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EMERGING FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

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Abstract

The most important emerging and rare fungal pathogens in solid organ transplant recipients are the Zygomycetes, *Scedosporium, Fusarium* and the dark molds. Factors impacting the emergence of these fungi include the combination of intensive immunosuppressive regimens with increasingly widespread use of long-term azole antifungal therapy; employment of aggressive diagnostic approaches (e.g. sampling of bronchoalveolar lavage fluid) and changes in patients' interactions with the environment. Early diagnosis, differentiation between colonization and infection and institution of appropriate therapy is vital when contending with these fungi. Moreover, effective treatment often requires a multi-disciplinary approach. This article reviews the epidemiology, microbiology and clinical impact of emerging fungal infections in solid organ transplant recipients and provides up to date recommendations on their treatment.

Introduction

Development of invasive fungal infections in solid organ transplant (SOT) recipients is dependent upon the interplay between host and fungal factors. Changes in either of these variables can favor emergence of infections in new populations and/or by previously nonpathogenic fungi.

Managing SOT recipients with emerging fungal infections can be a daunting task. Most clinicians have very limited personal experience in treating these infections. Therapy frequently requires a multidisciplinary approach that includes toxic medications and invasive procedures, and these infections have the potential for devastating outcomes including graft loss or death. The medical literature describing such infections is difficult to interpret, as it is mostly comprised of anecdotal experiences and small case series. Adding to the complexity is the evolving nomenclature of many of these fungi. The goals of this review are to demystify these infections and to serve as a resource for clinicians contending with emerging fungal infections in SOT recipients.

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Overview

Emerging fungi are increasingly recognized as potential pathogens in SOT recipients. They account for 7-10% of invasive fungal infections in this population (1-4).

Microbiology

Clinically significant emerging fungi include (1-3, 5, 6)(7-11):

- Zygomycetes (e.g. *Rhizopus, Mucor, Absidia* and *Mycoladu*s species)
- *Scedosporium (e.g. S. apiospermum, S. auranticum* and *S. prolificans*)
- *Fusarium* (e.g. *F. solani* and *F. oxysporum*)
- Dark molds- also called dematiaceous fungi (e.g. Ochroconis, Cladophialophora, Rhinocladiella, Bipolaris and *Fonsecaea species*)
- *Paecilomyces*, *Acremonium, Trichoderma*
- Yeast-like organisms (e.g. *Trichosporon*, *Cryptococcus gattii* and *Rhodotorula species)*

Environment

The emerging fungi are typically found in diverse environmental sources such as soil, water, decaying vegetation and sewage. Patients come into contact with these fungi either via inhalation of airborne spores, or less commonly by touching a contaminated source. The environmental microbiology and hence patients' exposures, can vary by geographic locale. For example, risk for infection due to the Zygomycetes and to *Scedosporium species* are particularly high in the Middle East and Australia respectively (12, 13).

Certain occupations and living circumstances can put patients at higher risk. Exposures to construction sites, farming operations, sandblasting work, air conditioning filters and flooded sites are important in that regard. Risks for contact with potentially pathogenic fungi and ways to reduce patients' exposure should be discussed with transplant recipients. If an infection is suspected, inquiring about a patient's travel, occupation and activities may provide important epidemiological clues. Sometimes exposures can occur within the healthcare setting (14, 15). Outbreaks of mucormycosis have been associated with contaminated adhesive bandages, wooden tongue depressors, ostomy bags, water circuitry damage, and adjacent building construction. Fusariosis may be acquired from contaminated hospital drains and showerheads.

Patterns of fungal exposure may also be impacted by environmental disruptions such as natural disasters and by the development of new ecological niches. Infections due to the Zygomycetes and *Scedosporium species* may be seen after floods, tornados and tsunamis (16, 17). The risk of transmitting such organisms may be relevant when evaluating potential organ donors who suffered drowning accidents (18, 19). The role of new ecological niches has been demonstrated in the recent outbreak of *Cryptococcus gattii* in the Pacific Northwest region of North America(20). Starting in 2004, cases of *C. gattii* infections have been identified in that region(21). Approximately 1/5 of those affected in that outbreak have been SOT recipients. With regards to climate change some have hypothesized that global warming may increase the prevalence of fungal diseases by increasing the geographic range of currently pathogenic species and by selecting for adaptive thermotolerance in species that are currently unable to survive at human body temperature(22).

