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Invasive fungal infections in solid organ transplant recipients

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Abstract

Invasive fungal infections are a major problem in solid organ transplant (SOT) recipients. Overall, the most common fungal infection in SOT is candidiasis, followed by aspergillosis and cryptococcosis, except in lung transplant recipients, where aspergillosis is most common. Development of invasive disease hinges on the interplay between host factors (e.g., integrity of anatomical barriers, innate and acquired immunity) and fungal factors (e.g., exposure, virulence and resistance to prophylaxis). In this article, we describe the epidemiology and clinical features of the most common fungal infections in organ transplantation. Within this context, we review recent advances in diagnostic modalities and antifungal chemotherapy, and their impact on evolving prophylaxis and treatment paradigms.

Keywords

antifungal; aspergillosis; candidiasis; cryptococcosis; fungal; galactomannan; kidney transplant; liver transplant; lung transplant; transplant

Improvements in therapeutic and diagnostic options are providing clinicians with unprecedented tools to evaluate, manage and prevent invasive fungal infection in solid organ transplant (SOT) recipients. Despite these advances, invasive fungal infections continue to be a major cause of morbidity and mortality in this population. Recent studies have shed new light on the epidemiology of invasive fungal infections in SOT recipients [1–3]. The overall cumulative incidence during the first year after transplantation is approximately 3%, although this varies depending on the type of organ transplanted [1]. However, the risk of infection, particularly due to inhaled fungi, persists for many years after transplant. Current epidemiological trends indicate a shift towards later infections. The consequences of fungal infection can be dire and include long hospitalizations, allograft damage and high mortality rates. Data from 15 centers involved in a prospective cohort study of invasive fungal infections in SOT recipients indicate that mortality at 12 months is approximately 40% for aspergillosis, 34% for candidiasis and 27% for cryptococcosis [1]. In this article, we review the epidemiology, clinical presentations, diagnostic techniques and therapeutic options for the most common invasive fungal infection in SOT recipients.

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General epidemiology

Host and environmental factors are critically important determinants in the epidemiology of fungal infections in transplantation. The highest risk is in small bowel (11.6%) and lung (8.6%) transplants, followed by liver (4.7%), heart (4.0%), pancreas (3.4%) and kidney (1.3%) [1]. Factors that impact the risk for developing an invasive fungal infection include the patient's environmental exposure and/or colonization with pathogenic fungi, use of antifungal prophylaxis, as well as the net state of immuno-suppression. The latter refers to the combined impact of immune suppressing factors, including antirejection therapies, breaches in mucocutaneous barriers, leukopenia, comorbid conditions (e.g., malnutrition, cirrhosis, diabetes mellitus and hypogammaglobulinemia) and chronic viral infections (e.g., CMV, HCV, HBV and HIV) [4].

The net state of immunosuppression varies widely depending on the type of transplant received. The interplay between host and environmental factors and the impact of antifungal prophylaxis strategies is more relevant to development of specific fungal infections than number of days after transplantation. For example, the median time to onset of invasive candidiasis ranges from several weeks to months in lung and liver transplant recipients, to over 2 years in kidney recipients [2]. Similarly, the median time to invasive aspergillosis is <6 months in liver transplant recipients, but occurs much later in kidney, heart and lung transplant recipients. The latter onset of invasive aspergillosis in lung transplant recipients is likely influenced by widespread use of mold-active prophylaxis in that population. Finally, cryptococcosis tends to occur between 2 and 5 years post-transplant, but can be observed much earlier in cases of donor transmission or heavy environmental exposure [2].

Candidiasis is the most common invasive fungal infection in SOT recipients and accounts for 50–60% infections [1]. *Candida* species, particularly *Candida albicans*, are frequent colonizers of the human gastrointestinal, respiratory and reproductive tracts, and the skin. The majority of invasive candidiasis is from an endogenous source – usually the skin or gut. Aspergillosis is the next most common infection, accounting for 20–25% of fungal infections. In lung transplant recipients, aspergillosis is the most common infection [2]. Infection may be due to reactivation of a previously quiescent process such as colonization or subclinical infection, or from *de novo* infection following inhalation of this ubiquitous mold after transplantation. The remaining infections are due to *Cryptococcus* species (6–7%), the endemic fungi (5%) and many other rare and emerging mycoses [1,2]. Reactivation of latent infection is a major mode of disease in cryptococcosis, histoplasmosis and coccidioidomycosis. Chronic carriage of fungi pretransplantation is a particular problem in unilateral lung transplant recipients and cystic fibrosis patients. In these patients, the retained lung and/or abnormal upper respiratory tract and sinuses can act as reservoirs for potentially pathogenic fungi that can then progress to cause invasive disease.

Donor-derived infections are an increasingly recognized mode of transmission [5]. Transplanted organs may act as reservoirs for potentially pathogenic fungi. Transmission of an array of pathogenic fungi including *Aspergillus* species, *Candida* species, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis* and *Scedosporium apiospermum* has been reported [6–19]. Active fungal disease in the donor is a

contraindication to transplantation, but infection may be latent and unknown to the donor and transplant team. This is particularly relevant to endemic mycoses and cryptococcosis, which are often present in dormant forms. Sometimes, unexplained symptoms in the donor are only understood in retrospect once the recipients develop infection. Differentiating donor-derived infection from reactivation of latent infection within the recipient may be difficult. Transplant centers should immediately notify the organ procurement agency if there is suspicion for transmission of a fungal pathogen, as it may impact care of the other recipients from a common donor. As yet, there are no uniform recommendations for donor screening for endemic mycoses [16].

Specific infections

Candidiasis

SOT recipients are at increased risk for invasive candidiasis, the most common fungal infection in this population. In a recent study, the overall annual estimated incidence of candidemia in SOT recipients was significantly higher than in other hospitalized patients (3 vs 0.21 per 1000 admissions; $p < 0.001$) [20]. As in other patients, *C. albicans* is the most common cause of invasive candidiasis and accounts for approximately 50% of cases. *Candida parapsilosis* is often associated with infections of indwelling medical devices and has emerged as an important pathogen in SOT. *Candida glabrata* (~30%) and *Candida krusei* (~5%) are important pathogens in SOT recipients, especially in those who have received prior antifungal therapy [2,21].

