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Candidaemia with uncommon *Candida* species: predisposing factors, outcome, antifungal susceptibility, and implications for management

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Abstract

The risk factors for and clinical features of bloodstream infection with uncommon *Candida* spp. (species other than *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicals* and *C. krusei*) are incompletely defined. To identify clinical variables associated with these species that might guide management, 57 cases of candidaemia resulting from uncommon *Candida* spp. were analysed in comparison with 517 episodes of *Candida albicans* candidaemia (2001–2004). Infection with uncommon *Candida* spp. (5.3% of candidaemia cases), as compared with *C. albicans* candidaemia, was significantly more likely to be outpatient-acquired than inpatient-acquired (15 of 57 vs. 65 of 517 episodes, p 0.01). Prior exposure to fluconazole was uncommon (n = 1). *Candida dubliniensis* was the commonest species (n = 22, 39%), followed by *Candida guilliermondii* (n = 11, 19%) and *Candida lusitaniae* (n = 7, 12%). *C. dubliniensis* candidaemia was independently associated with recent intravenous drug use (p 0.01) and chronic liver disease (p 0.03), and infection with species other than *C. dubliniensis* was independently associated with age <65 years (p 0.02), male sex (p 0.03) and human immunodeficiency virus infection (p 0.05). Presence of sepsis at diagnosis and crude 30-day mortality rates were similar for *C. dubliniensis*-related, non-*C. dubliniensis*-related and *C. albicans*-related candidaemia. Haematological malignancy was the commonest predisposing factor in *C. guilliermondii* (n = 3, 27%) and *C. lusitaniae* (n = 3, 43%) candidaemia. The 30-day mortality rate of *C. lusitaniae* candidaemia was higher than the overall death rate for all uncommon *Candida* spp. (42.9% vs. 25%, p not significant). All isolates were susceptible to amphotericin B, voriconazole, posaconazole, and caspofungin; five strains (9%) had fluconazole MIC values of 16–32 mg/L. Candidaemia due to uncommon *Candida* spp. is emerging among hospital outpatients; certain clinical variables may assist in recognition of this entity.

Keywords: antifungal susceptibility, candidaemia, outcome, risk factors, uncommon *Candida* species
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Introduction

Bloodstream infection with *Candida* spp. (candidaemia) is associated with significant morbidity [1–3]. Whereas the epidemiological, clinical and microbiological features of candidaemia due to *Candida albicans* and the most common non-*albicans Candida* spp. (*Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei*) are well defined [1,4–9], relatively little is known about other or less frequently encountered non-*albicans Candida* spp. [10–13]. Given that candidaemia due to such uncommon *Candida* spp. appears to be increasing, and that certain species, e.g. *Candida dubliniensis* and *Candida guilliermondii*, have been reported to be less susceptible or resistant to antifungal agents [10,14–16], local epidemiological trends have important implications for clinical management.

Most epidemiological surveys of uncommon *Candida* spp. have been limited to single institutions or specific patient populations, and have focused on only one pathogen

[11–14], which may not be broadly representative. The epidemiological, clinical and antifungal susceptibility data associated with candidaemia due to uncommon *Candida* spp. were therefore analysed during a 3-year prospective survey in Australia [5]. Clinical features or risk factors that discriminate among fungaemia caused by these species and those due to *C. albicans*, the commonest cause of candidaemia, including that in Australia [4–7], could guide selection of antifungal therapy pending species confirmation. As *C. dubliniensis* shares many phenotypic and virulence characteristics with *C. albicans*, and, indeed, may be misidentified as *C. albicans* [17,18], the clinical and laboratory features of *C. dubliniensis* candidaemia were compared with those of *C. albicans* candidaemia. To better understand the pathogenic potential of other uncommon *Candida* spp. (i.e. those other than *C. dubliniensis*), the predisposing factors for candidaemia due to these species were also examined.

Materials and Methods

Study design

Prospective laboratory-based surveillance of all episodes of candidaemia within Australia was undertaken during the period August 2001 to July 2004, as described elsewhere [5]. Clinical information concerning each episode was collected on day 5 and day 30 after the first isolation of *Candida* from blood, and included: demographic data, healthcare setting, risk factors within the preceding 30 days, major comorbidities, clinical features including sepsis [19], complications of candidaemia, treatment, and clinical outcome 30 days after diagnosis.

