Allergy & Rhinology
Volume 10: 1–8

DOI: 10.1177/2152656719827253
journals.sagepub.com/home/aar
SAGE

Successful Treatment of *Scedosporium* Sinusitis in Two Lung Transplant Recipients: Review of the Literature and Recommendations for Management

Elisabeth H. Ference, MD, MPH[1,2], Bernard M. Kubak, MD[3], Paul Zhang, MD, MPH[1], and Jeffrey D. Suh, MD[4]

Abstract

Background: *Scedosporium* fungal infection is an emerging disease which is difficult to diagnose and treat. Patients undergoing lung transplant may be colonized prior to transplantation and are at risk for lethal allograft infection after transplantation.

Objectives: To identify and evaluate treatment options.

Methods: This study is a retrospective review of patients treated at a tertiary academic medical center from 2007 to 2017 with positive sinonasal cultures. A review of the literature was also performed to identify additional cases.

Results: Two lung transplant patients had a positive culture for *Scedosporium*. The literature search resulted in 37 citations, which yielded only 2 prior cases of *Scedosporium* paranasal sinus colonization or infection in lung transplant recipients. Three of the 4 patients had cystic fibrosis. Two of the patients were colonized before initial transplant, while 1 patient was colonized before subsequent transplant. Three of the 4 patients survived, and all 3 had disease isolated to their sinuses and lungs treated with sinus surgery, while the fourth had disseminated disease and did not undergo sinus surgery. All patients were treated with multiple antifungals due to resistance patterns. One surviving patient cleared both sinus and lung cultures in less than 1 month, while the other 2 surviving patients achieved negative cultures after a minimum of 6 months.

Conclusions: Surgery may be especially important in patients with fungal sinus colonization or infection before or after lung transplantation. Chronic sinusitis is an important source for persistent fungal colonization and reinfection of the allograft which could be removed with surgical debridement before causing highly morbid pulmonary disease.

Keywords

Scedosporium apiospermum, lung transplantation, endoscopic sinus surgery, *Lomentaspora prolificans*, *Scedosporium prolificans*, cystic fibrosis, isavulconazole, inhaled amphotericin

Introduction

Although *Aspergillus* species remain the most common fungi to cause invasive infection, *Scedosporium* species are an emerging, potentially life-threatening disease category which is difficult to diagnose and treat.[1–4] *Scedosporium apiospermum* (the asexual form of *Pseudoallescheria boydii*) and *Scedosporium prolificans* (recently renamed *Lomentaspora prolificans* but for the purpose of this article will be discussed as part of the *Scedosporium* genus) are the main human pathogens of the genus.[5] These fungi cause a broad range of disease: from transient colonization of the respiratory tract to

[1]Rick and Tina Caruso Department of Otolaryngology—Head and Neck Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California
[2]Department of Otolaryngology—Head and Neck Surgery, Children's Hospital Los Angeles, Los Angeles, California
[3]Department of Infectious Disease, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California
[4]Department of Head and Neck Surgery, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California

Corresponding Author:
Elisabeth H. Ference, Rick and Tina Caruso Department of Otolaryngology—Head and Neck Surgery, Keck School of Medicine, University of Southern California, 1540 Alcazar Street, Suite 204M, Los Angeles, CA 90033, USA.
Email: Ference@usc.edu

localized, extended, or hematogenously disseminated infections.[1,2] Diagnosis is difficult as *Scedosporium* has a similar appearance to other hyaline molds, such as *Aspergillus* or *Fusarium*, on pathology.[1,5,6] Culture is necessary both for identification and susceptibilities, but even on culture, the species is frequently not recognized due to its morphological plasticity.[1,5] Treatment of *Scedosporium* infections is especially challenging due to their resistance to many antifungals.[1–3] Reported mortality rates among transplant patients with any type of *Scedosporium* infection are between 58% and 73%, possibly higher in lung transplant recipients.[7,8]

