Scedosporiosis in patients with acute leukemia: a retrospective multicenter report

Morena Caira,[1] Corrado Girmenia,[4] Caterina Giovanna Valentini,[1] Maurizio Sanguinetti,[2] Alessandro Bonini,[3] Giovanni Rossi,[1] Luana Fianchi,[1] Giuseppe Leone,[1] and Livio Pagano[1]

From the [1]Istituto di Ematologia, Università Cattolica S. Cuore, Roma; the [2]Istituto di Microbiologia, Università Cattolica S. Cuore, Rome; the [3]Struttura Complessa Ematologia, Azienda Ospedaliera ASMN Reggio Emilia; and the [4]Dipartimento di Biotecnologie Cellulari ed Ematologia, Università di Roma "La Sapienza", Italy

ABSTRACT

We retrospectively analyzed 542 proven/probable mould infections registered, in the course of 2 studies, in 8,633 patients with acute leukemia, focusing on scedosporiosis. We aimed to define scedosporiosis incidence and mortality rate over a 15-year period. Only 5 cases of scedosporiosis were identified, all of them involving patients with acute myeloid leukemia (AML). We also reviewed all cases of *Scedosporium spp.* infections in acute leukemia reported to date in the international literature. The 52 cases analyzed confirmed that acute myeloid leukemia is the category with the highest risk of scedosporiosis.

Clinical features of scedosporiosis were extremely variable and closely related to patient immune status. Infection disseminated to multiple sites in a very high percentage of patients and outcome was confirmed to be very poor. In our surveys all patients died, in spite of Amphotericin B compounds or voriconazole administration. Our review of literature found scedosporiosis attributable mortality rate (AMR) to be 77%.

In conclusion, scedosporiosis, although extremely rare, represents a big problem for clinicians because of its aggressive clinical presentation and the lack of an effective therapy. New drugs with *in vitro* activity against *Scedosporium spp* (voriconazole, posaconazole) should be considered. However, their clinical activity should be more widely demonstrated.

Key words: fungal infection, *scedosporium*, *pseudallescheria*, epidemiology, acute leukemia

Citation: Caira M, Girmenia C, Valentini CG, Sanguinetti M, Bonini A, Rossi G, Fianchi L, Leone G, Pagano L. Scedosporiosis in patients with acute leukemia: a retrospective multicenter report. Haematologica. 2008 Jan; 93:(1)104-110. DOI: 10.3324/haematol.11740

Introduction

Scedosporium spp is a saprophyte mould with worldwide distribution. It is usually isolated from soil, polluted water or sewage. In rare cases it can be responsible for serious fungal infections, particularly in immunocompromised hosts. *S. apiospermum* (anamorphic form *Pseudallescheria boydii*) and *S. prolificans* are the two major pathogens responsible for human infections.[1] Despite the growing interest in all fungal infections, little is known about its current epidemiology. Therefore, a retrospective study was conducted to increase our understanding of the epidemiological, clinical and therapeutic aspects of this infection. We will report hereinafter all cases of scedosporiosis we observed over a 15-year period in a large series of patients with acute leukemia, enrolled in two different multicenter surveys in Italy. We also reviewed all cases of scedosporiosis in acute leukemia patients reported so far in the international literature.

We retrospectively analyzed all new cases of mould infections registered in patients with AL between January 1988 and December 1997 and between January 1999 and December 2003 in 2 epidemiological multicenter studies.[2-3] The consensus criteria proposed by the EORTC/MSG were used to define invasive fungal infections (IFIs)[4] and the analysis was limited to infections classifiable as *proven* or *probable*. Every centre which had experienced a *Scedosporium spp* infection was invited to fill in a form, providing information on the episode.