Invasive candidiasis is nearly always preceded by colonization [22]. The risk for invasive disease is related to intensity of colonization, which can be increased by exposure to broad-spectrum antibiotics, corticosteroid use, diabetes mellitus, prolonged stay in an intensive care unit (ICU) and urinary catheterization [23–25]. Although colonization is generally a prerequisite for infection, even heavy colonization does not invariably lead to invasive disease. The development of invasive candidiasis depends upon the virulence of the organism and impairment of critical host defenses. Examples of the latter include disruptions of mucosal and cutaneous barriers with chronic indwelling intravascular devices and prolonged operative time, and abnormalities in neutrophil function and number as can be caused by high-dose immunosuppressants [26].

Transplant recipients, particularly of abdominal organs, have multiple risk factors for invasive candidiasis. These include receipt of broad-spectrum antibiotics, presence of central venous catheters, abdominal surgery and corticosteroid use. Complicated operative courses, renal dys-function and dialysis, receipt of parenteral nutrition and hyperglycemia all increase the risk for invasive candidiasis in SOT recipients [27–29]. Iron overload is emerging as a risk for invasive fungal infection. For example, in liver transplant recipients, stainable iron in the hepatic explant has been associated with post-transplantation candidiasis [30]. The type of anastomosis can also impact the risk of infection. In that regard, liver transplant recipients with a choledochojejunostomy are at higher risk for candidiasis compared with those having a choledocho–choledocho anastomosis. Similarly, pancreas transplant recipients with enteric drainage have higher rates of candidiasis compared with those with bladder drainage [31]. Bowel transplant recipients are at

particularly high risk for invasive candidiasis, especially when there is rejection or dysfunction of the enteric graft, when the anastomosis is disrupted and in instances of enhanced immunosuppression, abdominal reoperation or multivisceral transplantation [31–33].

Transmission of *Candida* species during the transplantation process has been documented. *Candida* may contaminate the organ while the donor is still alive, or during the procurement, processing and transplantation process. In cases of renal transplantation, the infection may involve the wound site, urinary tract, renal parenchyma or renal vasculature and can lead to organ loss [17,34,35]. Organ preservation fluid may also become contaminated with *Candida* species and serve as a conduit for transmission. Avoiding use of organs from patients with active candidiasis and routinely monitoring culture of preservation media are important preventative strategies [36].

Most cases of invasive candidiasis involve the bloodstream and/or the abdomen. In a recent ana lysis of 266 SOT patients with invasive candidiasis, 141 (53.0%) had candidemia and 98 (36.8%) had abdominal infection [2]. Bloodstream candidiasis may originate from translocation of organisms across damaged intestinal mucosa or occur at the site of a central venous catheter. Intra-abdominal candidiasis (e.g., peritoneal, perinephric and biliary infections) mainly affects recipients of abdominal organs [37,38]. Postoperative intra-abdominal infections are a frequent complication of liver transplantation. *Candida* species are present in approximately 10% of such infections [39]. Bilomas, which are infected hepatic fluid collections, are a potentially devastating complication of liver transplantation. They are associated with high rates of death and need for retransplantation. *Candida* species can account for approximately 25% of such infections [40,41]. Compared with other pathogens, candidal bilomas are less likely to respond to nonsurgical therapy and are associated with increased mortality [41].

Invasive candidiasis continues to be associated with high rates of morbidity, mortality and excess medical costs [20]. Central venous catheters generally need to be removed in cases of bloodstream candidiasis. However, such devices may be difficult to replace and catheter management should be individualized for each patient. Moreover, host characteristics, including severity of illness, older age and immune status, are likely more important factors than early catheter removal [42]. Overall mortality at 12 weeks is in the 20–40% range and may be particularly poor in heart transplant recipients. Risks for poor outcomes in SOT patients with invasive candidiasis include dialysis dependence, mechanical ventilation and neutropenia, infections due to non-*albicans Candida* species and infections that break through antifungal prophylaxis [2,29]. Organ loss may ensue when infection involves the renal vasculature, pancreas and biliary tree.

The diagnosis can be straightforward, as when *Candida* species are identified from a normally sterile site such as bloodstream, intra-abdominal fluid or abscess material. However, interpretation of culture results from nonsterile sites can be challenging. Isolation of *Candida* species from stool, skin surfaces, drains, respiratory secretions and urine does not necessarily indicate infection, but may be a clue to patients at higher risk for developing an infection. Moreover, the sensitivity of bloodstream cultures for detecting *Candida* is

suboptimal and many patients with disseminated disease can have negative blood cultures [43]. Identifying *Candida* to the species level is important because of interspecies variability in pathogenic potential and susceptibility to anti-fungal agents. Germ tube formation in the presence of serum is a rapid test that is suggestive (but not diagnostic) of *C. albicans*. Assays commonly used for speciation include appearance of colony growth on selective media (CHROMagar™ Candida), metabolic testing (e.g., API® Yeast) and fluorescent *in situ* hybridization (PNA FISH®).

Use of nonculture diagnostic tests such as PCR and 1,3-β-D-glucan (BG) assays may provide another avenue for detecting invasive candidiasis. Performance characteristics of *Candida* PCR were recently evaluated in a meta-ana lysis that included nearly 5000 patients, 963 of whom had proven/probable or possible infection. In that ana lysis, sensitivity and specificity were in the 90–100% range and use of whole-blood samples, rRNA or P450 gene targets and a PCR detection limit of ≤10 CFU/ml were associated with improved test performance [44]. The role of *Candida* PCR is as yet unclear in SOT recipients, but it appears to be an attractive option. Another approach is BG testing, and this assay may be further along in development. Patients with a range of pathogenic fungi including *Aspergillus*, *Candida* and *Pneumocystis* may have detectable serum BG levels. The sensitivity and specificity of the BG assay have been estimated to be in the 75–85% range [45]. However, the true sensitivity and specificity of these assays are not known in SOT recipients. Estimates of test performance characteristics are further hampered by the lack of a ‘gold standard’, as even blood cultures can be insensitive for detecting candidemia. Falsely elevated BG levels (≥60 pg/ml) have been described in association with multiple conditions common to transplant recipients, including receipt of hemodialysis, infections due to *Pseudomonas aeruginosa*, exposure to gauze and receipt of amoxicillin/clavulanate [46–49]. Although promising, the role of this assay for diagnosing candidiasis remains unclear in SOT recipients. Nevertheless, difficulties in diagnosing invasive candidiasis in a timely manner and the potential for early diagnosis and treatment to impact outcomes is necessitating a move toward preemptive treatment strategies that rely on nonculture-based tools such as serum BG levels.

