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Clinical manifestations, treatment and outcome of *Paecilomyces lilacinus* infections

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ABSTRACT

The fungus *Paecilomyces lilacinus* is an emerging pathogen that causes severe human infections, including devastating oculomycosis. Usually, it shows low susceptibility to conventional antifungal drugs *in vitro*, and variable susceptibility to novel triazoles. A review of the published literature identified 119 reported cases of human infection by *P. lilacinus* between 1964 and 2004. Most were cases of oculomycosis (51.3%), followed by cutaneous and sub-cutaneous infections (35.3%), and a smaller group of miscellaneous infections (13.4%). Lens implantation is the most frequent predisposing factor for oculomycosis. Cutaneous and sub-cutaneous infections occur mainly in solid organ and bone marrow transplant recipients, although surgery and primary or acquired immunodeficiency are also relevant predisposing factors. Infections in apparently immunocompetent patients have also been reported. Surgical debridement combined with antifungal drug therapy, or the correction of predisposing factors, such as neutropenia, are usually required to obtain improvement. Treatment with traditional antifungal drugs often fails. Voriconazole has demonstrated good activity in both cutaneous and ocular infections in the few cases in which this drug has been used. The new triazoles ravuconazole and posaconazole show good in-vitro activity against *P. lilacinus* and could be promising therapeutic alternatives.

Keywords Fungal infections, oculomycosis, *Paecilomyces lilacinus*, review, risk-factors, voriconazole

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INTRODUCTION

Fungal infections have become an important cause of morbidity and mortality in recent years, especially in the ever-expanding population of immunocompromised patients. Antibacterial treatment, bone marrow and solid organ transplantation, oncological chemotherapy, and primary or acquired immunodeficiency are all predisposing circumstances for the development of severe fungal infection [1]. In addition to the traditional and well-known opportunistic fungi, such as *Candida*, *Aspergillus* and *Cryptococcus*, many other fungi have now emerged as causes of human infection. *Paecilomyces* is among the latter, and is of clinical interest because of its pathogenicity and resistance to antifungal agents.

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Paecilomyces is a hyaline hyphomycete that exists worldwide. It can be recovered from soil and air, and can cause the deterioration of grain, food and paper [2]. Its potential resistance to sterilising methods, its frequent contamination of creams and lotions used clinically, and its colonisation of clinical materials, e.g., catheters and plastic implants, increases the clinical importance of this fungus [3,4]. Although *Paecilomyces* spp. are uncommon pathogens, they can produce serious infections in immunocompromised patients, and the incidence of infections in immunocompetent hosts is increasing [5]. *Paecilomyces lilacinus* and *Paecilomyces variotii* are the two species associated most frequently with human disease. Other species reported to infect humans occasionally are *Paecilomyces marquandii* [6,7] and *Paecilomyces javanicus* [8]. This article reviews cases of *P. lilacinus* infection reported between 1964 and 2004, and summarises the available data concerning the main clinical manifestations, predisposing factors, treatments and outcome. Data

concerning the in-vitro susceptibility of this fungus are also reviewed.

CLINICAL RELEVANCE OF *P. LILACINUS*

Despite its apparently moderate virulence [9], *P. lilacinus* is able to infect both immunocompromised and immunocompetent hosts [2]. The portal of entry of the fungus usually involves breakdown of the skin barrier, indwelling catheters or inhalation. On some occasions, fluids contaminated by *P. lilacinus* have caused infections of eye structures [10,11] or the skin [12]. The ability to sporulate in tissue and to produce numerous conidia could explain the tendency of this species for dissemination in the human body [13]. Most clinical manifestations correspond to oculomycosis and cutaneous and subcutaneous infections, although other types of infection have also been reported less commonly.

Ocular infections

P. lilacinus shows a special tropism for ocular structures. Table 1 summarises the 23 reports of oculomycosis caused by *P. lilacinus*, involving 55 patients, published between 1964 and 2004. Also included in Table 1 are five new cases from Brazil that were recently confirmed in our laboratory. Although details of these cases are incomplete, they are included in order to emphasise the wide distribution of this pathogen, as its involvement in ocular infection had not been reported previously in Brazil. Oculomycosis caused by *P. lilacinus* seems to occur worldwide, but interestingly, nine of the 60 cases reported were from Australia [14–19]. The age of patients was 20—92 years, and no significant gender differences were noticed. Keratitis and endophthalmitis were the most common clinical manifestations. The most common predisposing factors were intra-ocular lens implantation (32.8%), non-surgical trauma with or without a foreign body (20%), ophthalmic surgery (10%), and the wearing of contact lenses (3.3%). Significantly, in most cases, patients received topical and/or systemic costicosteroid treatment at the start of infection. In some cases, no predisposing factors were identified [13,18]. Mortality has never been associated with primary oculomycosis caused by *P. lilacinus*, but enucleation of the affected eye (38%) and loss of vision (25%) were the outcome of the infection in many cases.

In practically all cases of oculomycosis reported (57/60), *P. lilacinus* was isolated from the lesions. In two cases, the aetiology of the infection was established only through histological studies and was not confirmed by culture [16,20], and in one case the isolate was not identified to the species level [16]. However, these three cases were attributed erroneously to *P. lilacinus* in retrospective reviews [21,22]. A case in which the aetiological agent was *Paecilomyces viridis* [23] was also attributed erroneously to *P. lilacinus* [21,22,24,25].