The following patients' characteristics were taken into consideration: sex and age, clinical signs, symptoms and site of infection, laboratory data (i.e. neutropenia, neu-

Manuscript received May 17, 2007. Manuscript accepted October 17, 2007.
Correspondence: Morena Caira, M.D., Istituto di Ematologia, Università Cattolica del Sacro Cuore, Largo Francesco Vito, I-00168 Rome, Italy. E-mail: morenacaira@yahoo.it

trophil count $<1\times10^9$/L), microbiologic isolates, treatment received (prophylaxis and therapy), outcome, cause of death, autopsy findings. Death due to scedosporiosis was defined when death occurred in the presence of microbiologic, histologic, or clinical evidence of active fungal infection. In addition, a MEDLINE-based search was performed to identify all reported cases of scedosporiosis in acute leukemia from January 1976 to December 2006. The search terms used were *Scedosporium*, *Pseudallescheria*, *acute leukemia*. Other reports were taken from references of available works. For each reported case, the following data were collected: age, sex, underlying hematologic malignancy, IFI risk factors, geographic location, identified etiologic agent, involved sites, symptoms, diagnostic procedures, antifungal prophylaxis and treatment, and outcome.

We performed univariate (χ^2 test) analysis to identify variables that could predict patients' death. The parameters we tested as independent variables were: age, sex, type of underlying acute leukemia, dissemination of infection, detected etiologic strain (*S. apiospermum vs S. prolificans*) and certainty of diagnosis (proven *vs.* probable IFI).

Retrospective analysis of cases in Italy

During the 15-year period, a total of 8,633 patients with a newly diagnosed acute leukemia (6,303 myeloid and 2,330 lymphoid) were admitted to the participating centers for treatment other than hematopoietic stem cell transplantation. We collected a total of 542 proven/probable mould infections (252 cases in the first study and 290 in the second) for an overall incidence of 6.3% in acute leukemia (5.7% in the first study and 6.9% in the second). Possible cases of IFI were excluded. Data pertaining to the two study populations are summarized in Table 1.

Among all mould infections, only 5 cases (5/542, 0.9%) of proven scedosporiosis were diagnosed in 3 different centres, with an incidence of 0.08% (6/6,603) in acute leukemia. *S. apiospermum* was responsible for all 5 cases. Patients' epidemiologic data have been summarized in Table 2. Acute myeloid leukemia (AML) was the underlying hematologic malignancy in all cases. Only one patient developed scedosporiosis in an early stage of the hematologic disease. The remaining 4 were resistant to (3 pts, 60%) or relapsed after prior cytotoxic treatments. All patients had chemotherapy induced severe neutropenia at onset of IFI (mean duration before the onset of IFI: 9 days, range 4-13 days).

Disseminated disease was the most common clinical presentation. Non-specific reported symptoms were fever, cough, and pain. The lung was the most frequently affected site (75% of patients). Other involved sites were sinuses, skin and orbit. Fungemia occurred in 2 patients.

According to the EORTC/MSG criteria, all infections were classified as *proven*. In two patients histological data were acquired only in the *post mortem* phase.

Amphotericin B (AmB) was administered in 4 patients, in its deoxycolate (D-AmB) (1 patient) or liposomal (L-AmB) (3 patients) formulation. The remaining patient received voriconazole. This triazole was also administered as a second line therapy in 1 patient, after failure with L- AmB treatment.

Outcome was dramatically poor and all patients died: four of them died due to fungal infection while the fifth patient improved after a salvage treatment with voriconazole but died afterwards for causes other than scedosporiosis. The mean survival from the onset of infection was 17 days. Treatment data are reported in Table 2.