Scedosporium species are found ubiquitously in the environment, including in soil and polluted water, and have a global distribution.[1,2] *Scedosporium* may grow inside poorly draining bronchi without causing invasive disease, and pulmonary fungal colonization among lung transplant recipients is a risk factor for subsequent invasive pulmonary infection.[2,9] Patients awaiting lung transplantation are commonly colonized with fungi as a result of their underlying disease, for example *Scedosporium* colonization is found in 5.7% to 10% of cystic fibrosis patients ranking second after *Aspergillus* among all hyaline molds.[4,9–11] However, little data exist in the literature regarding management of sinus, separate from pulmonary, colonization, or infection in lung transplant recipients. Of concern, the sinuses are poorly penetrated by systemic antifungal therapy and may act as a reservoir for subsequent allograft colonization or infection. Therefore, we reviewed cases of *Scedosporium* sinusitis at a tertiary care institution and performed a systematic review of the literature in order to detail treatment strategies and outcomes.

Patients and Methods

Institutional review board approval was obtained from the University of California, Los Angeles. A query of the microbiology database was performed for all patients with *Scedosporium* on sinus culture or nasal drainage culture from 2007 to 2017. A retrospective chart review was performed to determine age, gender, site of infection, underlying immune status, past medical history, past surgical history, presenting symptoms, involved sinuses, susceptibilities and resistance patterns, medical and surgical treatment, and outcome.

The PubMed database was searched using the keywords representing all previous designations of the fungi now classified within the *Scedosporium* genus: *Scedosporium, Scedosporium apiospermum, Lomentaspora prolificans, Pseudallescheria boydii*, *Verticillium graphii*, *Allescheria*, *Glenospora*, *Indiella americanus*, *Acremoniella lusii*, *Petriellidium*, *monosporium*, and "sinusitis." Search results were reviewed for cases with a history of lung transplantation. The citations of all relevant papers were also reviewed for additional articles.

Results

Two patients at the tertiary academic center during a 10-year period had a positive culture for *Scedosporium* and a history of lung transplantation. All cases were diagnosed within the last 3 years. The literature search resulted in 37 citations, which yielded only 2 prior cases of *Scedosporium* paranasal sinus colonization or infection in lung transplant recipients (Tables 1 and 2).[4,12] The 2 patients from the retrospective chart review and the 2 patients from the literature review were combined for the following analysis.

Three patients had a history of cystic fibrosis. Three of the 4 patients had *S. apiospermum* infection, while 1 had *L. prolificans*. All patients with reported results had other organisms on cultures. Two of the patients were colonized before initial transplant, while 1 patient was colonized before subsequent transplant. All surviving patients had disease isolated to their sinuses and lungs treated with sinus surgery, while the fourth had disseminated disease and did not undergo sinus surgery. All patients were treated with multiple antifungals due to resistance patterns. One surviving patient cleared both sinus and lung cultures in less than 1 month, while the other 2 surviving patients had a prolonged clinical course with negative cultures achieved after a minimum of 6 months.

Case 1

A 40-year-old man with a history of cystic fibrosis, 4 prior sinus surgeries, and bilateral lung transplant 3 years prior complicated by tuberculosis and rejection with declining lung function presented with nasal congestion, postnasal drip, facial pain/pressure, and mucopurulent discharge. Sinus cultures grew *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, and *L. prolificans* (Table 3) which were resistant to all antifungals. He had previously been on posaconazole and was started on posaconazole and anidulafungin after sensitivities resulted. He underwent bilateral endoscopic sinus surgery 1 month after diagnosis with *Scedosporium* as lung function allowed (Figure 1). Postoperatively, he was started on daily dilute acetic acid via irrigation. Repeat sinus cultures 2 months after surgery again grew *L. prolificans*, and 3 months after surgery, he developed respiratory *L. prolificans*. He developed worsening lung function and underwent a repeat double lung transplantation 4 months after sinus surgery; postoperatively, he was discharged on intravenous anidulafungin and oral voriconazole with repeat respiratory and sinus cultures positive for *L.*

Table 1. Demographics, Past Medical History, Culture Results, and Transplant Status of Cases.