Treatment of invasive candidiasis in SOT recipients is similar to that of other patients. In general, initial therapy should be with an echinocandin (caspofungin, micafungin or anidulafungin) [50]. An echinocandin should also be considered as part of empiric therapy for sepsis of unclear etiology in SOT recipients, particularly in the early postoperative period and in recipients of abdominal organs. *C. parapsilosis* and *Candida guilliermondii* demonstrate less *in vitro* susceptibility to the echinocandins, and may need to be treated with alternative agents.Patients who are stable, not neutropenic and have not had recent azole exposure may be candidates for initial therapy with fluconazole. Independent risk factors for nonsusceptibility to fluconazole in SOT recipients include prior exposure to that drug, female gender, post-transplant diabetes mellitus and receipt of ganciclovir. Lipid formulations of amphotericin B (AmB) or voriconazole can be used as alternative agents, but are associated with increased toxicity. As indicated above, when feasible, removal of central venous catheters is strongly recommended [31]. Duration of therapy should be at

least 2 weeks after clearance of the bloodstream cultures and resolution of symptoms attributable to candidemia.

Once patients have stabilized, they can be considered for conversion to fluconazole or voriconazole based upon the species of *Candida* isolated and susceptibility profile. Both agents have the advantage that they can be given by mouth, but voriconazole is associated with increased toxicity and drug interactions. The latter's use for the treatment of candidiasis should be reserved for cases of fluconazole resistance with maintained voriconazole susceptibility. As in other populations, fluconazole resistance in *C. albicans*, *C. tropicalis* and *C. parapsilosis* isolates is low (~1%) in transplant recipients [21]. A substantial proportion of *C. glabrata* isolates and all *C. krusei* have reduced susceptibility to fluconazole. Voriconazole may be an option for these patients. The spectrum of activity of posaconazole with respect to *Candida* is generally similar to that of voriconazole [21,50]. However, the role of posaconazole in invasive candidiasis is not clear.

Invasive candidiasis is less common in lung transplants. When infection does occur, it is usually as bloodstream infection and is much less common than pleural space infection or other forms of invasive disease [51]. *Candida* species are frequently found in respiratory samples from lung transplant recipients and donors [52]. These are rarely clinically relevant, although transmission of *Candida* from a donor lung has been reported, with resultant pulmonary, peritoneal and bloodstream involvement in the recipient [14].

Candidal airway or lung infection (as opposed to colonization) is rare in the current era of anti-fungal prophylaxis. Infection of the anastomosis, before it has had time to heal, may occur in the early postoperative setting. In such cases, the infection can lead to failure of the anastomosis, parenchymal lung infection and even mediastinitis [51,53–56]. Another type of infection can occur in patients with artificial bronchial stents. These devices are used to prevent airway closure in cases of airway or anastomotic narrowing, bronchomalacia and bronchial stenosis or stricture. The stents have a tendency to become plugged with debris and secretions, which can then serve as a site of airway and/or lung infection with a variety of fungi, including *Candida* and *Aspergillus* species [55]. Evidence of candidal tracheobronchitis is based on visual inspection and histologic confirmation and are usually supported by a positive culture from an appropriate specimen [31]. Therapy is not routinely commenenced solely on the basis of a positive respiratory culture; however, some authors recommend antifungal treatment for patients with *Candida* from bronchoalveolar samples and otherwise unexplained decline in respiratory function [55].

The clinical importance of candiduria in kidney transplant recipients is not completely understood. Candiduria is common with an estimated incidence of 3–11% in kidney transplant recipients [57,58]. The infection is almost always ascending in nature from a periurethral source or from urinary catheterization. Much less frequently, urinary candidiasis occurs as a consequence of disseminated diseases with secondary seeding of the kidney and urinary tract. Risk factors for candiduria include female gender, admission to ICU, antibiotic use, the presence of an indwelling bladder catheter, diabetes mellitus, neurogenic bladder and malnutrition [58]. Candiduria is associated with decreased survival rate in transplant recipients, but this is thought to be due to greater severity of illness and comorbidities. Not

all patients with candiduria need to be treated beyond removal of urinary catheters [31,58]. Patients who have symptoms of infection, renal involvement, neutropenia and those undergoing urological procedures should be treated with an antifungal agent.

For those patients in whom treatment of candiduria is indicated and who have infection due to fluconazole-susceptible *Candida* spp., treatment with that antifungal agent is fairly straightforward. Treatment options for cystitis due to fluconazole resistant organisms are more complicated. Neither voriconazole nor the echinocandins penetrate into the urine well. Lipid formulations of AmB and flucytosine may be options, but these are associated with substantial risks for toxicity and many isolates develop resistance to flucytosine. For patients with fluconazole-resistant pyelonephritis, or hematogenous renal candidiasis, an echinocandin may be a reasonable option, as success typically depends on therapeutic serum and tissue (as opposed to urine) concentrations [31,59].

Antifungal prophylaxis against candidiasis has a role in some liver, pancreas and small bowel transplant recipients. Liver transplant recipients with multiple risk factors for candidiasis (≥two of the following risk factors: prolonged or repeat operation, retransplantation, renal failure, high trans-fusion requirement, choledochojejunostomy and *Candida* colonization in the perioperative period) should receive prophylaxis. Pancreas transplant recipients with enteric drainage, vascular thrombosis and post-perfusion pancreatitis and nearly all small bowel transplant recipients should also be considered for prophylaxis [31]. Owing to the potentially devastating impact of invasive candidiasis in terms of morbidity and mortality in immunocompromised patients, prophylaxis strategies are increasingly employed beyond the above groups. Many critically ill transplant recipients are now placed on agents active against *Candida* species during their stays in the ICU. Risk stratification using intensity of *Candida* colonization, clinical characteristics and local infection patterns are employed by many institutions as a guide to prophylaxis [60–62]. The ideal agent is unclear, but fluconazole, an echinocandin and AmB products are reasonable options [31,63–66]. The latter two may also protect against aspergillosis, which can sometimes complicate high-risk liver transplants. The length of prophylaxis is not known, but is generally 4 weeks or longer, depending upon time to healing of anastomosis and resolution of risk factors.