Host factors

Multiple arms of the immune system are impaired in transplant recipients. The first lines of defense are intact anatomical barriers. If there is exposure to an emerging fungal pathogen when such barriers are disrupted and there is ongoing high-level immunosuppression, a "perfect storm" can develop resulting in invasive infection. This can occur in any SOT recipient, but lung transplant recipients are at highest risk (1, 3, 23-25). Factors favoring fungal infections in lung transplant recipients include ongoing exposure of the graft to environmental fungi, underlying chronic respiratory disease and concomitant sinus and airway abnormalities impeding fungal clearance. Patients with impaired cutaneous barriers due to traumatic injury or an invasive medical procedure are also at risk. Skin infections due to the *Zygomycetes, Scedosporium, Fusarium* and the dark molds have been described in such circumstances (14, 26-28).

Primary site of infection (by route of exposure)

- Inhalation of airborne spores: Most likely sites are the sinuses, airways and/or lung parenchyma. Disease may then extend to involve adjacent sites or disseminate to distant organs.
- Direct inoculation: Most likely site is the skin and adjacent soft tissue structures
- Donor derived (e.g. Zygomycosis via contamination of the preservation fluid or from the organ itself): infection can be localized to the transplanted organ and the graft anastomosis or disseminate widely. Such cases are associated with high rates of graft loss and mortality and may be particularly problematic in commercial transplantation (19, 29, 30).

An additional factor in the evolution of infection due to emerging fungi may be the impact of antifungals used for prophylaxis and therapy. Decreased susceptibility to one or more commonly used antifungals is common in emerging fungi (Table 1). For example, the Zygomycetes are not susceptible to voriconazole and to the echinocandins. Use of these agents has been associated with increased risk for development of mucormycosis in some, but not all studies (31-33). *Trichosporon* and *Fusarium* species are frequently resistant to amphotericin B (AmB), and *Scedosporium prolificans* may be resistant to all commonly used antifungal agents. It is likely that development of infections with these fungi is related to antifungal selection pressure.

Specific fungi

Mucormycosis

Infections due to the Zygomycetes are the best characterized of the emerging fungal infections in SOT recipients(1-3). Exposure is generally via inhalation, but may also occur at the skin or GI tract. Direct contact with soil or water following natural disasters or near drowning episodes, and exposure to contaminated medical devices (as described above) are additional routes to infection (14).

Clinically important Zygomycetes include species of *Rhizopus*, *Mucor*, *Rhizomucor, Cunninghamella, Absidia*, *Apophysomyces* and *Mycocladus*. The predominant infecting organism can vary by geographic site of exposure (34). Additionally, pathogenic potential may differ by organism. For example *Mycocladus corymbifer* pulmonary infection has been associated with higher rates of disseminated disease (35).

Epidemiology (6)

- Zygomycosis accounts for approximately 2% of fungal infections in SOT recipients.
- Lung and liver transplant recipients are the most affected
- Infections tend to occur at a median of 6 months after transplant except in liver transplant recipients where infection can occur in 1st month.
- Risk factors in SOT recipients include: Renal failure, diabetes mellitus, exposure to high doses of corticosteroids, and prior use of voriconazole.
- "Traditional" risk factors for mucormycosis (e.g. ketoacidosis, prolonged and profound neutropenia and deferoximine) are infrequently seen in SOT recipients.

Clinical Presentations (6, 35)(36)(37)

- Lungs are the most common sites of infection. Disease presents as consolidation/ mass lesions nodules and cavities
- Infection at the sinuses and nose may remain localized or extend to orbits, brain and other intracranial structures.
- Primary cutaneous infection occurs at sites of surgical wounds or drains, intravenous catheter sites and after skin trauma. The typical appearance is of black necrotic lesions surrounded by cellulitis, thrombophlebitis or extension to deeper structures.
- Disseminated disease can involve virtually any organ including the lungs, pericardium, myocardium, endocardium, brain, liver, esophagus, stomach, small and large intestine, kidney, retroperitoneum, thyroid gland and skin.