Literature review

The literature search yielded 29 reports of 52 cases of Scedosporium spp infection over the last 30 years in patients affected by acute leukemia.[5-33] Cases occurred after stem cell transplant procedures and those published without complete information were excluded. Characteristics of 52 previously published patients are listed in Table 3. Mean age was 47 years (range 3-79), and male/female *ratio was* 1.9:1. Lineage was not specified in 13 cases, otherwise patients were mostly affected by myeloid leukemia (25/39 cases, 64%) and almost all of them were neutropenic at the onset of infection. Thirty-seven cases (71%) were attributed to *S. prolificans.*

The geographic distribution of cases was almost exclusively restricted to Spain, with the exception of 8 and 6 cases reported from Australia and USA respectively. Only sporadic cases were found in the other countries. It is worth noticing that almost all cases due to *S. prolificans* occurred in Spain (27/37, 73%), while *S. apiospermum* showed a worldwide distribution.

In the majority of cases (43/52, 83%) diagnosis was proven, but in some of them (11/ 52, 21%) was only obtained in the *post mortem* phase.

Dissemination of infection (defined as involvement of 3 or more organs) occurred in 40 cases (77%). In particular, scedosporiosis was already disseminated at the onset of symptoms in 14 patients (27%). Other frequently involved sites in the early phase were lung (14/52, 27%), skin (12/52, 23%) and central nervous system (7/52, 13%). Endophthalmitis was the first clinical manifestation of scedosporiosis in 4 out of 52 patients (8%).

The fungal pathogen was isolated from the blood in a large number of patients (29/52, 56%). Only in few cases was it cultured from bronchoalveolar lavage or cerebrospinal fluid. Except for 4 patients, none had received systemic antifungal prophylaxis. In 1 patient, infection occurred during D-AmB administration as

Table 1. Scedosporiosis observed among moulds infections in 2 cohorts of patients with acute leukemia.

	N. of AL patients	*N. of identified moulds infections (incidence %)*	*N. of scedosporiosis (% of moulds)*
1° study (Pagano *et al.*, 2001)	4448	252 (5.7%)	2 (0.8%)
AML	3291	193 (5.9%)	2 (0.9%)
ALL	1157	59 (5.1%)	0
2° study (Pagano *et al.*, 2006)	4185	290 (6.9%)	3 (1%)
AML	3012	239 (7.9%)	3 (1.2%)
ALL	1173	51 (4.3)	0
Total	8633	542 (6.3%)	5 (0.9%)

AL: acute leukemia; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia.

prophylaxis. Five patients died before starting a targeted antifungal therapy. D-AmB was the most frequently employed drug as first line treatment, alone (44%) or in combination with azoles (17%). Outcome was extremely poor: 40 patients (77%) died, 7 of them in spite of a salvage antifungal therapy. The presence of disseminated infection predicted a lower survival (AMR 95% *vs*. 23%, *p*-value <0.0001).

Other variables which influenced outcome of infection were *S. prolificans* as detected etiologic agent (AMR 89% *vs* 47%, *p*-value <0.001) and the certainty of diagnosis (AMR 88% *vs* 12%, *p*-value <0.0001).

Some successful cases, after the administration of the new triazoles voriconazole and posaconazole as salvage therapy, have been reported.[21,31]

Since the first case of scedosporiosis reported in acute leukemia in 1977,[32] hematologists have shown a growing interest in this pathogen, particularly over the last decade. Both our literature review and our case series demonstrated that, among patients affected by hematologic malignancies, those affected by AML are at the highest risk, usually during a period of chemotherapy induced severe neutropenia. However, our retrospective studies in Italy showed that the incidence rate still seems to be very low, even in this category of patients. Despite the limitations of its retrospective approach, this study has collected and made available a large amount of relevant information on all the patients admitted to the participating hematology departments during the study period.

Thanks to the long duration of our survey, we were able to register any change in the IFI incidence rate over the years. As diagnosis of infections has gradually improved, the absolute number of IFI has increased.[3]

By contrast, the incidence of scedosporiosis remained constantly very low and did not show any

Table 2. Epidemiological data of patients with scedosporiosis collected in 2 retrospective multicenter surveys in Italy.