Aspergillosis

Exposure is almost exclusively with inhalation of *Aspergillus conidia* from an environmental source. As such, infection nearly always involves the respiratory tract and/or sinuses. The most common infecting species is *Aspergillus fumigatus*. Infections due to *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* are less common [67,68]. Clinically apparent infection may be from progression of a previously quiescent subclinical process or due to infection after transplantation. The latter can sometime occur in clusters due to a common source, such as building construction [69,70]. Nosocomial transmission leading to colonization and even infection has been described [71]. In one notable case, debridement and dressing of wounds from a patient with aspergillosis resulted in aerosolization of spores and airborne person-to-person transmission in a transplant ICU [72].

Transmission of *Aspergillus* via transplantation may occur directly from the organ or as a consequence of contamination of organ preservation fluid by airborne spores. Transmission to recipients has been documented following organ donation from patients who had themselves received organ transplantation shortly before they died [9,13]. In one of these cases, culture of a tracheal aspirate from the donor obtained at the time of organ donation eventually grew *A. fumigatus* [13]. Unusual sites of infection such as the urinary tract, graft anastomosis and heart valve are suggestive of donor-derived infection [9]. Prompt treatment of other organ recipients from the source patient can help avert their development of invasive aspergillosis [9]. Antifungal prophylaxis should also be considered in patients receiving organs from donors with positive *Aspergillus* respiratory cultures.

Key factors in development and timing of invasive aspergillosis are the recipient's net state of immunosuppression, intensity of exposure and the type of organ transplanted. Overall, invasive aspergillosis is more likely to occur in patients with renal failure, hemodialysis, repeated bacterial infections, leukopenia, CMV disease and in those requiring high levels of immunosuppression or retransplantation [73–76]. Highly immunosuppressed and chronically ill patients who then become critically ill can be at high risk for early-onset aspergillosis. Typical of such patients are liver transplant recipients, who require emergent transplantation, renal replacement therapy, large amounts of blood products and prolonged ICU stays. Conversely, patients who develop later-onset aspergillosis tend to be older, are heavily immunosuppressed and have chronically impaired graft function [73]. In the current era, where use of prophylactic and pre-emptive mold-active antifungal agents is increasingly used in the highest risk patients, the onset of invasive aspergillosis may be delayed by many months.

The highest risk for aspergillosis infection occurs in lung transplant recipients. In these patients, invasive aspergillosis accounts for nearly 50% of fungal disease [1]. In addition to the risk factors described above, chronic exposure of the transplanted lung to the environment and abnormal anatomical and physiological function of the transplanted and, if still present, the native lung, all predispose to infection. Lung transplant recipients frequently have *Aspergillus* colonization of the transplanted and/or native lung and upper respiratory tract. Colonization may lead to infection and has also been associated with development of bronchiolitis obliterans syndrome post-lung transplantation [77]. Additional risk factors for invasive aspergillosis in this population include airway ischemia, hypogammaglobulinemia (especially when IgG levels are less than 400 mg/dl), concomitant CMV pneumonia, cystic fibrosis, placement of a bronchial stent and single lung transplantation [78–80].

Clinical manifestations may range from asymptomatic colonization to tracheobronchitis, invasive pulmonary aspergillosis, empyema and disseminated disease [81]. The presentation may be subtle with chronic cough, fever or malaise. *Aspergillus* tracheobronchitis may cause airway obstruction, ulcerations and pseudomembrane formation. As described above, airway stents have a tendency to become plugged and can be a site of airway and/or lung infection with a variety of fungi, including *Aspergillus*. Sites of infection beyond the respiratory tract include the skeletal system, thyroid, skin and CNS [82,83]. These are frequently due to dissemination from a primary respiratory tract site. Liver transplant recipients may be at

particularly high risk for disseminated disease and CNS involvement compared with other transplant recipients [73]. Urinary tract aspergillosis has been reported in association with transmission through the graft. Such infections may also involve the vascular anastomosis site and almost invariably lead to loss of the transplant [9,13].

Diagnosis of invasive aspergillosis can be challenging and frequently require histological evidence for infection and culture. Specimens (e.g., smears and tissue) can be stained with Gomori's Methenamine Silver and periodic acid-Schiff or with fluorescent dyes such as Calcofluor white [84]. Immunohistochemistry techniques are another promising diagnostic modality, but are not in widespread use as of yet. Culture remains an important modality for identification of *Aspergillus* to the species level and to improve sensitivity in cases of negative fungal staining. Identifying the species of *Aspergillus* can provide important clues to antifungal susceptibility and pathogenic potential of the organism identified. *Aspergillus* tends to grow well on routine media, but yields can be increased with fungal media such as Sabouraud's dextrose agar. Specimens that are obtained from nonsterile sites should be cultured in the presence of antibiotics to reduce bacterial growth.

Potentially infected specimens may require invasive procedures (e.g., bronchoscopy and/or lung biopsy) in order to be obtained, and typical staining and culture techniques are often insensitive. Radiographic approaches to early diagnosis have become increasingly important. However, radiographic characteristics of pulmonary infection are variable and can include nodules or masses. On CT these may be associated with surrounding ground-glass opacity, central low density, central air cavity or air bronchograms [85]. In contradistinction to patients with hematological malignancies, halo signs are rarely observed in SOT patients with invasive aspergillosis. In cases of tracheobronchitis without lung parenchyma involvement, radiography may fail to reveal lesions that are visualized by bronchoscopy.

Major advances in nonculture techniques are allowing earlier diagnosis and reducing the need for invasive procedures. These include serum BG, nucleic acid assays (e.g., qualitative and quantitative PCR) of blood, bronchoalveolar lavage fluid and tissue and galactomannan testing. Of these, serum galactomannan, an assay that is now commercially available, is the furthest along. The utility of this test in SOT recipients for ruling out aspergillosis is limited. A recent meta-analysis of studies in SOT recipients reported that the sensitivity and specificity of the test were 22 and 84%, respectively [86]. Application of this assay to bronchoalveolar lavage fluid facilitates the diagnosis of invasive pulmonary aspergillosis in organ transplant recipients [87]. Using a GM index of ≥0.5–1.0, the specificity exceeds 90% and sensitivity has ranged from 60–90% [88–91]. False-positive results have been associated with certain antimicrobials (e.g., piperacillin/tazobactam and ampicillin) but this has not been consistent [92,93]. False positives can also be observed in lung transplant recipients, likely reflecting frequent filamentous fungi colonizing the airways in this population [87].