Cutaneous and sub-cutaneous infections

Details of 42 patients with cutaneous and subcutaneous *P. liacinus* infections between 1977 and 2004 are summarised in Table 2. The majority (50%) of these infections were reported from the USA, although cases from other countries, e.g., Australia, Brazil, France, Germany, Iceland, Japan, Korea, Spain, Switzerland and the UK, have also been reported. Patient age ranged from 4 to 86 years and there were no significant gender differences. The most common predisposing factors were solid organ (27.9%) and bone marrow transplantation (11.6%), corticosteroid therapy (9.3%), malignancies (20.9%), primary immunodeficiency (2.4%), AIDS (2.4%), diabetes mellitus (2.4%) and hepatic cirrhosis (2.4%). In eight cases (18.6%), predisposing factors for infection were unknown or not reported [4,26–31].

Cutaneous infections are usually sporadic, but an outbreak affecting nine immunocompromised patients in a bone marrow transplant unit, related to the common use of a skin lotion, was described in Switzerland [12,32]. The outbreak lasted for a period of 3 months, and affected five patients following allogeneic bone marrow transplantation and four patients with aplasia after chemotherapy for haematological malignancies; two of the patients died.

Cutaneous and sub-cutaneous infections usually appear insidiously and can manifest with a wide range of clinical features. They consist of solitary or disseminated skin eruptions with erythematous macules, papules, vesicles or

Table 1. Reported cases of oculomycosis caused by *Paecilomyces lilacinus*

Case	Year	Reference	Country	Age/ gender	Infection	Predisposing factors	Treatment	Outcome
1	1964	[81]	USA	81/F	Keratitis	Ocular surgery (cataract extraction)	Surgery, topical and systemic AMB	Recovery
2	1973	[93]	Argentina	41/M	Endophthalmitis	Ocular surgery (iridenclisis)	Sub-conjunctival/intra-vitreal AMB	Loss of vision
3	1977	[10]	USA	61/M	Endophthalmitis	Lens implantation	Surgery	Eye enucleation
4–15	1977	[77]	USA	NR	Endophthalmitis	Lens implantation	AMB, 5FC	Eye enucleation in six cases, loss of vision in six cases
16	1978	[78]	USA	76/M	Endophthalmitis	Lens implantation	Surgery, 5FC, intra-ocular and systemic AMB, intra-ocular 5FC and MCZ, topical and oral TBZ	Recovery
17	1980	[20]	USA	61/M	Endophthalmitis	Lens implantation	Surgery	Eye enucleation
18	1980		USA	70/M	Endophthalmitis	Lens implantation	Local and oral 5FC	Loss of vision
19	1980		USA	72/M	Endophthalmitis	Lens implantation	Surgery	Eye enucleation
20	1980		USA	92/F	Endophthalmitis	Lens implantation	Local AMB	Eye enucleation
21	1980		USA	84/F	Endophthalmitis	Lens implantation	Topical AMB	eye enucleation
22	1980		USA	70/F	Endophthalmitis	Lens implantation	Sub-conjuntival/intra-ocular AMB, 5FC	Loss of vision
23	1980		USA	81/F	Endophthalmitis	Lens implantation	Surgery	Eye enucleation
24	1980		USA	79/M	Endophthalmitis[a]	Lens implantation	Antibiotics[b]	Loss of vision
25	1980		USA	89/M	Endophthalmitis	Lens implantation	Intra-ocular AMB, 5FC	Eye enucleation
26	1980		USA	76/M	Endophthalmitis	Lens implantation	Intra-vitreal AMB	Eye enucleation
27	1980		USA	76/F	Endophthalmitis[a]	Lens implantation	Topical AMB, 5FC	Recovery
28	1980		USA	72/F	Endophthalmitis	Lens implantation	AMB	Eye enucleation
29	1984	[24]	USA	70/M	Keratitis	Lens implantation	Surgery, intra-ocular AMB and MCZ, intra-ocular MCZ, 5FC	Eye enucleation
30	1984		USA	72/F	Keratitis	Herpes zoster	Surgery, intrao-cular MCZ, 5FC, MCZ	Eye enucleation
31	1984		USA	76/F	Keratitis	Local corticosteroids	Surgery, topical MCZ	Recovery
32	1985	[65]	USA	76/F	Keratitis	Corneal transplant	Topical pimaricin, MCZ and AMB, systemic MCZ, second corneal transplant	Recovery
33	1987	[82]	USA	79/M	Endophthalmitis	Lens implantation	Surgery, intra-vitreal AMB and MCZ, MCZ, KTZ	Recovery
34	1987	[94]	USA	76/F	Keratitis	Contact lens	Topical AMB, NTM, surgery, topical MCZ	Recovery
35	1987		USA	71/F	Keratitis	Contact lens	Topical and subconjunctival MCZ, topical AMB, topical KCZ, surgery	Recovery
36	1989	[14]	Australia	43/NR	Endophthalmitis	Trauma/keratoplasty	Topical NTM and MCZ, surgery, intra-vitreal AMB, MCZ and 5FC, systemic AMB, intra-vitreal AMB	Recovery
37	1991	[15]	Australia	20/M	Endophthalmitis	Minor trauma	Systemic AMB	Recovery
38	1992	[16]	Australia	21/M	Keratitis	Eye sore/dexametasone	Topical and systemic AMB, corneal transplant, Intra-ocular AMB, ITZ, surgery	Loss of vision
39‡	1992		Australia	72/F	Keratitis	Topical prednisolone	Topical and systemic AMB, surgery, surgery, intra-vitreal and systemic AMB	Loss of vision
40	1994	[79]	France	65/F	Endophthalmitis	Corneal ulceration	Topical NTM, KCZ, surgery, intra-vitreal AMB	Recovery
41	1994	[95]	Japan	84/F	Endophthalmitis	Ocular surgery	Surgery, ECZ, MCZ	Loss of vision
42	1996	[13]	USA	NR	Keratitis	Unknown	NR	NR
43	1996		USA	NR	Keratitis	Unknown	NR	NR
44	1996	[12]	Switzerland	48/M	Endophthalmitis	Chronic myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF, G-CSF, GM-CSF	Death
45	1997	[21]	UK	34/M	Endophthalmitis/ keratitis	Corticosteroid therapy	Surgery, antibacterials, intra-vitreal AMB, KCZ, FCZ, ITZ, topical ECZ, intra-ocular MCZ, KCZ	Recovery
46	2001	[17]	Australia	30/M	Endophthalmitis	Corneal trauma	Intra-ocular AMB, ITZ, topical NTM and FCZ, intra-ocular FCZ and AMB	Recovery
47	2001	[25]	Spain	62/M	Endophthalmitis	Corneal/crystalline trauma	Surgery, intra-vitreal and systemic AMB, ITZ	Eye enucleation
48	2001	[80]	USA	37/M	Endophthalmitis	Lens implantation	Surgery, intra-ocular AMB	Eye enucleation
49	2001		USA	68/F	Endophthalmitis	Corneal ulceration	Surgery, topical and intra-ocular AMB, FCZ, topical, sub-conjunctival and intra-vitreal MCZ	Recovery
50	2001		USA	48/F	Endophthalmitis	Corneal ulceration	Surgery, intra-vitreal FCZ	Recovery
51	2001		USA	23/M	Endophthalmitis	Lens implantation	Surgery, intra-vitreal AMB, intra-vitreal MCZ	Eye enucleation