Patient Number.	Sex	Age (Year)	Cystic Fibrosis	Diabetes	Organism	Other Organisms on Culture	Length of Time From Scedosporium Sinus Culture to Positive Lung Culture (Months)	Disseminated Beyond Sinopulmonary Tract	Colonized Before Lung Transplant	Length of Time Since Transplant to Positive Sinus Culture	Source
1	M	30–50	Yes	No	*Lomentaspora prolificans*	Stenotrophomonas Maltophilia, Pseudomonas aeruginosa	4.5	No	Colonized before second but not first transplant	14 Years, then retransplant 5 months after culture	Current study
2	F	30–50	No	Yes	*Scedosporium apiospermum*	Pseudomonas aeruginosa, Staphylococcus aureus	−3.5	No	No	5 Months	Current study
3	F	<30	Yes	No	*S. apiospermum*	Unknown	−24	Skin, endopthalmitis, chest wall cellulitis, vertebral osteomyelitis,	Yes	1 Month	Sahi et al.[12]
4	F	<30	Yes	No	*S. apiospermum*	Aspergillus fumigatus	−11.5	No	Yes	11 Month	Hartmann et al.[14]

Table 2. Surgical and Medical Treatment with Outcomes of Cases.

Patient Number	Number of Sinus Surgeries After Culture	Number of Washout-Only Procedures	Initial Medical Treatment	Subsequent Medical Treatment	Length of Time Until Last Positive Sinus Culture (Months)	Length of Time Until Last Negative Lung Culture (Months)	Survival After Diagnosis	Source
1	1	3	Voriconazole, Caspofungin, Terbinafine	Posaconazole, Anidulafungin, dilute acetic acid irrigation	6	8	Alive	Current study
2	3	0	Posaconazole	Isavulconazole, Terbinafine, Amphotericin irrigation	1	No further + cultures	Alive	Current study
3	0	0	Voriconazole	Voriconazole, Caspofungin, Terbinafine, Pentamidine, Amphotericin	Deceased	Deceased	14 Months	Sahi et al.[12]
4	1	0	Voriconazole	Posaconazole, Caspofungin, Voriconazole lavage	Unknown	24	Alive	Hartman et al.[14]

Table 3. Sensitivities of Cases.

Antifungal	Case 1: *Lomentaspora prolificans*		Case 2: *Scedosporium apiospermum*	
		Interpretive Criteria		Interpretive Criteria
Amphotericin	>16 μg/mL	None available	1 μg/mL	None available
Anidulafungin	8 μg/mL	Not susceptible	4 μg/mL	None available
Caspofungin	8 μg/mL	Not susceptible	8 μg/mL	None available
Fluconazole	>64 μg/mL	Resistant	16 μg/mL	None available
Isavulconazole			4 μg/mL	None available
Itraconazole	>16 μg/mL	Resistant		
Posaconazole	>16 μg/mL	None available	1 μg/mL	None available
Terbinafine	>2 μg/mL	None available	2 μg/mL	None available
Voriconazole	>16 μg/mL	Resistant	0.5 μg/mL	None available

prolificans. During this time period, he continued to have symptoms consistent with chronic rhinosinusitis. He underwent sinus washout procedures in the operating room 2 and 3 months after lung transplantation with amphotericin solution. He developed photosensitivity and so was switched from voriconazole to posaconazole. His last positive cultures were 8 months after his initial culture, and, therefore, his anidulafungin was stopped 1 month after his negative culture. He has been maintained on daily oral posaconazole for the last 4 years with no further positive bronchial or sinus cultures. His sinus symptoms improved after treatment of the fungus.

Case 2

A 35-year-old woman with a history of bilateral lung transplant for Sweet's Syndrome was found to have *S. apiospermum* on bronchial culture 2 months after transplant and on sinus culture 5 months after transplant (Table 3). She was initially treated with posaconazole after bronchial culture and then switched to voriconazole and inhaled amphotericin. She underwent sinus surgery for symptoms of nasal obstruction, postnasal drainage, loss of smell, and facial pressure and operative cultures were positive for *S. apiospermum*. Three weeks after surgery, she presented with right-sided retro-orbital and temporal pain, with magnetic resonance imaging concerning for retro-maxillary fat stranding and bedside cultures concerning for continued fungal infection (Figure 2). She returned to the OR for right-sided endoscopic medial maxillectomy with biopsy of the bone of the posterior maxillary wall. Pathology showed the posterior maxillary bone with small aggregates of degenerative fungal hyphae (unable to be further speciated on pathology) without invasion of the pterygopalatine fossa tissue, and operative cultures were negative. She was switched to isavulconazole and terbinafine and with inhaled amphotericin based on culture results and given intravenous immunoglobulin and filgastrim due to her underlying immunodeficiency. All subsequent cultures were negative, so she was treated