	Cases (%)
Underlying hematologic malignancy	
AML	5 (100%)
Phase of acute leukemia	
Diagnosis	1 (20%)
Resistant disease	3 (60%)
Relapsed disease	1 (20%)
Risk factors	
Steroids	3 (60%)
CVC	5 (100%)
Neutropenia	5 (100%)
Involved sites at onset*	
Lung	2 (40%)
Lung + blood + skin	1 (20%)
Lung + blood	1 (20%)
Sinus + skin + orbit	1 (20%)
Previous fungal infection	0
Antifungal prophylaxis	
none	3 (60%)
topical	2 (40%)
1st line treatment	
L-AmB (3 mg/Kg)	3 (60%)
- treatment mean duration (days)	10
D-AmB (1mg/Kg)	1 (20%)
- treatment mean duration (days)	14
Voriconazole (6-4mg/Kg)	1 (20%)
- treatment mean duration (days)	9
Mean survival in days (range)	17 (7-37)
Cultured from	
skin biopsy specimens + sputum	1 (20%)
BAL + blood	1 (20%)
BAL + blood + skin biopsy specimens	1 (20%)
autopsy specimens	2 (40%)

*AML: acute myeloid leukemia; CVC: central venous catheter; CNS: central nervous system; D-AmB: deoxycolate amphotericin B; L-AmB: liposomal amphotericin B; BAL: bronchoalveolar fluid. *all patients presented a subsequent dissemination of infection.*

temporal clustering. These data do not match the recent report by Lamaris *et al.*[34] In their experience, the incidence rate in cancer patients significantly increased from 0.82 cases per 100,000 patients-inpatient days in the period 1993-1998 to 1.33 in the period 1999-2005. The lack of evidence of nosocomial transmission has led the authors to relate these data to improvements in microbiologic diagnosis or to the selection pressure produced by new drugs particularly active against *Aspergillus spp*.

In our literature review, a spatial clustering of cases was evident. Whether the geographic distribution represents a particular ecologic characteristic of the fungus is still to be determined. The proportion of patients with a proven diagnosis was as high in our series (100%) as in the literature data (83%). However, our analytical method does not allow us to firmly conclude that our diagnostic ability has improved, since only a small proportion of cases are published.

We did not make a proven diagnosis *in vivo* in every patient and this could explain the low incidence observed. Epidemiologic studies about *Scedosporium* have been always overshadowed by diagnostic limits and the species is often mistakenly identified as *Aspergillus spp*.[1] Some cases classifiable as breakthrough infections occurring during AmB treatment, have been recently reported[35] but only one of the 52

Table 3A. Literature review: 52 reported cases in acute leukemia (present 5 cases were excluded).

	Cases (%)	*Exitus (AMR)*
Population	52 (100%)	40 (77%)
Median age (range)	47 (3-79)	
Sex		
Male	34 (65%)	25 (73%)
Female	18 (35%)	15 (83%)
Underlying hematologic malignancy		
AML	25 (64%)	20 (80%)
ALL	13 (33%)	8 (61%)
Multilineal	1(3%)	1 (100%)
AL	13	11 (85%)
Involved sites at onset		
Disseminated	14 (27%)	14 (100%)
Lung	11 (21%)	9 (82%)
Skin	9 (17%)	5 (56%)
CNS	7 (13%)	4 (57%)
Orbit	4 (8%)	3 (75%)
Skin + lung	3 (6%)	2 (67%)
Bone	2 (4%)	1 (50%)
Blood	2 (4%)	2 (100%)
Cultural positivity		
Blood	29	28 (100%)
BAL	4	3 (75%)
CSF	3	3 (100%)
Articular liquor	1	1 (100%)
Vitreous humor	2	2 (100%)
Biopsy specimens[1]	19	14 (74%)
Dissemination (+ fungemia)		
Yes[2]	40 (75%)	37 (95%)
No	12 (25%)	3 (23%)
Detected etiologic agent		
S. apiospermum[3]	15 (29%)	7 (47%)
S. prolificans	37 (71%)	33 (89%)

Table 3B. Literature review: 52 reported cases in acute leukemia (present 5 cases were excluded).