Table 1. Reported cases of oculomycosis caused by *Paecilomyces lilacinus*

Case	Year	Reference	Country	Age/ gender	Infection	Predisposing factors	Treatment	Outcome
52	2002	[22]	Switzerland	61/F	Endophthalmitis	Lens implantation	Surgery, FCZ, ITZ, intra-ocular FCZ, VCZ	Recovery
53	2003	[18]	Australia	69/M	Endophthalmitis	Unknown	Surgery, intra-cameral AMB, VCZ	Loss of vision
54	2003		Australia	44/M	Endophthalmitis	Unknown	Surgery, AMB, intra-vitreal AMB, VCZ	Recovery
55	2003		Australia	23/M	Endophthalmitis	Corneal foreign body	Topical NTM and AMB, ITZ, voriconazole	Recovery
56	2004	[19]	Australia	61/M	Keratitis	Intra-corneal hair	Surgery, topical NTM, FCZ, VCZ plus TBF	Recovery
57	2004	PR	Brazil	69/M	Keratitis	Retro-orbital lymphoma	NR	NR
58	2004		Brazil	28/M	Keratitis	Surgery	AMB	NR
59	2004		Brazil	63/M	Keratitis	Surgery	NTM	NR
60	2004		Brazil	28/F	Keratitis	NR	NR	NR
61	2004		Brazil	32/F	Keratitis	Corneal ulceration	NR	NR

[a]*P. lilacinus* infection not confirmed; [b]not specified; [c]*Paecilomyces* spp. not identified.
NR, not reported; PR, present report.
G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
AMB, amphotericin B; ECZ, econazole; FCZ, fluconazole; ITZ, itraconazole; KCZ, ketoconazole; MCZ, miconazole; NTM, natamycin; TBZ, thiobendazole; TBF, terbinafine; VCZ, voriconazole; 5FC, flucytosine.

nodules with a necrotic centre [12,32]. Some cases of soft-tissue infections, e.g., cellulitis, have also been described [3,29,33–35].

Six (14.3%) of the 42 reported patients with cutaneous infection caused by *P. lilacinus* died. Although it is probable that the fungal infection contributed to the fatal outcome, this was not proven in all cases. Two patients suffered severe graft vs. host disease after bone marrow transplant, including one patient in whom the infection disseminated [12,32]. In two other cases, the cause of death was pneumonia, probably unrelated to the infection [36], and multiple organ failure with no documented dissemination of the infection [28]. In two cases, the cause of death was not described [13].

Non-ocular, non-cutaneous infections

Sixteen cases of non-ocular, non-cutaneous infections caused by *P. lilacinus* were described between 1972 and 2003 (Table 3), seven of which were from the USA. In five cases, no predisposing factors were identified. The patients' ages ranged from 18 months to 57 years, and no differences existed between genders. These infections involved onychomycosis [37], vaginitis [5], lung abscess [38], pleural effusion [39], sinusitis [40–43], osteomyelitis [44], disseminated infection [13,45] and fungaemia [46–49]. Sinusitis was the most frequent type of non-cutaneous, non-ocular infection (31.3%), followed by fungaemia (25%). The cases of fungaemia were related to indwelling central venous catheters. All of these cases were resolved successfully following medical and surgical treatment.

Diagnosis

As with most fungal infections, diagnosis of *P. lilacinus* infection is based on culture of the fungus and histology of the lesions. The fungus grows well in routine media used for fungal culture. For example, it grows rapidly on malt extract 2% w/v agar, developing flocculant vinaceous to violet colonies [2], while it produces brownish colonies on Sabouraud dextrose agar [50]. The vinaceous pigmentation of the colonies and a careful study of the microscopical features are the most useful criteria for distinguishing this fungus from common contaminants, e.g., *Penicillium*, which shows a similar arrangement of the fertile hyphae, or from other more common pathogenic fungi, e.g., *Aspergillus* and *Candida* spp.