Diagnosis usually requires an invasive procedure such as biopsy, fine needle aspiration, bronchoscopy, or surgical exploration, but occasionally the organism can be grown from expectorated sputum (37). Upon direct staining the Zygomycetes tend to appear as broad, ribbon-like and non-septate hyphae. Not infrequently, the organisms are identified on either histology or culture, but not both. Increasingly, PCR is being used for detection of Zygomycetes (34).

Outcomes depend upon timely initiation of appropriate antifungal therapy, the host immune status and the site and extent of infection. The cornerstones of management are effective antifungal therapy, improvement in host defenses and surgical resection of necrotic tissue generated by this angioinvasive fungus. Medical therapy alone can be attempted in some patients with pulmonary infection. However, surgery is typically required if there is extensive necrosis, infection at lung transplant anastomosis, or a threat to major vascular structures. Debridement of airway or sinus disease may be performed endoscopically.

Antifungal treatment options

- Drugs of choice: Lipid formulation amphotericin B (5.0-7.5 mg/kg/day)
- Combination of an echinocandin + Lipid formulation amphotericin B may be considered based on data from animal studies and retrospective reports.
- Posaconazole may be considered for maintenance once clinical stability has been achieved and for salvage therapy in patients intolerant to or failing AmB (38-40).

Dark (Dematiaceous) Molds

The dark molds are a diverse group of pigmented fungi that are associated with a variety of infections (41). Their nomenclature can be confusing and many organisms have undergone name changes in recent years. Invasive infection is called phaeohyphomycosis. Colonization of the respiratory tract and sinuses is common and does not necessarily indicate infection. Such colonization may be particularly common in lung transplant candidates and recipients. Infections tend to occur late, often several years after transplantation. The site of infection depends upon the mode of exposure and the fungal species (see below). Certain species tend to cause cutaneous infections at sites of inoculation, presenting as papules, nodules or pustules, while others cause pulmonary or disseminated (including CNS) disease. (7, 8, 42-45)(46, 47)(48).

Phaeohyphomycosis by site and organism

- Primary Skin: *Alternaria, Curvularia, Exophiala*
- Pulmonary: Ochroconis gallopavum, Cladophialophora bantiana, Exophiala, Alternaria, Curvularia and Fonsecaea
- CNS: *Cladophialophora bantiana*, *Ochroconis gallopavum*, Rhinocladiella mackenziei, Exophiala dermatitidis, Bipolaris and *Fonsecaea*

The diagnosis can be straightforward as in the case of symptomatic disease and evidence of the fungus in histopathology and culture. However, simply growing these molds in culture (particularly from the nose or sinuses) does not necessarily imply infection. In tissue these fungi may be identified by the golden-brown coloration in the walls of the hyphae(44).The presence of melanin can be highlighted by Fontana-Masson staining.

Treatment depends upon the infecting organism and site of infection. In general, surgical excision or debridement is recommended whenever feasible. This may even be sufficient for isolated cutaneous disease. Conversely, when disease is limited to the respiratory tract, medical management alone may suffice. Voriconazole, posaconazole or itraconazole are typically first line agents, but there may also be a role for AmB and the echinocandins (48, 49). Susceptibility testing can be useful to guide therapy.

Fusarium

Among SOT patients, fusariosis predominantly affects lung transplant recipients. Such infections accounts for <1% of fungal infections in SOT recipients (1, 3). Most of the infections are caused by *F. solani* and *F. oxysporum,* and to a lesser extent *F. proliferatum, F. moniliforme* and *F. sacchari* (15). Exposure is primarily via inhalation of airborne conidia or by contact with contaminated material (e.g. soil, plants and organic matter). *Fusarium* may also be found in water distribution systems, tap water, sinks and showerheads (15).

The clinical spectrum includes superficial, localized and disseminated infections (50). The specific presentation depends upon portal of entry, extent of immunosuppression and transplant type (51)(52)(53-55)(56).