	Cases (%)	*Exitus (AMR)*
Certainty of diagnosis		
Proven	43 (83%)	38 (88%)
Probable	9 (17%)	2 (12%)
Time of diagnosis		
In vivo	41 (79%)	29 (71%)
Post mortem	11 (21%)	
Antifungal prophylaxis		
Not administered	48 (92%)	38 (79%)
D-AmB	1 (2%)	0
Fluconazole	2 (4%)	1 (50%)
Itraconazole	1 (2%)	1 (100%)
1st line treatment		
None	5 (10%)	5 (100%)
LF-AmB	8 (17%)	6 (75%)
D-AmB	23 (49%)	20 (87%)
Azoles[4]	5 (11%)	3 (60%)
D-AmB + 5-FC	2 (4%)	2 (100%)
D-AmB + azoles[5]	9 (19%)	6 (67%)
2nd line treatment		
L-AmB	2	2 (100%)
L-AmB + voriconazole	1	1 (100%)
L-AmB + itraconazole	1	0
Itraconazole	4	3 (75%)
Voriconazole	1	1 (100%)
Posaconazole	1	0
Voriconazole + terbinafine	1	0
Country		
Spain[6]	28 (54%)	24 (86%)
Australia	8	7 (88%)
USA	6	3 (50%)
Italy	1	1 (100%)
Others[7]	9	5 (56%)

AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; AL: acute leukemia (lineage not specified); CNS: central nervous system; D-AmB: deoxycolate amphotericin B; LF-AmB: lipid formulations of amphotericin B; BAL: bronchoalveolar fluid; CSF: cerebrospinal fluid. [1] included 3 autoptical specimens positivity; [2] in 14 patients infection was already disseminated at the onset of symptoms; [3] included 7 cases due to Pseudallescheria Boydii; [4] itraconazole or fluconazole; [5] itraconazole, ketoconazole, miconazole or fluconazole; [6] 27/28 cases were due to S. prolificans; [7] only 1 reported case in each Country.

published cases was similar.

Clinical features of scedosporiosis are extremely variable, ranging from superficial and localized forms to disseminated disease. They are closely connected to patient immune status, and the most severe forms are always observed in severely neutropenic patients.[36] As previously reported,[34] fungemia was common, occurring in 2 out of 5 patients (40%) in our series and in 29 out of 52 pts (56%) in literature. This possibly reflects the *Scedosporium* ability to sporulate *in vivo*[37] and the high frequency of CVC use. In spite of the coexistence of CVC and scedosporiosis in our series, the low number of cases and the absence of similar data in literature do not allow us to come to any conclusions about this association. The high frequency of positive blood cultures is one of the important features of this mould infection which assists its identification, despite its clinical and radiographic similarity to other IFIs. Other characteristics are the cutaneous involvement with erythematous non-prurigenous skin nodules (often with a necrotic center), the presence of CNS involvement with consequent neurological signs and symptoms, and the high incidence of visual complaints due to endophthalmitis. However, these features do not allow us to make a definite diagnosis since this would require the hystopathologic evidence of hyphal tissue or the evidence of a positive culture from a sterile site.

As demonstrated in a mouse model, *S. prolificans* isolates are more virulent than *S. apiospermum* strains, thus showing a positive tropism to the kidney and brain.[38] Even if none of our cases were sustained by *S. prolificans*, infection was disseminated in all patients and each outcome was extremely poor. Similarly, among published cases, there was a high proportion of patients with disseminated disease at the onset of infection (16/52, 31%) and/or during the course of the disease (40/52, 75%).