A peculiar characteristic of *P. lilacinus* mentioned above, i.e., its ability to sporulate in infected tissue, can also be helpful in the diagnosis of these infections. This type of sporulation, called 'adventitious' sporulation, involves the production of reproductive structures similar to those observed *in vitro*, i.e., phialides and conidia [13]. Although definitive identification of this fungus requires culture, it can often be identified provisionally in histological sections using routine stains that allow such structures to be observed. Correct diagnosis of *P. lilacinus* is important because of its intrinsic resistance to conventional antifungal drugs.

Table 2. Reported cases of cutaneous and sub-cutaneous infections caused by *Paecilomyces lilacinus*

Case	Year	Reference	Country	Age/gender	Infection	Predisposing factors	Treatment	Outcome
1	1977	[85]	Japan	28/F	Cutaneous	Renal transplant	AMB	Chronic course
2	1977	[26]	Japan	20/F	Cutaneous	Unknown	Topical CTZ, GSV	Partial recovery
3	1979	[6]	USA	56/F	Sub-cutaneous	Renal transplant	MCZ	Recovery
4	1984	[27]	Korea	19/M	Cutaneous	Unknown	GSV, KTZ	Recovery
5	1985	[83]	USA	55/F	Sub-cutaneous	Renal transplant	Surgery	Recovery
6	1986	[33]	USA	47/M	Sub-cutaneous	Chronic lymphocytic leukaemia	AMB, AMB plus 5FC	Recovery
7	1986	[90]	Italy	80/M	Cutaneous	Diabetes mellitus	KTZ	Recovery
8	1990	[69]	Brazil	46/F	Cutaneous	Renal transplant	GSV	Died
9	1990	[36]	USA	6/F	Cutaneous	Biphenotypic leukaemia	AMB, AMB plus 5FC	Died
10	1992	[87]	USA	4/M	Sub-cutaneous	Chronic granulomatous disease	AMB	Recovery, died from other causes
11	1996	[91]	USA	55/M	Cutaneous	Lymphocytic lymphoma	GSV, KTZ	Recovery
12	1996	[9]	USA	45/M	Cutaneous	Renal transplant	Surgery	Persistent infection, recurrences
13	1996		USA	59/NR	Sub-cutaneous	Heart transplant	Surgery, KTZ	Persistent asymptomatic nodules
14	1996	[12]	Switzerland	50/M	Cutaneous	Chronic myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF	Recovery[a]
15	1996		Switzerland	14/F	Cutaneous	Acute myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF	Died
16	1996		Switzerland	48/M	Cutaneous	Chronic myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF, G-CSF, GM-CSF	Died
17	1996		Switzerland	50/M	Cutaneous	Acute myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF	Recovery
18	1996		Switzerland	47/M	Cutaneous	Chronic myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF	Recovery
19	1996		Switzerland	42/M	Cutaneous	Acute myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF	Recovery
20	1996		Switzerland	48/M	Cutaneous	Non-Hodgkin Burkitt lymphoma	AMB, ITZ, FCZ, GSV, 5FC, TBF	Recovery
21	1996		Switzerland	54/M	Cutaneous	Myelodysplastic syndrome	AMB, ITZ, FCZ, GSV,	Recovery
22	1996		Switzerland	32/F	Cutaneous	Acute myelogenous leukaemia	AMB, ITZ, FCZ, GSV, 5FC, TBF	Recovery
23	1996	[70]	USA	35/M	Cutaneous, bursitis	Local corticosteroid injection	MCZ, KTZ, surgery	Recovery
24	1997	[28]	USA	56/M	Cutaneous	Liver transplant	ITZ, AMB, i.v and topical MCZ	Died
25	1997		USA	86/M	Cutaneous	Unknown	ITZ	Recovery
26	1997	[13]	USA	NR	Cutaneous/ sub-cutaneous	Heart transplant	NR	Recovery
27	1997		USA	NR	Cutaneous/ sub-cutaneous	Renal transplant	NR	Recovery
28	1997		USA	NR	Cutaneous/ sub-cutaneous	Acute lymphocytic leukaemia	NR	Died
29	1997		USA	NR	Cutaneous/ sub-cutaneous	Acute myelogenous leukaemia	NR	Died
30	1998	[88]	USA	72/M	Sub-cutaneous	Corticosteroids	ITZ	Recovery
31	1999	[3]	USA	48/M	Cutaneous/ sub-cutaneous	Heart transplant	ITZ, AMB, FCZ L-AMB, ITZ solution, TBF	Recovery
32	1999	[4]	Spain	36/M	Cutaneous	Unknown	ITZ	Recovery
33	2000	[29]	UK	58/M	Cutaneous/ sub-cutaneous	Unknown	FCZ, TBF, surgery, GSV, TBF	Recovery
34	2000	[89]	Iceland	59/M	Cutaneous	Renal transplant	ITZ, VCZ, immunosuppression reduction	Recovery
35	2001	[30]	Australia	59/F	Cutaneous	Unknown	ITZ	Recovery
36	2002	[86]	USA	40/M	Cutaneous/ sub-cutaneous	AIDS	ITZ, AMB, AMB lipid complex, VCZ	Recovery
37	2002	[34]	USA	64/F	Cutaneous	Diabetes mellitus, metastatic carcinoma of the pancreas	ITZ, CSP	Recovery
38	2003	[35]	Germany	43/M	Sub-cutaneous	Liver cirrhosis	Surgery, AMB	Recovery
39	2004	[84]	France	84/M	Cutaneous	Prednisone therapy	Surgery, VCZ	Recovery
40	2004	[31]	USA	73/F	Cutaneous	Prednisone therapy	ITZ	Recovery
41	2004		USA	65/M	Cutaneous	Unknown	ITZ, FCZ, surgery	NR
42	2004		USA	63/M	Cutaneous	Heart transplant	Surgery	Died but probably from other causes

NR, not reported.
G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
AMB, amphotericin B; CSP, caspofungin; CTZ, clotrimazole; FCZ, fluconazole; GSV, griseofulvin; ITZ, itraconazole; KCZ, ketoconazole; L-AMB, liposomal amphotericin B; MCZ, miconazole; TBF, terbinafine; VCZ, voriconazole; 5FC, flucytosine.