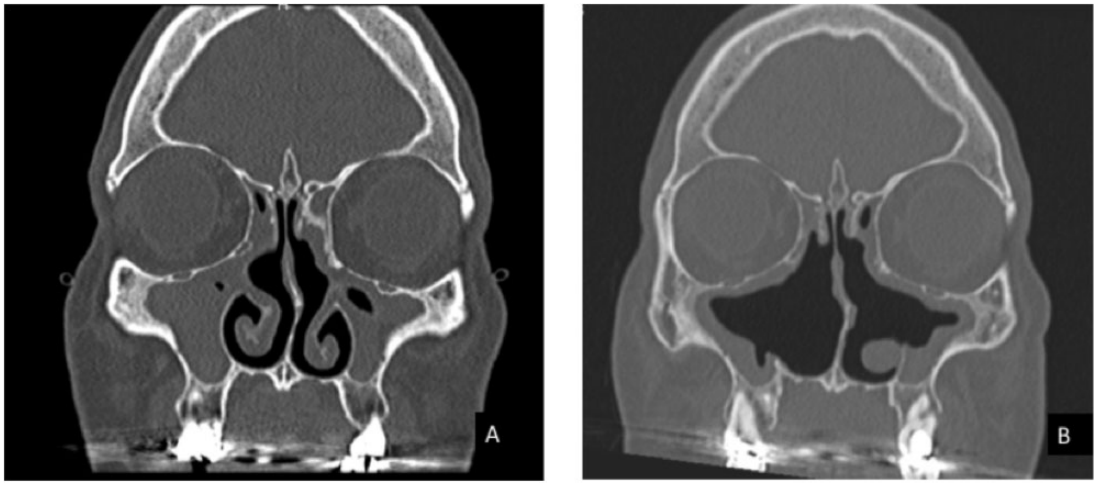

Figure 1. Coronal CT of sinuses of Patient 1. A, At the time of diagnosis with sinus *Scedosporium* (note near complete opacification of bilateral maxillary sinuses) and after (B) bilateral medial maxillectomies and Draf IIB procedures with the improvement in aeration and eventual negative cultures.