Despite the improved diagnostic tools and the availability of new antifungal drugs, no progress has been made in treating scedosporiosis in participating centers. Perhaps this reflects the absence of specific guidelines to help clinicians to achieve better results. In fact, at the time of the cases reported in our survey, there was no effective therapy for disseminated scedosporiosis. This was due to the lack of response to AmB, including new formulations.[39] Over the last few years, the situation has changed thanks to the availability of new triazoles with a superior activity against *S. apiospermum*. In particular, in a recent work by Carillo *et al.*[40], voriconazole, posaconazole and ravuconazole were all seen to be active against any strain, with interesting *MICs*. Our literature review showed that therapeutic options for *S. prolificans* infection are more limited because of its resistance profile: *in vitro* susceptibility studies have invariably demonstrated an almost total resistance to AmB and to other available antifungal agents.[41] However, voriconazole has shown some promising *in vitro* activity, alone or in combination with terbinafine.[40,42-43]

The routine use of these new antifungal drugs seems to suggest an improved outcome in the future. However, available data is for the moment limited. In fact, present data only concerns a small number of patients and cases are not the specific focus of published reports.

In conclusion, the clinical spectrum of scedosporiosis in acute leukemia mimics that of more common infections caused by filamentous fungi. Although, extremely rare, it still represents a big problem for clinicians, due to the lack of a well-defined optimal therapy and to the severe impairment of clinical conditions of patients at risk. At present, the new triazoles, voriconazole and posaconazole, as well as a combined treatment should be considered as a possible option to modify outcome.[41,44-45] Even though the antifungal drugs registered for empiric therapy (AmB formulations and caspofungin) are not intrinsically active against *Scedosporium spp*, the very low incidence of scedosporiosis also in AML patients does not justify the use of other antifungal drugs active against these highly pathogenic fungi in the empiric setting.

Authorship and Disclosures

MC and LP co-ordinated the study; MC wrote the paper; MC and LP analyzed the data; LP, CG, MS, GL critically reviewed the paper; all other co-authors collected the clinical data. All authors read and approved the final version. The authors reported no potential conflicts of interest.