Definitions

Candidaemia refers to the incident isolation of *Candida* spp. from blood during the study period. The term 'uncommon *Candida* spp.' (UCS) encompasses species other than *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. Relapses were defined as recurrent positive blood cultures within 30 days of the first positive culture after an initial clinical and microbiological response. Episodes were considered to be inpatient healthcare-associated if candidaemia was diagnosed ≥48 h after hospital admission and patients had no clinical manifestations on admission [20]. Outpatient healthcare-associated cases were defined as those occurring <48 h after admission and associated with an indwelling medical device, surgical procedure, or chemotherapy-related neutropenia ($<1 \times 10^9$ cells/L). Community-acquired infections were those in outpatients without such healthcare-related risk factors. Attributable mortality was judged by treating physicians as death that occurred in the presence of ongoing clinical manifestations of candidaemia. Endocarditis was classified according to modified Duke criteria [21].

Microbiological methods

Candida organisms were speciated by participating laboratories using standard phenotypic methods [22], and forwarded to a reference laboratory for species confirmation [23] and for antifungal susceptibility testing using CLSI M27-A2 broth microdilution methodology [24]. MICs were read at 48 h of incubation; breakpoints for susceptibility were adopted according to CLSI methodology [24]. Species identity of all UCS isolates was also determined by PCR fingerprinting as previously described [25].

Data analysis

Clinical data were analysed using SPSS version 10.0.7 (SPSS Inc., Chicago, IL, USA). Variables associated with *C. dubliniensis* candidaemia and with non-*C. dubliniensis* UCS bloodstream infection were each compared with those associated with *C. albicans* infection. Univariate analyses were performed using Student's *t*-test or non-parametric tests as appropriate (for continuous variables) or the chi-square or Fisher's exact tests (for categorical variables). p-Values <0.05 were significant. Multivariate logistic regression analyses were performed using the backwards selection method to identify risk factors for candidaemia due to one or more UCS after including all plausible variables and those with an unadjusted association of p <0.1 using univariate analysis.

Results

Patient demographics

Over the 3-year period, 57 episodes of UCS-associated candidaemia in 57 patients were reported (5.3% of candidaemia cases during this time). Demographic data were available for 54 (95%) episodes, and healthcare setting and clinical data were available for 51 (90%) cases. These data were compared with those reported for 517 cases of candidaemia associated with *C. albicans*.

Two-thirds (n = 36) of patients were males, and the median age was 45 years (interquartile range, 28–58 years). Adults aged 15–64 years accounted for 80% of cases; adults aged ≥65 years, children aged 2 months to 14 years and neonates aged ≤1 month accounted for 7%, 11%, and 2%, respectively.

Candida spp.

Eleven UCS were identified (Table 1); *C. dubliniensis* was the most common (39% of UCS episodes), followed by *C. guilliermondii* (19%), and *Candida lusitaniae* (12%). Two episodes

TABLE 1. Uncommon *Candida* spp. causing candidaemia, Australia 2002–2004

Candida spp.	No. (%)
Candida dubliniensis[a]	22 (39)
Candida guilliermondii	11 (19)
Candida lusitaniae	7 (12)
Candida kefyr	5 (9)
Candida rugosa	3 (5)
Candida pelliculosa	3 (5)
Candida famata	2 (4)
Candida colliculosa	1 (2)
Candida lambica	1 (2)
Candida lipolytica	1 (2)
Candida sake	1 (2)
All species	57 (100)

[a]Two episodes of *C. dubliniensis* candidaemia involved >1 *Candida* sp. (one episode of *C. dubliniensis*/*C. glabrata* and on e of *C. dubliniensis*/*C. albicans*).

involved mixed *Candida* spp. (*C. dubliniensis*/*C. glabrata* and *C. dubliniensis*/*C. albicans*) and were included in the '*C. dubliniensis* group' for analyses.

Comparison of *C. dubliniensis*-related and *C. albicans*-related candidaemia

Twenty-two episodes of *C. dubliniensis* candidaemia were reported. The setting for acquisition of the infection included inpatient healthcare (85%), outpatient healthcare (5%), and the community (10%), similar to the acquisition settings for *C. albicans* candidaemia (Table 2). Predisposing factors for *C. dubliniensis* infection were also broadly similar to those reported for *C. albicans* (Table 2). According to multivariate analysis, patients with *C. dubliniensis* candidaemia were significantly more likely to have been current/recent intravenous drug users (p 0.01) and to have chronic liver disease (p 0.03; Table 2). Although a greater proportion of patients were aged <65 years (90% vs. 65.2% for *C. albicans* candidaemia), younger age (<65 years) was not independently associated with *C. dubliniensis* infection. Manifestations of sepsis, 30-day crude mortality and length of hospital stay were similar in *C. dubliniensis*-related and *C. albicans*-related candidaemia (Table 3).