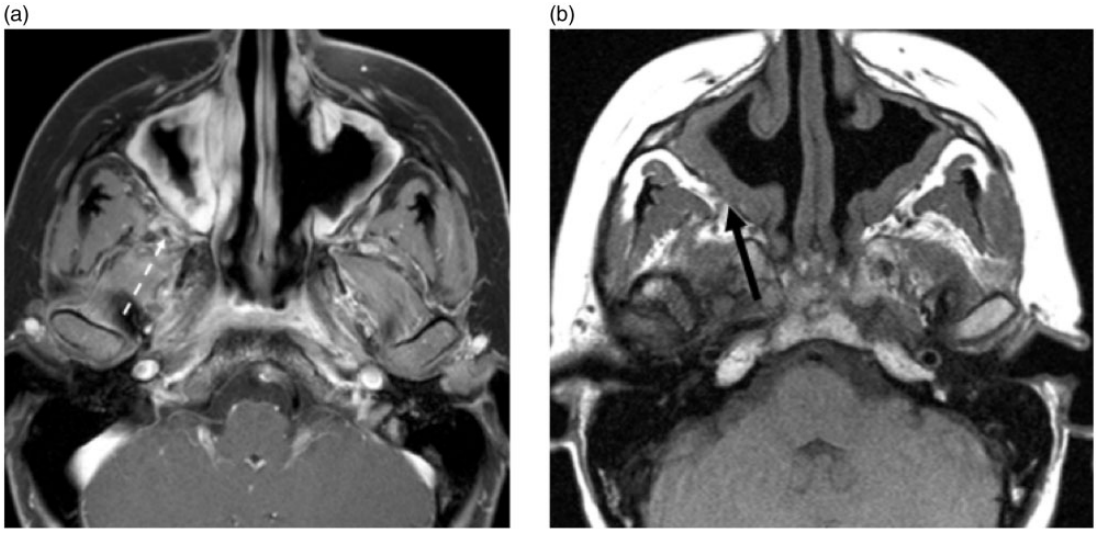

Figure 2. Axial magnetic resonance imaging of orbits of Patient 2. A, T1 fat saturated postcontrast at the time of diagnosis with sinus *Scedosporium* with dashed area highlighting concern for invasion into the retromaxillary space and (B) T1 without contrast 4 months later after right medial maxillectomy with black arrow highlighting area of posterior maxillary wall bone removal.

with 2 months of isavulconazole and inhaled amphotericin before being switched to maintenance posaconazole.

Discussion

Outcome of *Scedosporium* infection depends on infecting strain, location of infection, feasibility of surgical debridement, choice of antifungal therapy, and underlying immune status of the patient. Overall mortality is between 58% and 73% in organ transplant patients and 88% in patients with disseminated disease.[7,9,14] The invasive form of *Scedosporium* sinusitis is mostly limited to patients with hematologic malignancy, neutropenia, uncontrolled diabetes, or immunosuppression, although it has been occasionally reported in patients without underlying disorders.[1,6,13,15–18] It is necessary to distinguish between sinus colonization and invasive fungal infection, such as in Case 2. Surgical debridement and reducing immunosuppression when feasible are key elements in the treatment strategy of invasive fungal sinusitis, in addition to combination antifungal therapy tailored to minimum inhibitory concentration (MIC) results.

When susceptibility testing reveals no good antifungal options in a symptomatic, immunosuppressed individual, such as with Case 1, antifungal agents are

maintained, while management of the infection and underlying condition is reevaluated. Antifungal therapy is generally continued until all signs and symptoms, including radiographic and endoscopic signs, of infection have resolved. For immunocompromised patients with evidence of sinonasal tissue invasion, antifungal prophylaxis will continue for years.[3] As in reports of *Scedosporium* infections in other anatomic sites, other opportunistic pathogens, such as *Aspergillus* and *Pseudomonas*, were cultured in all 3 patients with culture results.[13] Therefore, bacterial cultures should be performed along with fungal cultures, and all opportunistic pathogens were treated appropriately.

Human infection results from the inhalation of spores from the environment into the lungs or paranasal sinuses or through direct inoculation, such as skin puncture.[1,2] Positive culture of the respiratory tract may simply represent colonization; however, both of the cases at our institution presented with symptoms of sinus disease as well as imaging and endoscopic findings consistent with infection.[4,9] Only 1 of the patients had evidence of invasion into bone on pathology and neither patient had evidence of angioinvasion on pathology, which differs from the classic pathology findings in sinonasal mucormycosis. Only the second patient had imaging evidence of direct spread of the fungus outside of the sinuses. Both patients had positive bronchial in addition to sinus cultures, and fungal lung infection was believed to have hastened the destruction of the first patient's allograft requiring repeat transplant.

The literature currently contains few cases regarding the management of *Scedosporium* sinus infections in organ transplant, especially lung transplant, patients. Multiple case series have discussed pulmonary infections or disseminated infections (without discussion of sinus involvement) in lung transplant patients.[19–21] Some series have discussed pulmonary colonization of patients before transplant, with or without later development of lung infection, but have not addressed the sinuses.[8,9,22] We could find only 2 cases in the literature of patients who were managed for *Scedosporium* sinus colonization and infections after lung transplant[4,12] and 2 patients who developed *Scedosporium* sinusitis after other solid organ transplant.[7,8]