Table 3. Reported cases of non-ocular, non-cutaneous infections caused by *Paecilomyces lilacinus*

Case	Year	Reference	Country	Age/ gender	Infection	Predisposing factors	Treatment	Outcome
1	1972	[39]	Malta	20/M	Pleural effusion	Unknown	AMB	Recovery
2	1980	[40]	USA	47/F	Chronic sinusitis	Unknown	Surgery	Recovery
3	1982	[92]	USA	47/F	Sinusitis	Previous nasoantrostomy	Surgery	Recovery
4	1992	[46]	Spain	7/M	Fungaemia	Acute lymphoblastic leukaemia	AMB	Recovery
5	1992	[47]	USA	1.5/M	Fungaemia	Rhabdomyosarcoma	AMB	Recovery
6	1996	[41]	USA	22/F	Sinusitis	Myeloid leukaemia	AMB, 5FC, ITZ	Recovery, died of other causes
7	1996	[13]	USA	NR	Lung, disseminated	Acute lymphocytic leukaemia	NR	Recovery
8	1997	[42]	USA	57/F	Sinusitis	Diabetes mellitus	Surgery, AMB plus ITZ	Recovery
9	1998	[37]	UK	59/F	Onychomycosis	Unknown	TBF, topical AMF, nail ablation	Stable disease in new nail
10	1999	[48]	USA	36/F	Fungaemia	Bone marrow transplant	AMB, 5FC, GM-CSF	Recovery
11	1999	[44]	USA	43/M	Osteomyelitis	Bone marrow transplant	AMB, MCZ, surgery	Recovery, died of other causes
12	1999	[38]	Japan	57/M	Lung abscess	Unknown	Lobectomy	Recovery
13	2000	[43]	India	8/M	Sinusitis	Unknown	Surgery, ITZ	Recovery
14	2002	[45]	USA	61/M	Disseminated	AIDS	AMB, ITZ	Recovery
15	2003	[5]	USA	48/F	Vaginitis	Unknown	FCZ, topical CTZ, topical TNZ, boric acid gel, ITZ	Recovery
16	2003	[49]	Chile	5/M	Fungaemia	Myeloid leukaemia	FCZ, AMB plus ITZ	Recovery

NR, not reported.
GM-CSF, granulocyte-macrophage colony-stimulating factor.
AMB, amphotericin B; AMF, amorolfine; CTZ, clotrimazole; FCZ, fluconazole; ITZ, itraconazole; TNZ, tioconazole; 5FC, flucytosine.

IN-VITRO SUSCEPTIBILITY

Data concerning the in-vitro antifungal susceptibility of *P. lilacinus* are scarce; some reports do not refer to a particular species, but to *Paecilomyces* in general [51–55]. As antifungal susceptibilities vary considerably among the different species of *Paecilomyces*, the usefulness of such reports is very limited without species identification [56].

Table 4 summarises the available data concerning the in-vitro activity of the various antifungal drugs against *P. lilacinus*. The important differences among the data provided from various studies can be explained by the different methods used. The CLSI broth microdilution method for yeasts (M27-A) [57] was used in some studies [51,56], while others [52–54,58–61] used the guidelines for moulds (M38-P, M38-A) [62,63]. Broth macrodilution, Etest and colourimetric methods were used in other studies [54,55,59,64]. With the exception of amphotericin B, for which all studies used 100% growth inhibition (MIC-0), important discrepancies also occurred in the endpoint criteria used. Thus, MIC-0 was often chosen as the endpoint criterion for all antifungal drugs tested [53,54,58–61], while other studies used 75% (MIC-1) or 50% (MIC-2) growth inhibition as the endpoint [51,52,56,64]. Diekema *et al.* [53] used the minimum effective concentration (MEC) as the endpoint for caspofungin.

Overall, amphotericin B has poor in-vitro activity against *P. lilacinus*. MIC values of this drug were always >2 mg/L, and usually >8 mg/L [18,20,24,56,58–60,65–68]. This absence of activity of amphotericin B was corroborated by its reported high minimum fungicidal concentrations (MFC) [56,58].

As with many other filamentous fungi, the in-vitro activity of flucytosine and fluconazole against *P. lilacinus* is practically nil, with very high MICs [3,12,20,48,56,65,69–71] and MFCs [56]. There are contrasting data concerning the activity of the older azoles, such as ketoconazole, miconazole, clotrimazole and itraconazole [3,5,12,18,24,65,70]. As an example, most studies report itraconazole MICs of >2 mg/L [56,58–60,68], while others report considerably lower MICs of ≤ 0.01–0.5 mg/L [18,66].