TABLE 2. Comparison of characteristics of bloodstream infection due to uncommon *Candida* spp. with *Candida albicans* candidaemia[a]

Variable (total no.)[b]	*Candida dubliniensis* (*n* = 22 episodes)	p[c]	Uncommon *Candida* spp. other than *C. dubliniensis* (*n* = 35 episodes)	p[c]	*C. albicans* (*n* = 517 episodes)
Univariate analysis					
Age ≥65 years (4)	2/21 (10)	0.02	2/33 (6)	<0.001	172/481 (35.8)
Male sex (36)	12/21 (57)	1.0	24/33 (73)	0.05	262/502 (52.2)
Adult ICU admission (5)	2/22 (10)	0.28	3/35 (9)	0.08	111/517 (21.5)
Acquisition of candidaemia					
OHCA (9)	1/20 (5)	1.0	8/31 (26)	0.01	42/441 (9.5)
CA (6)	2/20 (10)	0.30	4/31 (13)	0.08	23/441 (5.2)
IHCA (36)	17/20 (85)	1.0	19/31 (61)	0.002	376/441 (85.3)
Underlying disease					
Liver disease (6)	3/20 (15)	0.1	3/31 (10)	0.2	23/438 (5.3)
Haematological malignancy (14)	6/22 (27)	0.02	9/35 (26)	0.01	52/517 (10)
Non-haematological malignancy (7)	3/21 (14)	1.0	4/33 (12)	0.63	82/481 (17)
Diabetes (5)	2/22 (9)	0.76	3/35 (9)	0.60	68/517 (13.2)
Autologous HSCT (3)	1/20 (5)	0.24	2/31 (7)	0.07	5/438 (1.1)
Solid organ transplantation (2)	1/20 (5)	0.42	1/31 (3)	0.56	11/438 (2.5)
HIV (6)	1/20 (5)	0.13	2/31 (7)	0.02	2/438 (0.5)
Risk factors					
Intravenous drug use (6)	3/19 (16)	0.02	3/28 (11)	0.05	11/428 (2.6)
Vascular access device (33)	15/19 (79)	0.76	18/27 (67)	0.07	352 (68.1)
Recent surgery (13)	7/19 (37)	0.48	6/28 (21)	0.01	204/428 (47.7)
Recent TPN (9)	3/19 (16)	0.09	6/28 (21)	0.11	160/429 (37.3)
Neutropenia (17)	7/19 (37)	0.01	10/29 (35)	0.01	60/434 (13.8)
Recent corticosteroid receipt (11)	7/19 (37)	0.45	4/28 (14)	0.13	124/427 (29)
Cytotoxic chemotherapy (14)	7/20 (35)	0.003	7/31 (23)	0.03	42/438 (8.1)
Systemic antifungal exposure (1)	–	–	1/29 (3)	–	39/428 (9.6)
Recent antibiotic exposure (38)	15/19 (79)	0.25	23/29 (79)	0.12	383/429 (89.3)
Multivariate analysis	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p	
Age ≤65 years	–	NS	11.1 (1.4–86)	0.02	
Male sex	–	NS	3.0 (1.1–8.3)	0.03	
Intravenous drug use	7.3 (1.5–34)	0.01	–	NS	
Liver disease	2.4 (0.6–8.8)	0.03	–	NS	
HIV infection	–	NS	9.0 (1.0–83)	0.05	

CA, community-acquired; HIV, human immunodeficiency virus; HSCT, haematopoeitic stem cell transplantation; ICU, intensive-care unit; IHCA, inpatient healthcare-associated; NS, not significant; OHCA, outpatient healthcare-associated; TPN, total parenteral nutrition.
[a]No./total no. (%) for each category where the data were available, unless otherwise indicated.
[b]Refers to the total no. present in all episodes of bloodstream infection with uncommon *Candida* spp.
[c]Comparisons using *C. albicans* candidaemia as reference category.

