation of prophylaxis [7]. In liver transplant recipients, *Pneumocystis* is the underlying pathogen in 7% of all pneumonias [26]. Symptoms can be non-specific such as non-productive cough, dyspnea and fever and often lead to severe dyspnea and hypoxemia in just a few days. PJP can also be pauci-symptomatic sometimes because immunosuppressive agents can alter the clinical presentation [27]. On chest imaging, PJP often presents with ground-glass opacities and diffuse interstitial infiltrates. High risk populations constitute lung and combined heart-lung transplants, whereas prolonged corticosteroid use, CMV disease, allograft rejection, calcineurin inhibitors, sirolimus and defects in cell-mediated immunity are other risk factors for the development of PJP [7, 27, 28, 29]. Although mycophenolate mofetil (Cellcept, Roche) has demonstrated an anti-*Pneumocystis* effect in vitro and in animal models, prospective clinical trials did not affirm this effect [30].

3.2.2. Diagnosis

Because *P. jirovecii* cannot be cultured, standard diagnostic procedures include microscopic visualization of cysts or trophic forms with cytochemical staining, immunofluorescent staining with monoclonal antibodies (IF/MAb) or DNA amplification [31]. It is recommended to perform a bronchoscopy with BAL if the initial sputum specimen failed to demonstrate *Pneumocystis* infection [27].

Detection of PJP by IF/Mab in BAL had a sensitivity and specificity of 100% and 100%, whereas for GMS staining of BAL specimens, this was 82% and 98%, respectively [31]. As PCR cannot distinguish colonization from infection and many immunocompromised patients are colonized with *P. jirovecii*, diagnosing pneumocystosis with PCR has some disadvantages [27]. An adjuvant diagnostic marker can be BDG, which had a positive and negative predictive value in serum of 77.8% and 90.5% [31]. In a meta-analysis by Karageorgopoulos et al., the average (95% CI) positive and negative likelihood ratio of BDG in serum was 6.9 (5.1–9.3) and 0.06 (0.03–0.11), respectively [32]. However, BDG is not applicable for monitoring response to treatment and is not correlated with the gravity of infection [27].

3.2.3. Treatment

Treatment for PJP can best be administered under the form of trimethoprim–sulphamethoxazole (Bactrim, Roche) (TMP-SMX): 15 mg/kg/day of TMP, in IV doses every 6–8 h, corrected for renal impairment if necessary [27]. Common adverse effects are a rise in serum creatinine, hyperkalemia, gastrointestinal symptoms and leucopenia [3]. Intravenous administration of TMP-SMX at a daily dose of 720 mg trimethoprim and 3600 mg sulfamethoxazole can also be used as treatment [26].

A common alternative regimen in case of intolerance or side effects is primaquine (Primaquine phosphate, Bausch Health, Canada) combined with clindamycin (Cleocin, Pfizer), dosed as primaquine 30 mg once daily orally and clindamycin 600–900 mg IV or orally every 6–8 h. Antimicrobial therapy is required for at least 2 weeks and, according to patient characteristics, is sometimes continued for 3 weeks [27]. Kidney transplant recipients who received TMP-SMX were more often

Table 3
Suggested Aspergillus prophylaxis for solid organ transplant recipients.

Transplant organ	Agent	Dosage	Duration	Comments
Lung	Voriconazole	Universal, 200 mg bid.	4 months or longer.	Both targeted prophylaxis as well as universal prophylaxis are possible approaches, the number needed to treat is not clear yet.
	Inhaled amphotericin B	Targeted, 25 mg/day	Guided by regular respiratory monitoring, clinical risk factors and cultures.	
	Inhaled AmB lipid complex	Targeted, 50 mg/week.	Once every 2 days for 2 weeks, afterwards weekly for at least 13 weeks.	
	Itraconazole	Targeted, 200 mg bid.	4 months or longer.	
Liver	L-AmB	Universal, 3–5 mg/kg/day.	4 weeks.	
Heart	Itraconazole	Universal, 200 mg bid.	50–150 days.	Evidence for a beneficial effect of prophylaxis, but no single randomized controlled trial conducted yet.
	Voriconazole	Universal, 200 mg bid.	50–150 days.	
	Caspofungin	Targeted, 50 mg/day.	From beginning of risk factors, continue for 3–4 weeks after their resolution.	
	Micafungin	Targeted, 100 mg/day.		