Invasive aspergillosis can be a catastrophic complication in SOT recipients and is associated with high rates of graft loss and death. Data from 15 centers involved in a prospective cohort study indicate that mortality at 12 months for SOT recipients with aspergillosis exceeds 50% [1]. However, mortality varies according to clinical presentation and host factors. For

example, patients with limited disease, such as tracheobronchitis, who are diagnosed early and treated promptly, may have excellent outcomes. Conversely, liver transplant recipients, those with severe concomitant illness (e.g., dialysis dependence, hepatic insufficiency, malnutrition, mechanical ventilation or high transfusion requirements) and patients with dissemination to the CNS have much higher mortality rates [73,94,95].

The basic principles of therapy include effective antifungal therapy and reversal of immunosuppression as feasible. Timely initiation of effective antifungal treatment is likely essential for improving outcomes. Therefore, every effort should be made to establish the diagnosis as soon as possible, and empiric therapy should be strongly considered in cases where there is suspicion for invasive aspergillosis (e.g., subacute pulmonary processes, brain lesions). Even when the diagnosis is established and effective antifungal therapy is given, adjunctive surgical debridement is sometimes required. Length of therapy depends upon clinical and radiographic response, the patient's net state of immunosuppression and site and extent of infection. First-line treatment is with voriconazole [68]. Lipid formulations of AmB can be used as alternative agents in patients who cannot tolerate voriconazole, or whose disease progresses despite its use. However, initial therapy with an AmB preparation has been associated with increased risk of death in SOT recipients with invasive aspergillosis [95].

There is less experience with other agents. The role of echinocandins as monotherapy for invasive aspergillosis is unclear, but these agents are generally well tolerated and may be effective in selected patients [96]. Data regarding posaconazole in SOT patients with invasive aspergillosis are accumulating [97]. With the currently available formulation, steady state levels are not reached for several days after initiation of therapy, thereby limiting the utility of this drug as primary therapy. The main use of posaconazole for invasive aspergillosis in SOT patients at this time is as salvage therapy. The role of combination therapy for invasive aspergillosis remains unclear at this time. Treatment guidelines have not recommended routine use of primary combination therapy because clinical efficacy data have been lacking [68]. A recently completed clinical trial will hopefully shed light on this topic. Treatment with voriconazole and an echinocandin (e.g., caspofungin) may be beneficial for subsets of organ transplant recipients with invasive aspergillosis, such as those with renal failure, treatment failure with monotherapy and those with *A. fumigatus* infection [98].

Lung transplant recipients are at particularly high risk for development of invasive aspergillosis and should be considered for antifungal prophylaxis. Published guidelines recommend prophylaxis for those with *Aspergillus* colonization before or in the first year after transplantation, and those with two or more of the following: early airway ischemia, induction with alemtuzumab or thymoglobulin, single-lung transplant, CMV infection, rejection with augmented immunosuppression and acquired hypogammaglobulinemia (IgG <400 mg/dl) [99]. Prophylaxis approaches include inhaled AmB, itraconazole, and voriconazole [100]. The duration of antifungal prophylaxis depends on a dynamic assessment of risk factors. Most lung transplant centers employ universal prophylaxis with voriconazole alone or in combination with inhaled AmB in the first 6 months after transplant and many centers continue beyond that time [101].

The risk for invasive aspergillosis is significantly less for liver and heart transplant recipients. Antifungal prophylaxis is recommended for liver transplant recipients who are at risk for early invasive aspergillosis. These include patients receiving a liver retransplantation, and those with renal failure, particularly requiring renal replacement therapy. An additional risk is a reoperation involving the thoracic or abdominal cavity. Prophylaxis should include a lipid formulation of AmB or an echinocandin, and is continued for several weeks after transplant. Risk factors that should prompt consideration for prophylaxis in heart transplant recipients include isolation of *Aspergillus* species from respiratory tract cultures, reoperation, post-transplant hemodialysis and CMV disease. Voriconazole or itraconazole for several months after transplantation can be used [99].

Cryptococcosis

Cryptococcosis is the third most common cause of fungal infections in SOT recipients. It accounts for approximately 7–8% of fungal infections in this population. The majority of cases occur in kidney, and to a lesser extent, liver transplant recipients [1,2]. The infecting organism is generally *C. neoformans*, which has a worldwide distribution and is ubiquitous in the environment. In recent years, infections with *Cryptococcus gattii* have been increasingly reported in multiple locations in the USA, and in particular in the Pacific northwest region, and British Columbia in Canada. In a recent ana lysis of *C. gattii* cases, 20% of those patients from whom clinical details were available were SOT recipients [102].

Development of infection likely depends upon the interplay between the patient's net state of immunity and environmental exposure before or after transplantation. The time to onset of symptoms can be as short as 2–3 months after transplant, but the majority of cases occur between 2 and 5 years post-transplantation. Patients whose cryptococcosis is a result of reactivation of previous infection tend to develop disease earlier [103]. Risk factors for infection include corticosteroid use and receipt of multiple doses of T-cell depleting agents (e.g., antithymocyte globulin or alemtuzumab) [104]. Transmission *of C. neoformans* from a donor has been described in kidney, liver and lung transplant recipients [5,14,18]. Clues to such a transmission include onset of infection very early after transplantation and unusual sites of involvement such as the graft itself or the surgical site [105]. In a well-documented transmission event, three recipients contracted the infection from a common donor who had unexplained neurological symptoms at the time of his death. He was later discovered to have cryptococcal meningoencephalitis. All three developed cryptococcemia with either pneumonia or meningitis [18]. Differentiating donor-derived infection from reactivation of latent cryptococcosis may be difficult. Transplant centers should immediately notify the organ procurement agency if transmission is suspected, so that other recipients from a common donor can be notified.

The most common sites of infection are the lung and CNS. In approximately two-thirds of patients, the infection is disseminated to involve multiple organs [106]. The majority of patients with pulmonary cryptococcosis present with respiratory symptoms. Radiographic findings usually show single or multiple nodular lesions, or less commonly, pulmonary infiltrates [107]. Other manifestations include lung masses, cavities and pleural effusions. In some patients, pulmonary cryptococcosis is discovered incidentally when radiographic

imaging is performed for another indication. The serum cryptococcal antigen may be a useful screening tool, but serum antigen tests are frequently negative in patients with lower organism burden, such as those with single nodules and lung transplant recipients with infection limited to the lung. Many patients with pulmonary cryptococcosis also have CNS disease, which can sometimes be asymptomatic. Therefore, all SOT recipients with pulmonary cryptococcosis should also be evaluated for CNS infection with a lumbar puncture.