Clinical presentations

- Primary skin infection due to direct inoculation: Present as superficial or localized infection (e.g. nodules, ulcers, cellulitis, subcutaneous abscess) and usually very responsive to therapy.
- Respiratory tract and sinus infection: Due to inhalation and typically occurs in lung transplant recipients.

- Secondary dissemination to multiple organs including the GI tract, liver, heart valves, kidneys, lung, CNS and skin

Diagnosis(53)(57, 58)

- Targetoid skin lesions with darkish discoloration are a clue to disseminated fusariosis. Skin biopsy can establish the diagnosis.
- Occasionally, the organism grows in blood cultures
- The role of non-culture based diagnostic tests (e.g. beta glucan and galactomannan) is currently evolving, but these may be useful as adjunctive tests.

Treatment options and outcomes depend on site and extent of infection and upon the species (59). Identification of the organism to the species level and antifungal susceptibility testing can help guide therapy. Surgical excision or debridement should be employed whenever possible.

Treatment options(56)

- *F. solani* and F. *verticillioides*: AmB
- Other species: Voriconazole
- Limited skin disease: excision alone might suffice
- Combination therapy (AmB + voriconazole) for invasive infection while awaiting identification and susceptibility testing and in severe cases.

Scedosporium/Pseudallescheria

Infections due to *Scedosporium* and *Pseudallescheria* species can be particularly difficult to treat. The organisms are frequently resistant to multiple antifungal agents and outcomes with invasive infections can be devastating. The nomenclature is complicated and still evolving. The teleomorph (sexual form) is referred to as Pseudallescheria and the asexual form (anamorph) as Scedosporium. The predominant species are *S. apiospermum* (teleomorph: *P. apiosperma*), *S. aurantiacum, P. boydii* (anamorph: *S. boydii*), *S. dehoogii*, and *S. prolificans (60, 61).*

These organisms are typically found in soil and contaminated water, including in urban environments (12). Exposure is generally via inhalation of airborne spores but may also occur after contact with contaminated water. Patients with cystic fibrosis are often colonized with Scedosporium even prior to transplant. Infections are predominantly seen in lung transplant recipients, but occur across the spectrum of organ transplants (3, 62). Primary sites of infection include the respiratory tract, sinuses and skin. Infection may progress or disseminate to involve additional organs including bone, join, brain, eye, ear and vocal cords (62).

Treatment recommendations are listed below, however, antifungal susceptibility testing of all clinical isolates is essential for guiding therapy(63)(64)(65)(66, 67):

Treatment options

- *S. apiospermum*: Voriconazole +/- echinocandin
- *S. aurantiacum*: Voriconazole
- *S. prolificans:* Resistant to multiple antifungal agents, but there may be a role for voriconazole + echinocandin, AmB + terbinafine or voriconazole + terbinafine

- Surgical debridement should be considered whenever feasible. Particularly in cases of multi-drug resistant fungal infection.

Paecilomyces

Paecilomyces species, particularly *P. lilacinus*, have emerged as a cause of fungal infections in highly immunocompromised patients. These environmental fungi are generally found in the air and in soil, but have also been associated with an outbreak of infection related to contaminated skin lotion(68). The predominant clinical presentation in SOT recipients is subacute skin infection (69). Paecilomyces can sometimes cause such infections in association with other fungi or mycobacteria (70, 71). The antifungal agent with the best track record for P. *lilacinus* infections is voriconazole, but susceptibility testing may help guide therapy (72, 73).

Trichosporon

Trichosporon species, particularly T. asahii and T. mucoides can cause systemic infection in SOT recipients (74, 75). These yeasts are found in diverse setting including soil, water, and vegetables and as commensals of the human skin and GI tract. Clinical presentations include fungemia and widely disseminated infection. The significance of *Trichosporon* fungiuria in renal transplant recipients is unclear and may not require antifungal therapy(76). When treatment is indicated, as in systemic disease, azoles are the mainstay of treatment (74, 75, 77). However, resistance to azoles and AmB is common and antifungal susceptibility testing is necessary to help guide therapy(10).