TABLE 3. Clinical characteristics and outcomes of *Candida dubliniensis* and non-*C. dubliniensis* uncommon *Candida* spp.-related candidaemia as compared with *Candida albicans* candidaemia

Characteristic	*C. dubliniensis* (*n* = 22 episodes)	Non-*C. dubliniensis* uncommon *Candida* spp. (*n* = 35 episodes)	*C. albicans* (*n* = 517 episodes)
Clinical manifestations of sepsis, no. (%)	16/19 (84)	19/27 (70)	348/425 (81.9)
Ventilation on day 1, no. (%)	4/19 (21)	5/(19)	146/517 (34.3)
Length of stay (days) following candidaemia, mean (±SD)	38.1 (±22.7)	32.9 (±39.5)	50.6 (±56)
Thirty-day crude mortality, no. (%)	5/18 (27.7)	6/26 (23)	123/422 (29.2)

SD, standard deviation.

Comparison of non-*C. dubliniensis*-related and *C. albicans*-related candidaemia

Thirty-five cases of non-*C. dubliniensis* UCS infection occurred during the study period. A significantly greater proportion of episodes were outpatient-acquired, as compared with episodes of *C. albicans* candidaemia (39% vs. 15%, p 0.002); furthermore, more than one-quarter of cases were outpatient healthcare-associated (26% vs. 10%, p 0.01). As compared with *C. albicans* candidaemia (Table 2), independently significant variables associated with non-*C. dubliniensis* UCS were age <65 years (p 0.02), male sex (p 0.03), and human immunodeficiency virus (HIV) infection (p 0.05). A single patient (3%) had prior exposure to fluconazole, as compared to 39 of 517 (8%) patients with *C. albicans* candidaemia (p not significant). Thirty-day mortality did not differ from that associated with *C. albicans* candidaemia (Table 3).

Together, *C. guilliermondii* and *C. lusitaniae* accounted for approximately one-half of non-*C. dubliniensis* UCS infections. As in episodes of *C. dubliniensis* candidaemia, underlying haematological malignancy (with attendant cytotoxic chemotherapy exposure and neutropenia) was the most frequent predisposing factor, although both species were uncommon in other patient groups. The 30-day crude mortality of *C. lusitaniae* candidaemia was higher than that of *C. dubliniensis* (43% vs. 28%; Table 2). Other species of UCS included *Candida rugosa* (*n* = 3), which caused candidaemia in patients with haematological malignancy, with or without neutropenia. *Candida pelliculosa* caused infection in patients with HIV infection (*n* = 2), recent surgery (*n* = 3), and intravenous drug use (*n* = 1).

Outcome of candidaemia

Complications of UCS candidaemia were rare; one of 13 patients who underwent ophthalmological examination had intra-ocular candidiasis and one of 44 examined by echocardiography had probable endocarditis. Both manifestations were diagnosed within 30 days following the first positive blood culture. There were no relapses of candidaemia. The

TABLE 4. Species distribution and *in vitro* antifungal susceptibilities of uncommon *Candida* spp[a]

Agent	MICs (mg/L)	*Candida dubliniensis* (*n* = 22)	*Candida guilliermondi* (*n* = 11)	*Candida lusitaniae* (*n* = 7)	*Candida kefyr* (*n* = 5)	*Candida rugosa* (*n* = 3)	*Candida pelluculosa* (*n* = 3)	*Candida famata* (*n* = 2)
AMB[b]	MIC_{50}	0.06	0.25	0.06	0.5	–	–	–
	MIC_{90}	0.125	0.5	–	–	–	–	–
	Range (no. tested)	0.06–0.25	0.06–0.5	0.03–0.125	0.25–1	0.5 (2)	0.125–0.25	0.25 (1)
5-FC	MIC_{50}	0.06	0.03	0.03	0.03	–	–	–
	MIC_{90}	0.125	0.125	–	–	–	–	–
	Range (no. tested)	0.03–64	0.03–0.125	0.03	0.03–16	0.125–0.5 (2)	0.03–32	0.06 (1)
FLU	MIC_{50}	0.25	4	0.125	0.125	–	–	–
	MIC_{90}	1.0	16	–	–	–	–	–
	Range (no. tested)	0.05–32	1–32	0.5–8	0.25–0.5	1–16 (2)	4	4 (1)
ITC	MIC_{50}	0.03	0.5	0.125	0.03	–	–	–
	MIC_{90}	0.125	1	–	–	–	–	–
	Range (no. tested)	0.008–0.25	0.25–2	0.06–1	0.008–0.06	006–0.125 (2)	0.25	0.5 (1)
VOR	MIC_{50}	0.008	0.125	0.016	0.008	–	–	–
	MIC_{90}	0.016	0.25	–	–	–	–	–
	Range (no. tested)	0.008–0.06	0.06–0.5	0.008–0.125	0.008–0016	0.008–0.06 (2)	0.06–0.125	0.125 (1)
POS	MIC_{50}	0.06	0.25	0.06	0.25	–	–	–
	MIC_{90}	0.125	0.5	–	–	–	–	–
	Range (no. tested)	0.03–0.125 (10)	0.06–0.5 (7)	0.008–0.25 (5)	0.03–0.25	0.125 (2)	0.125–0.25	0.25 (1)
CAS	MIC_{50}	0.06	0.5	0.25	0.06	–	–	–
	MIC_{90}	0.25	0.5	–	–	–	–	–
	Range (no. tested)	0.008–0.5	0.25–2	0.25–0.5	0.03–0.125	0.25–2 (2)	0.06–0.25	0.5 (1)