Interestingly, some of the novel antifungal drugs have shown some degree of in-vitro activity against *P. lilacinus*. Among the triazoles, posaconazole has the lowest MICs, ranging from 0.12 to 0.5 mg/L [60]. The MICs of voriconazole were more variable, ranging from 0.12 to 4 mg/L [57,58,60]. Similar results were obtained with the new triazole albaconazole (UR-9825), for which MICs ranged from 0.06 to 0.5 mg/L [67] and from 0.5 to 8 mg/L [57]. Ravuconazole also shows good in-vitro activity against *P. lilacinus*, with MICs ranging from 0.2 to 2 mg/L [57,60]. MICs of

Table 4. In-vitro antifungal susceptibilities of *Paecilomyces lilacinus*

Ref.	No. of strains	Antifungal drugs (MICs mg/L) AMB	5FC	FLC	KCZ	MCZ	ITZ	ABZ	VCZ	RVZ	PSZ	TBF	MFG	CSP
[77]	1[a]	25	> 50	–	–	6.25	–	–	–	–	–	–	–	–
[78]	1[a]	> 20	> 200	–	–	20	–	–	–	–	–	–	–	–
[20]	3[a,b]	25	> 50	–	6.25	–	–	–	–	–	–	–	–	–
[94]	2[a,c]	> 32	> 250	–	0.62–1.25	0.62–10	–	–	–	–	–	–	–	–
[24]	3[c]	> 16	2– > 18	–	< 1–3	0.25–7	–	–	–	–	–	–	–	–
[65]	4[c]	> 4	> 250	–	0.31–0.62	0.15– > 20	–	–	–	–	–	–	–	–
[70]	1[d]	> 16	–	64	1	0.5	16	–	–	–	–	–	–	–
[12]	ND[a]	16	–	64	0.50	0.5–1	4	–	–	–	–	–	–	–
[41]	1	4.62	–	64	–	–	0.5	–	–	–	–	–	–	–
[21]	1[a]	> 64	–	–	16	32	> 64	–	–	–	–	–	–	–
[42]	1[a]	> 16	–	–	–	–	0.13	–	–	–	–	–	–	–
[64]	5[c,d]	–	–	–	–	–	–	–	–	–	–	–	–	3.12– > 100
[56]	11[b,e]	10.29	255.96	116.46	3.52	6.02	7.51	–	–	–	–	–	–	–
[51]	1[e,f]	4	> 128	–	–	–	4	–	–	–	–	–	–	0.5
[3]	1[a]	2	> 64	> 64	1	–	4		–	–	–	0.08	–	–
[48]	1[d]	> 16	> 64	> 64	–	–	1		–	–		–	–	–
[66]	2[c,e]	> 8	–	–	–	–	0.01–0.5	–	–	–	–	–	< 0.01	–
[89]	1[a]	> 25	–	–	–	–	> 25	–	1.56	–	–	–	–	–
[30]	1[g]	> 32	–	> 32	–	–	0.5	–	–	–	–	–	–	–
[25]	1[a]	16	128	–	–	–	–	–	–	–	–	–	–	–
[67]	10[b,c]	> 16	–	–	–	–	–	0.06–0.5	–	–	–	–	–	–
[58]	6[c,d]	> 8	–	–	–	–	2– > 8	–	0.12–0.5	–	–	–	–	–
[59]	4[c,e,g]	> 8	–	–	–	–	2– > 8	–	–	–	–	–	–	–
[86]	1[a]	> 8	–	–	–	–	2	–	0.12	–	–	–	–	–
[34]	1[a]	16	–	–	1	–	1	–	0.25	0.50	0.12	–	–	1.00
[22]	1[a]	> 16	–	–	–	–	0.5	–	0.25	–	–	–	–	–
[52]	2[e,f]	0.50	–	–	–	–	0.25–0.5	–	2–8	1–8	0.12–0.5	–	–	–
[60]	3[f,h]	> 8	–	–	–	–	1– > 8	–	0.20–1	0.20–2	0.12–0.5	–	–	–
[53]	6[e,f]	0.06– > 8	–	–	–	–	0.06–2	–	0.03–2	0.03–4	0.03–0.5	–	–	0.03–8
[35]	1[e]	> 16	–	–	–	–	> 16	–	2	–	–	1	> 8	–
[18]	3[c,e]	2	> 64	8–64	0.25–0.50	–	0.5	–	0.12	–	–	–	–	–
[5]	1[d]	> 16	> 64	32	0.5	–	0.5	–	0.25	–	0.12	–	–	–
[55]	1[f,h]	2	> 64	> 256	> 16	–	> 16	–	4	–	–	–	–	–
[61]	6[c,e]	–	–	–	–	–	–	–	–	–	–	0.25–0.5	–	–
[68]	3[c,e]	16	–	–	–	–	32	0.5–8	0.25–4	0.25–2	–	1–8	64	–

AMB, amphotericin B; 5FC, flucytosine; FLC, fluconazole; KCZ, ketoconazole; MCZ, miconazole; ITZ, itraconazole; ABZ, albaconazole; VCZ, voriconazole; RVZ, ravuconazole; PSZ, posaconazole; TBF, terbinafine; MFG, micafungin; CSP, caspofungin.
ND, number of strains not specified.
[a]Susceptibility method not reported; [b]geometric mean MICs; [c]MIC range; [d]macrodilution broth method; [e]microdilution broth method; [f]referred as *Paecilomyces* spp.; [g]Etest; [h]alamar blue.