CNS involvement is observed in nearly 50% of SOT recipients with cryptococcosis [108]. Clinical manifestations include headaches, changes in mental status, visual abnormalities and focal neurological findings. In addition to headaches and neurological abnormalities, clues to CNS involvement include late-onset disease (>2 years after transplantation), serum cryptococcal antigen titers exceeding 1:64 and presence of fungemia [109]. Because calcineurin inhibitors possess a degree of anticryptococcal activity, immuno-compromised patients who are not receiving such drugs are at increased risk for CNS disease [110]. Infection can be limited to meningitis or involve the brain parenchyma. Outcomes tend to be worse with parenchymal compared with meningeal disease [111]. Diagnosis can be established with visualization of the fungus on Gram stain or India ink stain and by culture of cerebro-spinal fluid (CSF) fluid. However, direct staining may only be positive in 50% and cultures in approximately 80% of those with CNS disease [111,112]. CSF cryptococcal antigen has excellent sensitivity and specificity (90%).

A critical component of the evaluation is measurement of CSF pressure [113]. Multiple factors contribute to elevated CSF pressure in cryptococcosis, including inhibition of CSF absorption. Elevated pressures in cryptococcosis can lead to neurological injury that ranges in severity from altered mental status to visual and hearing loss and even death. When pressures exceed 25 cmH_2O of CSF, fluid should be removed to reduce intracranial pressure to <20 cmH_2O. CSF taps should be repeated regularly until opening pressure remains below 25 cmH_2O [114]. In difficult to control cases, a lumbar drain or even a permanent ventriculoperitoneal shunt may need to be placed.

Besides the CNS and lung, cryptococcosis can involve almost any organ, including the skin, bones, joints, liver, kidney, prostate and the eye. Cutaneous cryptococcosis may be observed in nearly a fifth of cases in SOT recipients and typically manifests as nodules, masses, ulcers, abscesses and cellulitis. Skin involvement is usually observed as part of disseminated infection, but may be a lone finding and due to inoculation from an environmental source [115]. Cutaneous disease may be more common in certain regions such as the southern USA [116].

Overall survival in SOT patients with cryptococcosis is approximately 70–80% [1,2]. Higher mortality rates have been associated with parenchymal brain lesions and in those with renal failure at baseline [106,111]. Receipt of a calcineurin inhibitor for immunosuppression may be associated with lower rates of mortality [106].

Antifungal therapy in cryptococcosis varies by site and extent of infection. In the case of neurological and/or severe pulmonary disease the treatment of choice is an AmB product. If

possible, flucytosine should be added. Length of treatment with this initial therapy is usually 2 weeks, but ultimately depends upon clinical and micro-biological response to therapy. If flucytosine cannot be given, many authorities recommend extending AmB therapy to 4 weeks [114]. Once the patient has been stabilized with the above regimen, they can be transitioned to fluconazole at 400–800 mg daily for 8 more weeks and then 200–400 mg for 6–12 months. In cases of focal or incidentally detected pulmonary infection, fluconazole alone at 400 mg/day for 6–12 months may suffice. However, disseminated disease should be excluded with CSF ana lysis prior to embarking on this type of regimen.

An important aspect of anticryptococcosis therapy is reduction of immunosuppression. However, this should be done cautiously as too rapid a reduction may lead to an immune reconstitution syndrome (IRS). This complication occurs in 5–10% of patients [117]. Manifestations include aseptic meningitis, cerebral mass lesions, spinal arachnoiditis and hydrocephalus. Other presentations include lymphadenitis, cellulitis or pulmonary nodules. Cultures are usually negative. IRS typically presents 4–6 weeks after time of initiation of antifungal therapy and reduction of immunosuppression [118]. It may be associated with higher rates of allograft loss [119]. Some authorities recommend reduction as opposed to abrupt cessation of calcineurin inhibitors, with consideration given to tapering of corticosteroids first as a means of reducing immunosuppression without inducing IRS [120]. The optimal treatment of IRS is unclear. Corticosteroids may be considered in life-threatening situations or severe disease. Emerging therapies include statins and tumor necrosis factor inhibitors, but at this time these should be considered experimental.

Endemic mycoses

H. capsulatum, *Blastomyces dermatitidis* and *C. immitis* are fungal pathogens with a limited geographic distribution [121]. Most reports of infections with these fungi are from patients who have resided in endemic areas. Collectively, they are referred to as the endemic fungi. In North America, *H. capsulatum* is endemic in multiple regions, but the most intense exposure is thought to occur in the Caribbean basin and in areas of the Mississippi and Ohio River Valleys. Inhalation of *H. capsulatum* can occur with exposure to disrupted soil around construction sites and agricultural areas where there are large concentrations of bird droppings. *B. dermatitidis* is endemic in areas of the Mississippi and Ohio River Valleys, the Great Lakes region and the St Lawrence Seaway. It is a rare cause of infection and typically affects immunocompetent men with outdoor occupations or pastimes. *C. immitis* is found in the dessert soil of northern Mexico, the southwest USA and areas of California's Central Valley. Exposure occurs when spores are aerosolized and inhaled.

Active disease may develop following environmental exposure, or due to reactivation of a latent infection acquired prior to transplantation. Most infections are diagnosed within the first year after transplantation and occur in kidney and liver transplant recipients [1]. Overall, approximately 2–5% of fungal infections in SOT recipients are attributed to endemic fungi [1,2]. However, this is likely an underestimation as a diagnosis is not always established in mild-to-moderate infections. Histoplasmosis accounts for the majority of cases and the infection is usually disseminated at time of diagnosis. However, the rates of

infection vary by location. For example, in Arizona, USA, approximately 3–4% of kidney and liver transplant recipients may develop coccidioidomycosis [122,123].

Transmission of *H. capsulatum* via organ transplantation has been described. In one notable case, infection was transmitted by kidney donation to two patients. The donor, who was asymptomatic, had died from an unrelated cause and resided in an area heavily endemic for *H. capsulatum*. At 8 and 9 months after transplantation, the two recipients developed fever, weight loss, pancytopenia and *H. capsulatum* fungemia. Treatment with AmB was effective in both [12].