Surgical debridement, whenever feasible, can help decrease the burden of organism present, improve sinus drainage, allow access for topical medications, and remove devitalized tissue in cases of angioinvasion.[7,14] The extent of surgery should be tailored to the extent of the disease, with more aggressive surgical approaches reserved for patients with evidence of tissue invasion. Antifungal treatment can be difficult as azoles and amphotericin have varying levels of activity against *S. Apiospermum*, with extended spectrum azoles (such as voriconazole) typically having the lowest mean inhibitory concentration.[3] *L. prolificans*, as with Case 1, is resistant to most antifungal agents.[3] In some animal studies, combination therapy for *L. prolificans* appears to be more effective than monotherapy, including in immunosuppressed mice.[23,24] Of note for prolonged treatment, chronic voriconazole prophylaxis has been associated with an increased risk of squamous cell carcinoma in solid organ transplant patients and so the risks and benefits must be weighed carefully.[25]

Surgery may be especially important in patients with fungal sinus colonization or infection before or after lung transplantation.[4] For example, patients with cystic fibrosis often have chronic sinusitis predating lung transplant and have a high rate of pulmonary *Scedosporium* colonization, but the incidence of sinus colonization is unknown.[4,9–11] Chronic sinusitis may be an important source for persistent fungal colonization and reinfection of the allograft which could be removed with surgical debridement before causing highly morbid pulmonary disease.[4] Surgical intervention has previously been shown to have good curative effect in *S. apiospermum* sinusitis in immunocompetent patients and those compromised by hematologic malignancies, diabetes, and AIDS.[6] After double lung transplantation, there is a high mortality, up to 91%, in patients with *Scedosporium* pulmonary infections.[8,9] Early onset pulmonary *Scedosporium* infections following transplantation are associated with increased mortality compared to infection after the first year of transplant.[9] Given the high mortality and the possible benefits of surgical debridement, sinus surgery should be considered in combination with antifungal therapy in order to remove a reservoir of disease.

Our study has the limitations common to retrospective, small case series. Despite these shortcomings, the data are a useful addition to the published literature because of the extremely limited number of transplant recipients with sinus disease previously reported. *Scedosporium* is an emerging organism.[1–3] All sinonasal cases at our institution, both among immunocompetent and immunocompromised patients, were diagnosed within the last 3 years. Insights such as the usefulness of sinus surgery for debridement of active infection and removal of a reservoir of fungal colonization are likely to be broadly relevant to transplant teams and otolaryngologists managing these difficult cases. Further reports on transplant recipients with *Scedosporium* colonization or sinus infection will be valuable for expanding on our findings and offering prospective data.

Conclusion

Surgery may be especially important in patients with fungal sinus colonization or infection before or after lung transplantation. Chronic sinusitis is an important

source for persistent fungal colonization and reinfection of the allograft which could be removed with surgical debridement before causing highly morbid pulmonary disease.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by our institutional review board.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