AMB, amphotericin B; CAS, caspofungin; FLU, fluconazole; 5-FC, 5-flucytosine; ITC, itraconazole; POS, posaconazole; VOR, voriconazole.
[a]Remaining isolates: one isolate each of *Candida colliculosa*, *Candida lambica*, *Candida lipolytica*, and *Candida sake*.

crude 30-day mortality for all UCS was 25% (11 deaths in 44 episodes) and the attributable mortality was 11%. There were no deaths among 12 patients with outpatient-acquired infection, whereas 11 among 32 (34%) patients with inpatient healthcare-associated infection died (p 0.02).

Antifungal susceptibility

MICs for UCS of seven antifungal agents are shown in Table 4. Resistance was rare. However, five strains (three *C. guilliermondii* and one each of *C. rugosa* and *C. dubliniensis*) had susceptible-dose-dependent MIC values of fluconazole (MIC 16–32 mg/L): three of these were recovered from patients who subsequently died. Seven *C. guilliermondii* isolates and one isolate each of *C. dublinenis*, *Candida colliculosa*, *Candida famata* and *Candida lipolytica* were susceptible-dose-dependent to itraconazole (MIC 0.25–0.5 mg/L). All isolates were susceptible to voriconazole (MIC ≤1 mg/L) and demonstrated posaconazole MICs of ≤0.25 mg/L where tested. *C. lusitaniae* isolates had low MICs of amphotericin B (range 0.03–0.25 mg/L). Caspofungin demonstrated good activity against all species; one isolate each of *C. guilliermondii* and *C. rugosa* had MICs of 2 mg/L.

Discussion

The risk factors for, and clinical presentation of, infection due to uncommon but emerging (non-*C. albicans*) *Candida* species (UCS) [8,9,11–15] are incompletely defined.

Although 'uncommon' in most clinical settings, these species may pose therapeutic dilemmas in individual patients. The clinical relevance of such pathogens relates primarily to the association of a number of these species with antifungal drug resistance, and with reportedly poorer clinical outcomes [11,15,16,26]. This study has provided an overview of the epidemiology of candidaemia with UCS and has identified a number of clinical variables associated with the isolation of these species that may guide selection of initial antifungal therapy.

Only collaterally considered in other population-based surveys of candidaemia, the proportion of cases where UCS are isolated has ranged from 1.3% to 3% [7,27]. However, two hospital-specific studies from Latin America reported substantially higher rates of infection (11.7–18% of cases) [28,29]. This variation is not readily explained, but may be due to differences in case mix. In our cohort of unselected patients, UCS caused 5.3% of candidaemia episodes. Importantly, these infections were not restricted to hospital inpatients and, as compared with *C. albicans* candidaemia, were significantly more likely to be outpatient-acquired than inpatient-acquired. Indeed, population-based surveillance thus allowed us to identify nearly 30% of cases that would not have been captured by nosocomial surveillance. This is relevant to clinical practice, given the shift towards home-based management of patients with risk factors for candidaemia, and the overall emergence of candidaemia outside of hospitals [5,30]. As no other surveys have examined the clinical relevance of UCS in the general population, the generalization of our findings requires confirmation.