Prophylaxis with itraconazole may be appropriate for some patients. Radiographic evaluation of many potential donors from endemic areas may show signs of old, healed histoplasmosis. Findings include calcified pulmonary, hilar and splenic granulomata. However, radiographic evidence of quiescent or past infection are not considered a contraindication to donation [16]. Antifungal prophylaxis is recommended for lung transplant recipients whose donors have positive serology or incidental *H. capsulatum* detection in the donor lung [15].

Whether recipients of other organs from sero-positive donors should receive prophylaxis is controversial. Some authors recommend a course of at least 3–6 months, covering the period of more active immunosuppression [11]. Similarly, patients with history of histoplasmosis prior to their transplantation may benefit from prophylaxis. Such patients should have serial monitoring of urinary *Histoplasma* antigen during times of intense immunosuppression.

Transmission of coccidioidomycosis via organ transplantation has been also been described in lung, kidney and liver recipients. Most reports are from endemic areas or involved patients who had been former residents or visitors to those regions [7,10,11,124]. Published guidelines recommend antifungal prophylaxis if the donor had active *Coccidioides* infection or positive serologies [125]. Some authors recommend serological screening for coccidioidomycosis in donors from endemic areas to help guide prophylaxis [11]. A positive serology in the donor does not necessarily mandate rejection of the organ [15]. Patients with history of coccidioidomycosis or with positive *Coccidioides* serologies prior to their transplantation should receive fluconazole prophylaxis.

Clinical manifestations of endemic fungal infections can be varied and nonspecific. These may include fever, cough, shortness of breath and malaise. Nearly all patients have clinical or radiographic evidence of lung involvement [126]. The clinical course can be severe with high rates of disseminated disease and even death. Histoplasmosis has a predilection for organs of the reticuloendothelial system and infection can involve the bone marrow, lymphatic system, liver and spleen. Gastrointestinal mucosal ulceration, adrenal dysfunction, CNS involvement and fungemia may be observed with disseminated infection [127]. Blastomycosis may trigger acute respiratory distress syndrome and, when disseminated, can involve multiple organs including the skin, bones and spleen [128]. Coccidioidomycosis may disseminate to multiple sites including bones, joints, CNS and organs of the reticuloendothelial system [123,129].

Diagnosis can be made by identifying the organism on stain or culture from an affected site. Respiratory secretions, CSF, bloodstream, wound drainage and tissue specimen may all yield positive results. However, traditional microbiology and histopathology techniques often lack the sensitivity needed to detect infection. Additionally, appropriate specimens may be difficult to obtain. Nonculture-based techniques have greatly improved our diagnostic ability. In patients with disseminated histoplasmosis, testing of urine for *Histoplasma* antigen is highly sensitive and specific for infection. Sensitivity of the test declines with less severe infection and in immunocompetent patients [130]. Patients with more severe infection tend to have higher titers, which can facilitate measurement of the antigen to monitor response to therapy [131]. The urine antigen has substantial cross-reactivity with *B. dermatitidis* infection, thus assisting in diagnosis of that infection. Recent evaluation of serum *Histoplasma* antigen suggests that this test performs well in patients with disseminated disease. Antibody detection may have a role in diagnosis of histoplasmosis, particularly in immuno competent patients with subacute infection. However, the sensitivity of such assays may be suboptimal in SOT recipients [130]. Serological testing can be useful in diagnosis of coccidioidomycosis. Often, numerous simultaneous methods are used for identifying coccidioidal antibodies, including enzyme immunoassay and immunodiffusion for IgM and IgG, and the complement fixation test. The sensitivity of these assays may be suboptimal in SOT recipients and a negative serological test does not necessarily rule out infection [122,123].

Treatment varies by infecting pathogen and extent of infection. In cases of moderately severe and severe infection, the treatment of choice should be an AmB product. In general, AmB should be continued for approximately 2 weeks, but length of therapy depends upon the patient's response. Providing that the infection has been stabilized, the patient can be transitioned to oral fluconazole in the case of coccidioidomycosis and to oral itraconazole for histoplasmosis and blastomycosis. In cases of mild-to-moderate disease, the AmB portion of therapy can be omitted [125]. Total antifungal therapy course must be individualized, but in general, patients with blastomycosis and coccidioidomycosis should be treated for a minimum of 6–12 months and those with histoplasmosis for 12 months or longer.

Rare filamentous fungi

In recent years, dozens of fungal pathogens have been reported as rare causes of invasive fungal infections in SOT recipients. These include the Zygomycetes, which can cause potentially devastating infections that may complicate the course of SOT recipients [132–134]. Risk factors for zygomycosis include uncontrolled diabetes mellitus, receipt of corticosteroids and neutropenia, all of which are common to many SOT recipients. Additional risk factors that have been described in SOT recipients include renal failure and prior voriconazole and/or caspofungin use [135]. Cases typically develop within 3–6 months of transplant, but may occur much later [136]. Other rare fungal infections may be due to hyaline molds (e.g., *Fusarium* and *Scedosporium* species), darkly pigmented molds and dimorphic fungal infections such as paracoccidioidomycosis and sporotrichosis [137]. Treatment options for emerging filamentous fungal pathogens have improved with the advent of newer mold-active azoles (e.g., voriconazole and posaconazole). However,

susceptibility to these agents varies widely and data regarding ideal therapy in SOT recipients for many emerging fungi is scant. Moreover, an AmB product remains the drug of choice for treatment of zygomycosis and voriconazole lacks activity against the Zygomycetes.