Legend: L-AmB, Lipid formulation Amphotericin B; bid, twice daily.

switched to an alternative regimen due to treatment-limiting adverse reactions, compared to recipients on clindamycin-primaquine (17.6% versus 0%, $p = .071$) [33]. However, clindamycine-primaquine was associated with a higher failure rate due to lack of efficacy (30.4% versus 20.6%, $p = .545$) and this difference was more pronounced in cases regarding severe PCP (60% versus 37.5%, $p = .611$) [33]. Pentamidine (Nebupent, Fresenius Kabi, Germany) is another possible second-line therapy, with dosing being pentamidine isesthionate 4 mg/kg/day IV initially over 1–2 h. Adverse reactions encompass hypoglycemia, pancreatitis, renal impairment and bone marrow suppression. In PJP patients with hypoxemia, the administration of adjunctive corticosteroids is recommended [30].

3.2.4. Prophylaxis

The first months after transplantation, SOT recipients are frequently administered chemoprophylaxis, with TMP-SMX as the preferred drug. There consists some heterogeneity in doses, with proposed dosing varying from 80 mg TMP/ 400 mg SMX to 160 mg TMP/ 800 mg SMX po daily. Due to side effects or intolerance for TMP-SMX, other prophylactic drugs are being used as well. Table 4 displays possible prophylactic approaches for PJP.

Dapsone (Dapsone, Jacobus Pharmaceutical, Princeton, New Jersey) is a commonly used second-line prophylactic agent.

Although kidney and liver transplant recipients presented more breakthrough infections with dapsone 100 mg weekly compared to TMP-SMX prophylaxis (44% vs. 30%), there were no documented cases of PJP at one year in either group studied [34]. Side effects of dapsone can include hemolytic anemia and methemoglobinemia and although it is often administered in patients intolerant of TMP-SMX, it is not ideal in the case of prior severe TMP-SMX intolerance [35]. Methemoglobinemia (MHb) might be an underreported side effect of dapsone, as dapsone accounts for 42% of the cases of drug-induced MHb and many patients with MHb remain asymptomatic, despite considerable drops in hemoglobin level [36]. In patients with G6PD deficiency, dapsone should not be used. The use of 1500 mg/d of atovaquone (Mepron, GlaxoSmithKline, United Kingdom) combined with a fluoroquinolone as anti-bacterial prophylaxis for one month also resulted in no cases of PJP at 12 months post-transplant. The need for premature discontinuation of therapy as a result of adverse events, was less prevalent in this group than in TMP-SMX-treated patients [35]. Aerosolized pentamidine (AP) can also be used as a second-line prophylactic agent, with the monthly administration as a possible advantage. In a study by Macesic et al., the monthly administration of 300 mg of AP resulted in severe adverse reactions requiring AP discontinuation in 9% of renal transplant recipients [37]. Clinicians should therefore exercise caution when considering the administration of AP to SOT recipients with known chronic respiratory disease [37].

Although TMP-SMX is the drug of choice for PJP prophylaxis, the optimal length of administration is yet to be established.

Prophylactic agents can be recommended for all SOT types for at least 6–12 months post-transplant [30], whereas the Kidney Disease Improving Global Outcomes guidelines recommend a duration of 3–6 months, the American Society of Transplantation 6–12 months and the European Renal Association 4 months [27]. PJP prophylaxis should even be considered for >12 months in renal transplant recipients having risk factors such as chronic active CMV infection, extended high-dose steroid therapy or neutropenia [27].

3.3. Candidiasis

3.3.1. Epidemiology and risk factors

Candida is the most frequent fungal pathogen in almost all SOT types. In general, invasive candidiasis occurs earlier than other invasive mycoses, with time to onset of candidiasis often being within the first months after transplantation [7]. Approximately 50% of isolates involves *C. albicans*, while *C. glabrata* is the most common non-albicans species. *C. krusei* and *C. guilliermondii* are sometimes cultured in stem cell recipients but are uncommon in SOT recipients [38]. The 12-month survival after invasive candidiasis is 66% [1]. Recent use of a central venous catheter, intensive care unit stay and current steroid therapy are important risk factors for developing invasive fungal infections. Among kidney recipients, other risk factors for invasive candidiasis are diabetes, prolonged pre-transplant dialysis and graft failure requiring re-initiation of dialysis, while among liver recipients, surgical factors as well as hepatic and renal dysfunction constitute an elevated risk [7]. Furthermore, invasive candidiasis is often associated with candidemia (64%), urinary tract involvement (11%) and peritonitis (9%) [1].