References

1. Guarro J, Kantarcioglu AS, Horre R, Rodriguez-Tudela JL, Cuenca Estrella M, Berenguer J, et al. Scedosporium apiospermum: changing clinical spectrum of a therapy-refractory opportunist. Med Mycol 2006;44: 295-327.
2. Pagano L, Girmenia C, Mele L, Ricci P, Tosti ME, Nosari A, et al. Infections caused by filamentous fungi in patients with hematologic malignancies. A report of 391 cases by GIMEMA Infection Program. Haematologica 2001; 86:862-70.
3. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006; 91:1068-75.
4. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. Clin Infect Dis 2002;34:7-14.
5. Alvarez M, Lopez Ponga B, Rayon C, Garcia Gala J, Roson Porto MC, Gonzalez M, et al. Nosocomial outbreak caused by Scedosporium prolificans (inflatum): four fatal cases in leukemic patients. J Clin Microbiol 1995;33:3290-5.
6. Bell WE, Myers MG. Allescheria (Petriellidium) boydii brain abscess in a child with leukemia. Arch Neurol 1978;35:386-8.
7. Berenguer J, Diaz-Mediavilla J, Urra D, Munoz P. Central nervous system infection caused by Pseudallescheria boydii: case report and review. Rev Infect Dis 1989; 11: 890-6.
8. Berenguer J, Rodriguez-Tudela JL, Richard C, Alvarez M, Sanz MA, Gaztelurrutia L, et al. Deep infections caused by Scedosporium prolificans. A report on 16 cases in Spain and a review of the literature. Scedosporium Prolificans Spanish Study Group. Medicine (Baltimore). 1997;76:256-65.
9. Bouza E, Munoz P, Vega L, Rodriguez-Creixems M, Berenguer J, Escudero A. (1996) Clinical resolution of Scedosporium prolificans fungemia associated with reversal of neutropenia following administration of granulocyte colony-stimulating factor. Clin Infect Dis 1996; 23: 192-3.
10. Cunningham R, Mitchell DC. Amphotericin B responsive Scedosporium apiospermum infection in a patient with acute myeloid leukemia. J Clinl Pathol 1996;49:93-4.
11. de Batlle J, Motje M, Balanza R, Guardia R, Ortiz R. Disseminated infection caused by Scedosporium prolificans in a patient with acute multilineal leukemia. J Clin Microbiol 2000;38:1694-5.
12. Feltkamp MC, Kersten MJ, van der Lelie J, Burggraaf JD, de Hoog GS, Kuijper EJ. Fatal Scedosporium prolificans infection in a leukemic patient. Eur J Clin Microbiol Infect Dis 1997;16:460-4.
13. Fietz T, Knauf W, Schwartz S, Thiel E. Intramedullary abscess in a patient with disseminated Scedosporium apiospermum infection. Br J Haematol 2003;120:724.
14. Girmenia C, Luzi G, Monaco M, Martino P. Use of voriconazole in treatment of Scedosporium apiospermum infection: case report. J Clin Microbiol 1998;36:1436-8.
15. Jones J, Katz SE, Lubow M. Scedosporium apiospermum of the orbit. Arch Ophthalmol 1999;117: 272-3.
16. Le Gouill SL, Morineau N, Miegeville M, Milpied N, Harousseau JL, Moreau P. Pseudallescheria boydii osteoarthritis in a patient with acute lymphoblastic leukemia: a case report. Rev Med Int 1999;20: 434-8.
17. Lopez L, Gaztelurrutia L, Cuenca-Estrella M, et al. Infection and colonization by Scedosporium prolificans. Enferm Infec Microbiol Clin 2001;19:308-13.
18. Maertens J, Lagrou K, Deweerdt H, Surmont I, Verhoef GE, Verhaegen J, et al. Disseminated infection by Scedosporium prolificans: an emerging fatality among haematology patients. Case report and review. Ann Hematol 2000;79:340-4.
19. Marin J, Sanz MA, Sanz GF, Guarro J, Martínez ML, Prieto M, et al. Disseminated Scedosporium inflatum infection in a patient with acute myeloblastic leukemia. Eur J Clin Microbiol Infect Dis 1991; 10:759-61.
20. McKelvie PA, Wong EY, Chow LP, Hall AJ. Scedosporium endophthalmitis: two fatal disseminated cases of Scedosporium infection presenting with endophthalmitis. Clin Experiment Ophthalmol 2001; 29: 330-4.
21. Mellinghoff IK, Winston DJ, Mukwaya G, Schiller GJ. Treatment of Scedosporium apiospermum brain abscesses with posaconazole. Clin Infect Dis 2002;15;34:1648-50.
22. Nielsen K, Lang H, Shum AC, Woodruff K, Cherry JD. Disseminated Scedosporium prolificans infection in an immunocompromised adolescent. Pediatr Infect Dis J 1993; 12:882-4.
23. Ochiai N, Shimazaki C, Uchida R, Fuchida S, Okano A, Ashihara E, et al. Disseminated infection due to Scedosporium apiospermum in a patient with acute myelogenous leukaemia. Leuk Lymphoma 2003; 44:369-72.
24. Pickles RW, Pacey DE, Muir DB, Merrell WH. Experience with infection by Scedosporium prolificans including apparent cure with fluconazole therapy. J Infect 1996; 33: 193-7.
25. Ruxin TA, Steck WD, Helm TN, Bergfeld WF, Bolwell BJ. Pseudallescheria boydii in an immunocompromised host. Successful treatment with debridement and itraconazole. Arch Dermatol 1996;132: 382-4.
26. Shih LY, Lee N. Disseminated petriellidiosis (allescheriasis) in a patient with refractory acute lymphoblastic leukaemia. J Clin Pathol 1984;37:78-82.
27. Simarro E, Marin F, Morales A, Sanz E, Perez J, Ruiz J. Fungemia due to Scedosporium prolificans: a description of two cases with fatal outcome. Clin Microbiol Infect 2001;7:645-7.
28. Tapia M, Richard C, Baro J, Salesa R, Figols J, Zurbano F, et al. Scedosporium inflatum infection in immunocompromised haematological patients. Br J Haematol 1994; 87: 212-4.
29. Torok L, Simon G, Csornai A, Tapai M, Torok I. Scedosporium apiospermum infection imitating lymphocutaneous sporotrichosis in a patient with myeloblastic-monocytic leukaemia. Br J Dermatol 1995;133:805-9.
30. Westerman DA, Speed BR, Prince HM. Fatal disseminated infection by Scedosporium prolificans during induction therapy for acute leukemia: a case report and literature review. Pathology 1999; 31:393-4.
31. Whyte M, Irving H, O'Regan P, Nissen M, Siebert D, Labrom R. Disseminated Scedosporium prolificans infection and survival of a child with acute lymphoblastic leukemia. Pediatr Infect Dis J 2005; 24:375-7.
32. Winston DJ, Jordan MC, Rhodes J. Allescheria boydii infections in the immunosuppressed host. Am J Med 1977;63:830-5.
33. Wood GM, McCormack JG, Muir DB, Ellis DH, Ridley MF, Pritchard R, et al. Clinical features of human infection with Scedosporium inflatum. Clin Infect Dis 1992;14:1027-33.
34. Lamaris GA, Chamilos G, Lewis RE, Safdar A, Raad II, Kontoyiannis DP. Scedosporium infection in a tertiary care cancer center: a review of 25 cases from 1989-2006. Clin Infect Dis 2006;43:1580-4.
35. Safdar A, Papadopoulos EB, Young JW. Breakthrough Scedosporium apiospermum (Pseudallescheria boydii) brain abscess during therapy for invasive pulmonary aspergillosis following high-risk allogeneic hematopoietic stem cell transplantation. Scedosporiasis and recent advances in antifungal therapy. Transpl Infect Dis 2002;4:212-7.
36. Steinbach WJ, Perfect JR. Scedosporium species infections and treatments. J Chemotherapy, 2003; 15 [suppl 2]:16-27.
37. Lionakis MS, Bodey GP, Tarrand JJ,