Conclusion & future perspective

Invasive fungal infections are an important cause of morbidity and mortality in SOT recipients. In the past few years there have been major advances in our understanding of the epidemiology of these infections and development of improved diagnostic and therapeutic tools. However, outcomes in patients with these infections continue to be suboptimal. In the next 5–10 years, several key trends will likely impact the landscape of invasive fungal infections occurring in SOT recipients. Specifically, these include a changing epidemiology of transplant organ recipients, an improved ability to diagnose fungal infections and widespread availability of newer antifungal agents. The epidemiology of organ recipients will be affected by use of novel and highly immunosuppressive regimens to prevent and manage organ rejection episodes. Moreover, mirroring national trends, the population of organ recipients will likely become increasingly diverse with respect to age, ethnicity and comorbid medical conditions. The ability to detect fungal colonization and/or infection will improve with further development and increasing deployment of nonculture-based diagnostic tools (e.g., antigen, antibody and nucleic acid detection assays). These, coupled with the increasing use of potent, broad-spectrum antifungal agents (e.g., voriconazole and posaconazole) for prophylaxis and treatment, will significantly alter the timing and outcomes of invasive fungal infections in this population. At the same time, advances in understanding fungal pathogenesis, host immune mechanisms and the pharmacology of antifungal compounds will provide new avenues for prevention and treatment. New data that integrates the results generated from traditional prospective clinical trials, clinical and genomic databases and laboratory-based investigations will be needed to meet these challenges.

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Executive summary

General epidemiology

■ The major factors involved in development of invasive fungal infections are the patient's net state of immunosuppression, contact with pathogenic fungi (due to colonization or from environmental exposure) and use of antifungal prophylaxis.

■ The most common invasive fungal infections in solid organ transplant (SOT) recipients (except for lung transplant) are candidiasis followed by aspergillosis and cryptococcosis. Aspergillosis is the most common in lung transplant recipients.

Candidiasis

■ *Candida* is usually a harmless colonizer of the skin, GI tract and female genitourinary tract.

■ Invasive candidiasis is the most common fungal infection in SOT recipients.

■ Invasive candidiasis is associated with factors that increase yeast burden (e.g., antibacterial antibiotics, hyperglycemia), disrupt anatomical barriers (e.g., gastrointestinal mucosal injury, indwelling vascular devices) and impair neutrophil function and number (e.g., cytotoxic chemotherapy, corticosteroids).

■ Traditional culture techniques are often insensitive, and therefore newer diagnostic assays are desperately needed, and therapy is often empiric.

Aspergillosis

■ *Aspergillus* is ubiquitous in the environment and a frequent colonizer of chronically diseased airways (e.g., in patients with cystic fibrosis).

■ Invasive aspergillosis is the most common filamentous fungal infection in SOT recipients. Risk factors include neutropenia, neutrophil dysfunction (particularly with corticosteroids) and chronic lung disease.

■ Diagnosis typically relies on staining, culture and histopathology of relevant specimen. Because these are often insensitive or difficult to acquire (e.g., lung biopsy), newer assays, particularly serum and bronchoalveolar lavage galactomannan measurements have emerged as important alternatives.

Cryptococcosis

■ *Cryptococcus neoformans* is ubiquitous in the environment.

■ Infection typically involves the lungs and/or CNS. Cryptococcosis involving the CNS may have very few symptoms initially, but can lead to devastating neurological consequences if untreated.

■ Diagnosis is by culture and detection of cryptococcal antigen in cerebrospinal fluid and serum. Cerebrospinal fluid pressure management is an important component of CNS disease.

■ The length of treatment may be months to years.

Endemic mycoses

- *Histoplasma capsulatum* and *Coccidioides immitis* are limited to specific geographic regions.
- Infection typically involves the lungs, but can disseminate to organs of the reticuloendothelial system (histoplasmosis), skin and bone (coccidioidomycosis) and CNS (both).
- In addition to culture and histopathology, *Histoplasma* antigen and serology, and *Coccidioides* serology can assist with diagnosis.
- The length of treatment may be months to years.

Table 1

Comparison of main spectrum of activity, common toxicities and drug interactions of systemic antifungal agents.

Agent	Spectrum of activity	Major toxicity	Interaction with immunosuppressants	Comments	Ref.
Azoles					
Fluconazole	Candidiasis Cryptococcosis Coccidioidomycosis	Hepatotoxicity, QT interval prolongation	Increases levels of CNI and MTI	iv. and oral formulations	[21,50,138,139]
Itraconazole	Candidiasis Endemic mycosis Aspergillosis	Hepatotoxicity, QT interval prolongation, negative inotropic effect	Increases levels of CNI and MTI	Oral only, syrup solution better absorbed than tablets, but more costly, TDM may be helpful	[21,131,139]
Posaconazole	Candidiasis Aspergillosis Endemic fungi Rare and emerging molds	GI intolerance, hepatotoxicity, QT interval prolongation	Increases levels of CNI and MTI	Oral syrup solution only, several day delay to achieve steady state levels, TDM may be helpful	[21,97,140,141]
Voriconazole	Candidiasis Aspergillosis Rare and emerging molds	Hepatotoxicity, QT interval prolongation, psychosis, visual changes, dermatitis	Increases levels of CNI and MTI, extreme caution with sirolimus	iv. and oral formulations, TDM may be helpful	[142,143]
AmB					
Deoxycholate AmB	Broad range of yeasts and molds	Renal, electrolyte and infusion-related toxicities	Increased nephrotoxicity with CNI	iv., aerosolized; iv. rarely used in SOT due to nephrotoxicity	[50,68,101,138,144]
Lipid formulations of AmB	Broad range of yeasts and molds	Renal, electrolyte and infusion-related toxicities, but less than deoxycholate	Increased nephrotoxicity with CNI, but less than deoxycholate	iv., aerosolized	[50,68,101,138,144]
Echinocandins					
Anidulafungin	Candidiasis Aspergillosis	Rare: rash, hepatotoxicity	Cyclosporine increases anidulafungin level	iv. only	[145-148]
Caspofungin	Candidiasis Aspergillosis	Rare: rash, hepatotoxicity	Decreased tacrolimus level Cyclosporine increases caspofungin level	iv. only	[145-148]
Micafungin	Candidiasis Aspergillosis	Rare: rash, hepatotoxicity	Increased cyclosporine and sirolimus levels	iv. only, liver tumors in rats (black-box warning in Europe)	[145-148]
Others					
Flucytosine	Cryptococcosis (in combination with AmB)	Bone marrow and hepatotoxicity	Increased myelosuppression with sirolimus and mycophenolate mofetil	Oral only, drug levels are proportional to dose and renal dysfunction, TDM may be helpful	[138,149]

AmB: Amphotericin B; CNI: Calcineurin inhibitors (e.g., tacrolimus and cyclosporine); GI: Gastrointestinal; iv.: Intravenous; MTI: mTOR Inhibitors (e.g., sirolimus and everolimus); SOT: Solid organ transplant; TDM: Therapeutic drug monitoring.

Adapted from [150].