ORCID iD

Elisabeth H. Ference http://orcid.org/0000-0002-4177-6716

References

1. Guarro J, Kantarcioglu AS, Horré R, et al. *Scedosporium apiospermum*: changing clinical spectrum of a therapy-refractory opportunist. *Med Mycol*. 2006;44(4):295–327.
2. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. *Clin Microbiol Rev*. 2008;21(1):157–197.
3. Kubak BM, Huprikar SS. Emerging & rare fungal infections in solid organ transplant recipients. *Am J Transplant*. 2009;9(s4):S208–S226.
4. Hartmann C, Müller C, Weißbrodt H, et al. Successful prevention of scedosporiosis after lung transplantation in a cystic fibrosis patient by combined local and systemic triazole therapy. *Med Mycol Case Rep*. 2013;2:116–118.
5. Arif S, Perfect JR. Emergence of the molds other than Aspergillus in immunocompromised patients. *Clin Chest Med*. 2017;38(3):555–573.
6. Bates DD, Mims JW. Invasive fungal sinusitis caused by *Pseudallescheria boydii*: case report and literature review. *Ear Nose Throat J*. 2006;85(11):729–737.
7. Husain S, Munoz P, Forrest G, et al. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. *Clin Infect Dis*. 2005;40(1):89–99.
8. Castiglioni B, Sutton DA, Rinaldi MG, Fung J, Kusne S. *Pseudallescheria boydii* (Anamorph *Scedosporium apiospermum*). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. *Medicine (Baltimore)*. 2002;81(5):333–348.
9. Johnson LS, Shields RK, Clancy CJ. Epidemiology, clinical manifestations, and outcomes of *Scedosporium* infections among solid organ transplant recipients. *Transpl Infect Dis*. 2014;16(4):578–587.
10. Cimon B, Carrère J, Vinatier JF, Chazalette JP, Chabasse D, Bouchara JP. Clinical significance of *Scedosporium apiospermum* in patients with cystic fibrosis. *Eur J Clin Microbiol Infect Dis*. 2000;19(1):53–56.
11. Sedlacek L, Graf B, Schwarz C, Albert F, Peter S, Würstl B, et al. Prevalence of *Scedosporium* species and *Lomentospora prolificans* in patients with cystic fibrosis in a multicenter trial by use of a selective medium. *J Cyst Fibros*. 2015;14(2):237–241.
12. Sahi H, Avery RK, Minai OA, et al. *Scedosporium apiospermum* (*Pseudoallescheria boydii*) infection in lung transplant recipients. *J Hear Lung Transplant*. 2007;26(4):350–356.
13. Rodriguez-Tudela JL, Rodriguez-Tudela JL, Berenguer J, et al. Epidemiology and outcome of *Scedosporium prolificans* infection, a review of 162 cases. *Med Mycol*. 2009;47(4):359–370.
14. Cooley L, Spelman D, Thursky K, Slavin M. Infection with *Scedosporium apiospermum* and *S. prolificans*, Australia. *Emerg Infect Dis*. 2007;13(8):1170–1177.
15. Morgan MA, Wilson WR, Neel HB, Roberts GD. Fungal sinusitis in healthy and immunocompromised individuals. *Am J Clin Pathol*. 1984;82(5):597–601.
16. Salitan ML, Lawson W, Som PM, Bottone EJ, Biller HF. Pseudallescheria sinusitis with intracranial extension in a nonimmunocompromised host. *Otolaryngol Neck Surg*. 1990;102(6):745–750.
17. Gluckman SJ, Ries K, Abrutyn E. Allescheria (Petriellidium) boydii sinusitis in a compromised host. *J Clin Microbiol*. 1977;5(4):481–484.
18. Thiagalingam S, Fernando GT, Tan K, O'Donnell BA, Weeks K, Branley M. Clinical Case Notes. Orbital apex syndrome secondary to Pseudallescheria boydii fungal sinusitis in an immunocompetent patient. *Clin Exp Ophthalmol*. 2004;32(5):545–547.
19. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis*. 2010;12(3):220–229.
20. Musk M, Chambers D, Chin W, Murray R, Gabbay E. Successful treatment of disseminated *Scedosporium* infection in 2 lung transplant recipients: review of the literature and recommendations for management. *J Heart Lung Transplant*. 2006;25(10):1268–1272.
21. Morio F, Horeau-Langlard D, Gay-Andrieu F, et al. Disseminated *Scedosporium*/*Pseudallescheria* infection after double-lung transplantation in patients with cystic fibrosis. *J Clin Microbiol*. 2010;48(5):1978–1982.
22. Rolfe NE, Haddad TJ, Wills TS. Management of *Scedosporium apiospermum* in a pre- and post-lung

transplant patient with cystic fibrosis. *Med Mycol Case Rep*. 2013;2:37–39.
23. Bocanegra R, Najvar LK, Hernandez S, McCarthy DI, Graybill JR. Caspofungin and liposomal amphotericin B therapy of experimental murine Scedosporiosis. *Antimicrob Agents Chemother*. 2005;49(12):5139–5141.
24. Rodriguez MM, Calvo E, Serena C, Marine M, Pastor FJ, Guarro J. Effects of double and triple combinations of antifungal drugs in a murine model of disseminated infection by *Scedosporium prolificans*. *Antimicrob Agents Chemother*. 2009;53(5):2153–2155.
25. Kolaitis NA, Duffy E, Zhang A, et al. Voriconazole increases the risk for cutaneous squamous cell carcinoma after lung transplantation. *Transpl Int*. 2017;30(1):41–48.