0.25–0.50 mg/L have been reported for terbinafine [61], while other studies have reported MICs of 1–8 mg/L [57]. Limited and controversial data exist concerning the in-vitro activity of echinocandins. For caspofungin, MICs of 3.12 mg/L to > 100 mg/L (geometric mean of 49.98 mg/L) have been reported [64], while micafungin MICs of ≤ 0.01 mg/L were reported in one study [66], compared with 64 mg/L in another [57].

Because of the high resistance shown by *P. lilacinus* to conventional antifungal drugs, the potential activity of various in-vitro combinations has also been tested. In a study involving three isolates of this fungus, although the interaction was generally indifferent, amphotericin B MICs of > 16 mg/L were reduced to 0.12 mg/L when combined with voriconazole, ravuconazole, albaconazole or terbinafine [57]. Amphotericin B combined with terbinafine or albaconazole resulted in synergic interactions against two and one isolate(s), respectively. Combinations of terbinafine with voriconazole, itraconazole, ravuconazole or albaconazole also showed synergism against some of the isolates tested [57]. However, further studies are needed to evaluate the possible clinical significance of these observations.

ANIMAL MODELS

The virulence of some species of *Paecilomyces* has been evaluated in different animal models, e.g., mice, guinea-pigs, rats and rabbits, using intraperitoneal, sub-cutaneous, intra-testicular, intramuscular, intra-corneal and intra-orbital methods of infection [72–76]. In general, virulence was very low, requiring high inocula and immunosuppression of the animals to produce an established infection. Thus, experimental infection of immunocompetent mice by a strain of *P. lilacinus* using an intra-peritoneal route required a period of 2 months before peritoneal granulomas developed, and it was not possible to recover viable

fungi from the granulomas [73]. Agrawal *et al.* [72] reported a greater effect in animals treated with hydrocortisone acetate than in immunocompetent animals in a model of corneal infection in rabbits. More recently, an experimental murine model of disseminated infection using mice immunosuppressed with cyclophosphamide was used to compare the pathogenicity of *P. variotii*, *P. lilacinus* and *P. javanicus*, and demonstrated a higher virulence for strains belonging to the first two of these species [74]. With the development of these models, studies of pathogenesis, host response and therapy of paecilomycosis have become possible. The murine model has been used to evaluate the efficacy of amphotericin B deoxycholate and its liposomal formulation against disseminated infection caused by *P. variotii*, and demonstrated the usefulness of both compounds and the higher activity of the liposomal amphotericin B in the treatment of this experimental infection [75].

TREATMENT AND OUTCOME

The optimal treatment for *P. lilacinus* infections has not yet been established. In localised infections, removal of the infected foci and elimination of any foreign body should be attempted if feasible [1].

Ocular infections

No standard treatment exists for ocular infections caused by *P. lilacinus*. Outcomes of the various treatments used to date range from eye enucleation to total recovery (Table 1). Favourable outcomes were obtained in only 17 (28.3%) of the 60 cases described in the literature. Eye enucleation was required in 20 (33.3%) cases, which demonstrates the potentially devastating effects of this fungus for ocular structures. Other treatment regimens used one or several drugs administered by a topical, sub-conjunctival and/or intra-ocular route, sometimes combined with systemic treatment, and associated commonly with surgical procedures, e.g., keratoplasty, total or partial vitrectomy, removal of the intra-ocular lens or corneal transplant.

In general, in-vitro susceptibility of clinical isolates to amphotericin B and flucytosine is very low [18,20,21,24,25,77,78], which corresponds with observations that use of systemic amphotericin B alone was ineffective, with infection being resolved in only one (6.2%) of 16 cases in which this approach was used [15]. Local administration of amphotericin B resulted in similarly poor outcomes, with recovery in only three of 19 cases. In two of these three cases of recovery, success was achieved only after surgery [79,80], and in the other it was achieved following intra-ocular administration of amphotericin B and fluconazole [17]. The use of both systemic and local administration of amphotericin B did not improve outcome, with recovery achieved in only two of seven patients treated with this regimen [14,81].

Miconazole was used in nine cases [14,21,24,65,78,80,82], but resolved only two [24,65]; in one of these it was used topically [24], and in the other it was administered systemically, followed by surgery [65]. Systemic and local administration of flucytosine has also been used unsuccessfully, with improvement in only one (4.7%) of 21 cases; the one success was in combination with amphotericin B, but the aetiology of *P. lilacinus* could not be confirmed [20]. Fluconazole was administered to seven patients, only two of whom were cured; in one of the two favourable cases, fluconazole was used in combination with amphotericin B [17], and in the other fluconazole was administered intra-vitreally followed by surgical treatment [80]. Although voriconazole has been used in only five documented cases, this drug demonstrated a high level of efficacy, resolving four cases [18,19,22], in one of which voriconazole was combined with terbinafine [19].

Cutaneous and sub-cutaneous infections

The treatments and outcomes of the reported cases of cutaneous and sub-cutaneous infections caused by *P. lilacinus* are summarised in Table 2. In two cases, surgical debridement was sufficient to cure the infection [31,83]. In another case, infection persisted with recurrences, but no dissemination occurred after surgical debridements, which were repeated for a period of 2.5 years [9]. In six cases, surgical treatment was carried out either in association with antifungal drug therapy or following other surgery [9,31,35,70,84], curing the infection in all except one case, for which the outcome was unknown [31]. In 30 cases, therapy comprised antifungal drugs, e.g., amphotericin B, flucytosine, miconazole, fluconazole, ketoconaz-

ole, itraconazole, voriconazole, caspofungin and terbinafine, alone or in combinations. Successful outcomes were obtained in 22 (73.3%) cases, generally after the sequential administration of several antifungal drugs after failure of the drug(s) employed initially. On some occasions when antifungal treatment had failed, recovery was possible following correction of neutropenia [12].