3.3.2. Diagnosis

Diagnosis of candidiasis if often based on positive blood cultures. Nevertheless, blood cultures are only positive after 2–5 days [4] and the overall sensitivity is estimated at 70% [38]. Patients with proven candidemia should subsequently undergo a funduscopic exam for the detection of ophthalmic complications [38].

PCR detection of *Candida* DNA is a potential tool but its diagnostic performance is questionable, because of heterogeneity in the available results and techniques as well as the lack of reliable reference standards [4]. Of note, PCR was more sensitive (89%) than both BDG and blood cultures among SOT recipients with candidiasis of sterile sites, such as the peritoneal cavity or cerebrospinal fluid. Its sensitivity for candidemia, however, was only 59% [14].

Another possible marker for the detection of *Candida* is BDG. Based on combining two subsequent samples positive for BDG (>146 pg/ml) and a colonization index of>0.5, sensitivity, specificity, positive

Table 4
Prophylactic strategies for Pneumocystis Jiroveci Pneumonia.

Drug	Duration	Dosing	Side effects	Comments
First-line agent				
TMP-SMX	3–12 months, optimal length of administration is yet to be established.	80 mg TMP/ 400 mg SMX or 160 mg TMP/ 800 mg SMX po daily.	Rise in serum creatinine, gastrointestinal symptoms, leukopenia.	
Second-line agents				
Dapsone	6 months.	50–100 mg once daily po.	Hemolytic anemia and methemoglobinemia.	Not suited for patients with G6PD deficiency and severe TMP-SMX intolerance.
Atovaquone	12 months.	1500 mg po daily.	Gastro-intestal intolerance, liver dysfunction.	To be associated with a fluoroquinolone for 1 month.
Aerosolized Pentamidine	12 months.	300 mg monthly	Bronchospasm, vertigo	

Legend: TMP-SMX, trimethoprim–sulphamethoxazole; po, oral.; G6PD, Glucose-6-phosphatase dehydrogenase.

predictive value (PPV) and negative predictive value (NPV) of BDG were 83%, 89%, 50% and 97.6%, respectively [39]. Comparable results for BDG were seen in the study by Silveira et al., where the sensitivity and specificity of BDG in patients with proven invasive candidiasis was 70% and 87%, respectively [38]. Several situations can produce false-positive results however, such as Pseudomonas aeruginosa bacteremia, intravenously administered immunoglobulins, treatment with fungus-derived antibiotics and exposure to gauze [38].

The recently introduced T2 Candida test from T2 Biosystems is designed to detect *Candida* directly from blood samples. This fully automated assay requires <5 min hands-on time and allows detection of 5 *Candida* species (*Candida albicans*/*Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata*/*Candida krusei)* within 3–5 h.

Sensitivity of this assay for the detection of invasive candidiasis and candidaemia was shown to be superior (96.4%) to blood culture (60%), the current gold standard. However, the test does not provide any information on resistance, which is a major limitation. [40]

3.3.3. Treatment

Fluconazole (Diflucan, Pfizer) is regarded as the antifungal of choice for patients with non-severe illness, no recent azole exposure and *C. glabrata* as an implausible pathogen. Echinocandins are recommended as primary therapy in case of a severe illness, recent azole exposure, a history of allergy or intolerance to azoles or high risk for non-albicans species as the causative pathogens [38]. Table 5 displays the suggested therapeutic approaches for *Candida* infections. All patients with candidemia should have a dilated retinal examination, preferably performed by an ophthalmologist, within the first week of therapy to establish if endophthalmitis is present. In case of candidemia without obvious metastatic complications, therapy should be continued for 14 days after the first documented negative blood culture (follow-up blood cultures should be taken daily or every other day) [38, 41]. However, cases complicated by cardiac involvement or endophthalmitis should be treated for much longer periods, irrespective of clearance of blood cultures. This duration should be individualized for each patient. It is recommended to repeat eye examination and echocardiography before stopping the antifungal treatment.

Therapeutic regimens for mucosal infections differ from regimens for candidemia, with oral fluconazole 200–400 mg per day for 2–3 weeks being recommended for *Candida* esophagitis and topical antifungals or a 150-mg oral dose of fluconazole being the therapy of choice for *Candida* vulvovaginitis [41]. Furthermore, source control has shown to be an important determinant of outcome for patients with candidemia and the removal of central venous catheters, when possible, is thus advised [4].