Miscellaneous rare fungi

There are multiple rare fungi that have been described as causes of infection in SOT recipients at the case report level. These include Acremonium, Scopulariopsis and Trichoderma species (78-80). As general rules, surgical excision should be attempted when possible and therapy should be guided by susceptibility testing.

Conclusion

Development of invasive fungal infections depends upon the confluence of host factors and environmental exposure. Changes in either of these parameters can favor emerging fungal infections. We are in the midst of such changes. Current trends in transplantation include increasingly diverse patient populations, use of novel and potent immunosuppressive regimens and expanded use of antifungal agents for prophylaxis and treatment. When coupled with environmental disruptions including natural disasters, new ecological niches and perhaps climate change we can expect an ongoing evolution of fungal epidemiology in SOT recipients and an increasingly important role for emerging fungi (tables 2-3).

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Key Points

- The leading emerging fungal pathogens in transplant recipients are the Zygomycetes, Scedosporium/Pseudallescheria, Fusarium and the dark molds.
- Amphotericin B (AmB) products are the treatment of choice for mucormycosis.
- Identifying emerging fungi to the species level and performing susceptibility testing can help guide therapy.
- When there is evidence for an active infection even low virulence fungi that are isolated from the respiratory tract or sinuses generally require treatment.
- Treatment frequently necessitates a combined approach that includes antifungal therapy, debridement of infected material and efforts to improve host defenses.

Table 1

Commonly used antimicrobials for MDR pathogens. (62, 112, 113)

Organism	1st line antimicrobials	Contraindication to transplant
MDR. P. aeruginosa	2 of the following: Carbapenem, piperacillin/tazobactam, cefepime, aminoglycosides, quinolones	Rare
Pan resistant P. aeruginosa	any of above +/- colistin	
B. cenocepacia	Ceftazidime, tetracyclines, trimethoprim-sulfamethoxazole, carbapenem	Probable
B. gladioli	Piperacillin, aminoglycosides, carbapenem, ciprofloxacin	Possible
A. baumannii	Carbapenem, colistin, tigecycline, ampicillin/sulbactam	Possible
M. abscessus	Clarithromycin + amikacin	Possible
	2nd line: Clarithromycin + imipenem or cefoxitin	
M. avium complex	Clarithromycin, ethambutol, rifampin	Rare
S. apiospermum	Voriconazole +/- echinocandin	Possible
S. prolificans	Voriconazole +/- echinocandin +/-terbinafine	Possible
A. terreus	Voriconazole +/- echinocandin	Rare

Table 2

Emerging Fungal Pathogens in SOT

Category	**Important species**
Zygomycetes	Species of *Rhizopus, Mucor, Absidia* and *Mycoladus*.
Dematiaceous molds	Species of *Ochroconis, Cladophialophora, Rhinocladiella, Bipolaris* and *Fonsecaea*
Scedosporium/Pseudallescheria	*S. apiospermum, S. auranticum* and *S. prolificans*
Fusarium	*F. solani* and *F. oxysporum*
Other filamentous fungi	Species of *Paecilomyces, Acremonium* and *Trichoderma*
Yeasts	Species of *Trichosporon, Rodotorula* and *Cryptococcus gattii*

Table 3

Clinical Characteristics of Emerging Fungi

Infection	Characteristic transplant recipient	Median time to infection	Typical sites of infection
Mucormycosis	All, but esp. liver, lung, kidney	Liver transplant: 2-3 months, others ~18-24 months	Respiratory tract/sinuses/CNS
Dematiaceous molds	All	≥18-24 months	Respiratory, sinuses/CNS, skin
Scedosporiosis	Lung	≥18-24 months	Respiratory tract
Fusariosis	All, but especially liver and lung	Range from 1-3 to ≥9 months	Respiratory tract sinus, skin
Paecilomyces	All, especially heart and lung	≥ 12-18 months	Respiratory tract, sinus, skin
Trichosporon	All, but especially kidney, Liver	Within first few weeks or ≥18-24 months	Endovascular/bloodstream surgical wounds