Established risk factors for candidaemia [1,2] were evident among many of the patients in this study. As in other studies of UCS [11–14], patients with haematological malignancy were at particular risk; however, UCS were also recovered from patients with chronic medical conditions, including liver disease, diabetes mellitus, and HIV infection, and from intravenous drug users. In addition, a number of variables associated with isolation of UCS were identified; age <65 years, male sex and HIV infection were independent predisposing factors for infection with non-*C. dubliniensis* UCS, whereas chronic liver disease and intravenous drug use were associated with *C. dubliniensis* candidaemia (Table 2). Further studies of larger numbers of patients with infections due to UCS are required to confirm these associations.

Previous attempts to identify unique risk factors for the development of non-*C. albicans* candidaemia have necessarily focused on the more 'common' species (e.g. *C. glabrata*), with prior fluconazole exposure, in particular, being reported as a risk factor [9,31,32]. Data from the present study hint that there may be differences in risk factors for candidaemia due to UCS. UCS were isolated almost exclusively from patients without prior antifungal exposure, suggesting that, thus far, azole use has not played a major role in their selection. Patients aged <65 years were significantly more likely to develop candidaemia with UCS, whereas *C. glabrata* candidaemia has been associated with older age [33]. However, interpretation of these data must take into consideration species–species epidemiological differences within both 'common' and 'uncommon' non-*C. albicans Candida* pathogens (this study) [1,11–14].

This study extends previous epidemiological data regarding UCS. *C. dubliniensis* was the most common species, causing 2% of candidaemia episodes [5], consistent with previously reported rates (0.7–7%) [6,13,34]. However, other studies have reported dominant species such as *C. rugosa* [29], *C. pelliculosa* [28], or *C. guilliermondii* [7,11,29]. Direct comparison of rates of isolation of specific species is confounded by the differing tendencies of laboratories to identify *Candida* to the species level. Nevertheless, the data affirm the results of smaller series, that *C. dubliniensis*

causes candidaemia in patients with a range of clinical conditions [13,34]. As *C. dubliniensis* possesses many of the virulence characteristics associated with *C. albicans* [17], it may be expected to cause the same spectrum of disease; indeed, the epidemiology of *C. dubliniensis* candidaemia is more similar to that of *C. albicans* candidaemia than is the epidemiology of non-*C. dubliniensis* spp. (Table 2). As noted previously [11,12], immunocompromised patients with haematological malignancy were at particular risk of *C. lusitaniae* or *C. guilliermondii* candidaemia. *C. lusitaniae* infection has also been reported to be associated with prior antifungal treatment [12], but we were unable to confirm whether antifungal exposure selects for this species, due to insufficient patient numbers. Although only three cases of *C. rugosa* candidaemia were encountered in the present study, this species is notable for its association with nosocomial case clusters [14,29].

Importantly, candidaemia with UCS was not indicative of more severe disease or of poorer outcome, as compared with *C. albicans* candidaemia, although the mortality of *C. lusitaniae* infection was higher (p not significant). This relatively benign outcome contrasts with that reported elsewhere [11,12,35]. However, deaths occurred only in hospitalized inpatients, emphasizing the complexity of factors that influence outcome [1,3].

Finally, *in vitro* resistance to azole agents was rare among the present cohort of UCS isolates, although a small number, including three *C. guilliermondii* strains, tested susceptible-dose-dependent to fluconazole. In contrast, others have reported azole resistance rates of 10–15% among *C. guilliermondii* strains [11,26]. Data from yet another survey caution against the use of azoles to treat *C. rugosa* infections, as only 41% and 61% of strains were fluconazole-susceptible and voriconazole-susceptible, respectively [15]. In this study, voriconazole and posaconazole had good activity against all species tested. The differences in prevalence of resistance may reflect case mix or geographical differences, emphasizing the importance of understanding local epidemiological factors. Although resistance to amphotericin B among *C. lusitaniae* strains was not detected, this species rapidly acquires resistance to amphotericin B *in vitro*, and current opinion advises against its use for the treatment of such infections [12].

The limitations of the study are recognized; the patient cohort was small, and longitudinal data were not collected beyond 30 days. Some authors recommend follow-up of patients beyond 30 days to detect delayed complications [2,36]. In one report, meningitis following *C. dubliniensis* fungaemia developed 3 months after 'cure' of infection [36].

In conclusion, UCS are emerging among hospital outpatients. Certain clinical variables may enable recognition of candidaemia caused by these species. Resistance to azole and amphotericin B antifungal agents is uncommon, and clinical outcomes at day 30 are similar to those for *C. albicans* candidaemia. Nevertheless, identification of risk factors and identification of all *Candida* organisms at the species level from blood are of value in understanding the pathogenesis of invasive candidiasis.

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