The appropriate use of antifungal susceptibility testing is not yet determined. It can be recommended for all bloodstream infections with clinically relevant *Candida* isolates [39], whereas by others, it is proposed for clinically significant *C. glabrata* isolates, when azole resistance is strongly suspected and in case of treatment failure [38]. The resistance rate to one or more echinocandins among *C. glabrata* is >10% in many tertiary centers [14]. Testing for echinocandin susceptibility can be therefore be considered when there is a history of treatment with an echinocandin or when *C. glabrata* or *C. parapsilosis* are the causative species [41].

Table 5
Recommended therapies for Candida infections.

Drug	Dosing	Comments
Fluconazole	Candidemia: 800 mg (12 mg/kg) as loading dose, followed by 400 mg (6 mg/kg) daily. Symptomatic cystitis: 200 mg daily for 2 weeks. Vulvovaginal candidiasis: topical antifungal 3–7 days.	First-line treatment for non-severe illness, without recent azole exposure and *C. glabrata* as an implausible pathogen.
Echinocandins	Anidulafungin: loading dose of 200 mg followed by 100 mg daily; caspofungin: loading dose of 70 mg followed by 50 mg daily and micafungin: 100 mg daily.	Initial therapy for patients with serious illness, recent azole exposure, prior intolerance or allergy to azoles or high risk for non-Albicans species as causative fungi.

Legend: C.glabrata, Candida glabrata.

3.3.4. Prophylaxis

Candida prophylaxis can be administered for liver, bowel and pancreas transplant recipients. First, in pancreas recipients, it can be indicated for all procedures or can be started in the presence of a risk factor, such as enteric drainage, vascular thrombosis or post-perfusion pancreatitis [2,38]. Second, *Candida* prophylaxis in liver recipients is required in the presence of 2 or more of the following risk factors: re-transplantation, renal failure, choledocho-jejunostomy, colonization with *Candida*, prolonged operation time or high transfusion requirements. Finally, prophylaxis is indicated for all bowel transplant recipients [2]. The prophylactic agent should have anti-*Aspergillus* activity if there is also an augmented risk for aspergillosis in addition to the risk factors for candidiasis [38]. Fluconazole 400 mg/day or L-AmB 3–5 mg/kg/day as prophylaxis is indicated for at least 4 weeks in pancreas and small bowel recipients and up to 4 weeks in liver recipients. The risk of invasive candidiasis after kidney transplantation is too low to justify the use of prophylaxis [38].

3.4. Cryptococcosis

Cryptococcosis accounts for approximately 8% of IFIs in SOT recipients, with a median time to onset varying from 16 to 21 months. Cryptococcosis usually presents as central nervous system disease or pneumonia but it can also affect multiple other sites such as soft tissues, liver, kidney and bones [42]. Nodular opacities and less often consolidation or effusions are the typical radiographic findings. Of note, patients receiving calcineurin inhibitor-based therapy have an increased risk of nodular pneumonia [7].

A reduction of immunosuppressive therapy and the start of antifungal therapy can cause an immune reconstitution inflammatory syndrome (IRIS), but IRIS can also mimic worsening disease due to cryptococcosis. The symptoms in the case of IRIS however, should occur during the administration of antifungal therapy and diagnostic investigations should be negative for *Cryptococcus* [42]. When cryptococcosis is suspected, comprehensive evaluation for extra-pulmonary disease is necessary by lumbar puncture and blood and urine cultures. Antigen testing in serum, which can detect both *Cryptococcus neoformans* and *Cryptococcus gattii*, has a relatively high sensitivity for detecting cryptococcal meningitis. Cryptococcal antigen testing has a higher sensitivity and specificity than fungal cultures or India ink staining in cerebral spinal fluid [42]. Its sensitivity for isolated pulmonary cryptococcosis is lower, however (approximately 50%) [7].

Disseminated cryptococcosis and severe pulmonary disease can be treated as follows: liposomal amphotericin B 3–4 mg/kg/day or amphotericin B lipid complex 5 mg/kg/day plus flucytosine (Ancobon, Bausch Health) 100 mg/kg/day in 4 equally divided doses for a minimum of 2 weeks as induction therapy. Consolidation consists of fluconazole 400–800 mg/day for 8 weeks, with fluconazole 200–400 mg/day as suppression therapy for 6 to 12 months. Focal pulmonary disease and asymptomatic patients can be also treated with fluconazole 400 mg/day for 6–12 months. As there is no identified high-risk group, routine antifungal prophylaxis against cryptococcosis is not recommended [42].