Amphotericin B, alone or associated with surgery, was used in 17 cases, but was unsuccessful in 15 (88.2%) cases [3,12,28,33,36,85,86]. One of the two successful cases involved a child with chronic granulomatous disease, who was cured with amphotericin B [87], and the other was a cirrhotic male, who was cured with amphotericin B and surgical debridement [35]. In the latter case, the strain showed in-vitro resistance to amphotericin B (MIC >16 mg/L). In general, MICs of >2 mg/L were observed in those cases with unsuccessful outcomes for which the causative strain had been tested *in vitro* [3,12,86].

Itraconazole has been used to treat 20 patients [3,4,12,28,30,31,34,86,88,89], but a successful outcome was obtained in only four cases [4,30,31,88]. A relationship between in-vitro resistance of the clinical isolates to itraconazole and treatment failure was observed in two cases [3,89], but this correlation was not always found. For example, the strain in the case reported by Gottlieb *et al.* [30], which resolved, had an itraconazole MIC of 0.5 mg/L, but no clinical response was obtained with itraconazole in another case in which the isolate had similar in-vitro susceptibility [31]. A favourable outcome was obtained with itraconazole plus caspofungin in a cutaneous infection that failed to resolve with itraconazole alone. In this case the clinical isolate had MICs of 1–4 mg/L [34]. However, in most of the cases resolved with itraconazole, no data on in-vitro susceptibility were available [4,31,88].

Despite their known poor activity against *P. lilacinus*, flucytosine and fluconazole have also been used in the treatment of cutaneous and sub-cutaneous infections caused by this fungus, but usually with a negative outcome. Only one of 11 cases treated with flucytosine was resolved when this drug was added to a previous amphotericin B treatment that had failed [33]. Similarly, failure was the outcome in 12 cases treated with fluconazole.

In contrast, favourable outcomes were obtained in the few cases in which voriconazole was administered. This drug resolved the infection in four cases [34,84,86,89], although the MIC for the clinical isolate was relatively high (1.56 mg/L) [89] in one case. The MICs for isolates in another three cases were considerably lower [34,84,86]. Ketoconazole has also been used successfully in four cases of cutaneous and sub-cutaneous infection [27,70,90,91]; in one case it was combined with surgery [70]. No data have been published concerning the clinical use of posaconazole or ravuconazole. Therapy with terbinafine failed in the treatment of an outbreak that included nine patients with cutaneous and sub-cutaneous infection [12,32]. However, terbinafine was effective in one case for which the isolate showed in-vitro susceptibility [3], and in another case when used in combination with griseofulvin [29].

Non-ocular, non-cutaneous infections

In contrast to the infections mentioned above, in which the rate of successful treatment was very low, all described cases of non-cutaneous, non-ocular infections caused by *P. lilacinus* have been resolved with antifungal and/or surgical treatment (Table 3). Surgery was effective as sole treatment in three cases [38,40,92], and when combined with itraconazole in one case [43]. One case of osteomyelitis was resolved by surgery after the failure of initial treatment with amphotericin B and miconazole [44]. Itraconazole was used in five (31.2%) of the 16 reported cases of non-cutaneous, non-ocular infections by *P. lilacinus*, with a favourable outcome in all cases [5,41–43,49]. When tested, the in-vitro susceptibility of clinical isolates to itraconazole was high, which correlated with the positive clinical outcomes [5,41,42,45]. Amphotericin B resolved the seven cases in which this drug was used. Despite the high MICs of amphotericin B for the isolates from two [46,48] of the four reported cases of fungaemia, recovery was obtained in all four cases [46–49]. In one of these cases, amphotericin B was combined with flucytosine and granulocyte-macrophage colony-stimulating factor [48], and in another with itraconazole [49]. In two of these four cases of fungaemia, medical treatment was combined with the removal of a central venous catheter [46,47].

CONCLUSIONS

P. lilacinus is an emerging pathogenic mould that is able to cause severe cutaneous and sub-cutaneous infections and devastating oculomycosis. Less frequently, this fungus is reported as a causative agent of infections in other body locations. Although *P. lilacinus* infections have been described in previously healthy individuals, the majority of cases described in the literature involve patients with identified predisposing factors. In cases of oculomycosis, intra-ocular lens implantation and non-surgical trauma were the most frequent predisposing factors, followed by ocular surgery. Generally, oculomycosis patients had received topical or systemic corticosteroid therapy. The most common predisposing factors for cutaneous and sub-cutaneous infections were solid organ and bone marrow transplants, malignancy and corticosteroid therapy. Fungaemia was related to the use of central venous catheters.

In contrast to the other species belonging to the genus, *P. lilacinus* generally shows a poor response to conventional antifungal drugs. Therefore, correct identification of clinical isolates to the species level is mandatory for appropriate treatment of the disease. Many therapeutic regimens have been used to treat paecilomycosis, but with a high failure rate. Recovery of neutropenia and removal of central venous catheters, if present, are essential to resolve the infection. In many cases, surgery must be combined with medical treatment. The older antifungal drugs, such as amphotericin B, flucytosine, fluconazole, miconazole and itraconazole have been used in many cases of cutaneous, sub-cutaneous and ocular infections, but generally with unfavourable outcomes. Although there is limited clinical experience in the use of voriconazole, this drug seems to be the most effective agent for the treatment of these fungal infections. Posaconazole and ravuconazole may be good alternatives on the basis of their excellent activity *in vitro*.

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