Raad II, Kontoyiannis DP. The significance of blood cultures positive for emerging saprophytic moulds in cancer patients. Clin Microbiol Infect 2004;10:922-5.
38. Cano J, Guarro J, Mayayo E, Fernandez-Ballart J. Experimental infection with Scedosporium inflatum. J Med Vet Mycol 1992;30: 413-20.
39. Carrillo-Munoz AJ, Quindos G, Tur C, Ruesga M, Alonso R, del Valle O, et al. Comparative in vitro antifungal activity of amphotericin B lipid complex, amphotericin B and fluconazole. Chemotherapy 2000; 46: 235-44.
40. Carrillo AJ, Guarro J. In vitro activities of four novel triazoles against Scedosporium spp. Antimicrob Agents Chemother 2001;45:2151-3.
41. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL. Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi. Antimicrob Agents Chemother 2006; 50:917-21.
42. Meletiadis J, Meis JF, Mouton JW, Rodriquez-Tudela JL, Donnelly JP, Verweij PE; EUROFUNG Network. In vitro activities of new and conventional antifungal agents against clinical Scedosporium isolates. Antimicrob Agents Chemother 2002;46: 62-8.
43. Meletiadis J, Mouton JW, Meis JF, Verweij PE. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical Scedosporium prolificans isolates. Antimicrob Agents Chemother 2003; 47:106-17.
44. Gilgado F, Serena C, Cano J, Gene J, Guarro J. Antifungal susceptibilities of the species of the Pseudallescheria boydii complex. Antimicrob Agents Chemother 2006; 50:4211-3.
45. Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. Pediatr Infect Dis J 2002; 21:240-8.