3.5. Histoplasmosis

Histoplasma capsulatum is an endemic fungus in some regions, such as the Midwestern USA, Africa and parts of Central and South America.

The median time to diagnosis is 27 months, but 34% of patients are diagnosed with histoplasmosis within the first year post-transplant [43].

Since disseminated histoplasmosis can present itself with both constitutional symptoms and unspecific symptoms including enteritis, pancytopenia, enlarged lymph nodes and arthralgia, establishing a diagnosis can be difficult [44]. Biopsy and tissue culture of cutaneous lesions in disseminated histoplasmosis are necessary for the detection of the fungal pathogen [44]. Antigenuria has the highest sensitivity for histoplasmosis, being positive in 93% of patients, whereas antigenemia is positive in 86% of cases [43]. In patients with diffuse pulmonary disease, the sensitivity of antigenuria was only 80% [7]. Moderately severe and severe progressive disseminated histoplasmosis should be treated with liposomal amphotericin B for 1–2 weeks, followed by oral itraconazole for at least one year [44]. IDSA guidelines propose that antigen concentration should be <2 ng/mL before therapy can be stopped, with monitoring of concentrations being recommended for at least 12 months after the discontinuation of therapy [43].

3.6. Phaeohyphomycosis

Dematiaceous fungi, which comprehend >100 causative species worldwide, are molds with pale brown to black walls that cause phaeohyphomycosis, chromoblastomycosis and mycetoma [45]. Incidence of phaeohyphomycosis ranges from 0.16% to 3.6%, depending on transplant type. In the majority of cases, lesions are seen on the extremities, with pulmonary and central nervous system involvement being possible but rare [7]. Phaeohyphomycosis can present itself with papules, nodules or ulcers not responsive to antibiotics, with an average onset of infection at 20 months post-transplant. The characteristic histologic appearance consists of purulent granulomas and diagnosis with GMS staining is consistently positive. Treatment of phaeohyphomycosis in the case of non-severe cutaneous infections can comprehend the administration of a single antifungal, such as itraconazole or voriconazole, along with debridement and a diminution of immunosuppression if necessary. Disseminated infection should be treated with multiple agents, with the combination of itraconazole, 5-fluorocytosine and liposomal amphotericin B as a possible approach [45].

4. Discussion

This review summarizes the current evidence-based appropriate use of diagnostic tests and treatment strategies for fungal infections in SOT recipients. For patients with suspected invasive aspergillosis, the cornerstones of diagnosis have been culture and microscopic examination. Serum galactomannan can be a possible adjunctive marker for IA due to the high specificity, whereas BDG has a poor specificity and reproducibility in BAL. So far, PCR has not yet been included in the EORTC/MSG consensus definitions as a reliable biomarker. BDG can be an adjunctive diagnostic marker for the diagnosis of PJP, since the high negative likelihood ratio can help to exclude PJP in patients without a high pretest probability. However, BDG is not applicable for monitoring response to treatment and is not correlated with the gravity of infection. Blood cultures for the detection of *Candida* remain essential when there is a clinical suspicion for candidiasis. BDG showed to be a possible marker for the detection of *Candida*, having an average sensitivity and a good specificity for invasive candidiasis. The use of PCR is not yet standard clinical practice due to the heterogeneity in the available results and techniques as well as the lack of reliable reference standards, but newer diagnostic methods like the T2 *Candida* test will likely change current diagnostic approaches in the near future.

There is still some margin for improvement regarding the evidence for certain prophylactic strategies. First, the effectiveness of prophylaxis for IA in lung transplant recipients remains unclear as the number needed to treat shows significant variation within studies executed so far.

Second, the optimal length of administration of TMP-SMX as prophylaxis in SOT recipients is yet to be established and third, the appropriate use of antifungal susceptibility testing for *Candida* species is also not yet determined.

There are certain limitations for this review. First, the lack of randomized controlled trials limits the available evidence for some prophylactic modalities. Secondly, variation in the recommendations by current guidelines reflect the need for additional evidence-based research. Prospective studies could focus for instance on the implementation of PCR as a reliable biomarker. Large RCT's are awaited to further guide the current recommendations for fungal infections in SOT recipients.

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None.

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