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Short report

Candidaemia in an Irish intensive care unit setting between 2004 and 2018 reflects increased incidence of *Candida glabrata*

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SUMMARY

The cumulative incidence of candidaemia in an Irish intensive care unit (ICU) setting between January 2004 and August 2018 was 17/1000 ICU admissions. *Candida albicans* was responsible for 55% (*N*=41) of cases. *C. glabrata* (*N*=21, 28%) was the next most prevalent species, and has been identified most frequently since 2012. *C. glabrata* was associated with a higher mortality rate (57%) than *C. albicans* (29%). All isolates were susceptible to caspofungin (0.05 μg/mL). Notably, 37% of *C. glabrata* isolates were resistant to fluconazole, with 13% resistant to amphotericin B, highlighting the need for prudent antifungal stewardship to impede development of multi-drug-resistant *C. glabrata* in the ICU setting.

Introduction

Invasive candidiasis is a challenging complication in the intensive care unit (ICU) setting. A UK study in 2003 reported an incidence rate for candidaemia of 7.4/1000 ICU admissions [1]. Predominantly nosocomial, *Candida* spp. represent the fourth most frequently isolated pathogens in bloodstream infections in the USA [1].

Candidaemia is characterized by a high mortality rate of 36–63% [2]. Performed in the UK, the prospective NEMIS study of risk factors for development of candidaemia in ICUs reported a mortality rate of 41% among patients with candidaemia compared with non-candidaemia patients [3]. The study listed surgery as a major risk factor, with the strongest association found for abdominal procedures, followed by sepsis and acute renal failure. Parenteral nutrition and administration of antimicrobials targeting anaerobic pathogens were also identified as risk factors [3].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidelines in 2012 supporting

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clinical decisions regarding management of invasive candidiasis. The guidelines attempted to clarify the eligibility of patients for prophylaxis. Specifically, prophylaxis was only recommended moderately in cases of recent abdominal surgery and recurrent intestinal perforations [4]. Traditionally, fluconazole has been considered to be most useful for treatment of candidaemia [4], but the introduction of echinocandins (including anidulafungin, caspofungin and micafungin) has reduced reliance on fluconazole. This is important as the efficacy of fluconazole against non-*C. albicans* spp., including *C. glabrata* and *C. krusei*, is unreliable [5], and increasingly a limitation in the context of increased prevalence of non-*C. albicans* spp.

Invasive candidiasis is caused typically by one of five *Candida* spp. (*C. albicans, C. glabrata, C. tropicalis, C. parapsilosis* and *C. krusei*) [6]. The ARTEMIS DISK surveillance study compiled candidaemia isolate data from 127 medical centres, and found *C. albicans* to be the primary causative agent (62%) [7]. However, the prevalence of *C. albicans* has decreased steadily [6], concomitant with an increase in *C. glabrata* and *C. parapsilosis*. Factors determining species distribution include geography, antifungal therapy and patient factors [8]. In northern Europe and the USA, increased incidence of *C. glabrata* has been observed, while both Spanish and Brazilian reports describe increased prevalence of *C. parapsilosis* [6]. A large French study, investigating the potential association of antifungal drugs with species distribution, stated that fluconazole therapy increased the prevalence of fluconazole-resistant strains of *C. glabrata* and *C. krusei* [9].

However, such trends have not yet been reported in Ireland. Therefore, this study determined whether changes in the incidence of *Candida* spp. and antifungal susceptibility had occurred in the ICU of a large tertiary hospital, assessing records between January 2004 and August 2018. The objective of this study was to provide insight into the evolving epidemiology of candidaemia in Ireland.

Methods

Setting

University Hospital Limerick (UHL) in Ireland's mid-West has approximately 480 inpatient beds for a catchment population of 400,000. At the time of writing, UHL ICU is an eight-bedded facility with approximately 300 admissions per annum. ICU admissions are received from the emergency department, other UHL departments, and five hospitals within the UHL group.

Study design

Data analysis was undertaken, including chart reviews, relevant to any patient in the ICU with a candida-positive blood culture between January 2004 and August 2018. Patient demographics, clinical management and empirical therapy, length of stay (LOS), presence of a central venous catheter (CVC), outcomes, identification of *Candida* spp. isolates and antifungal susceptibility were reviewed. The Sepsis-related Organ Failure Assessment (SOFA) score was used as a marker of predicted mortality.

Laboratory methods

BacT/Alert 3D (bioMérieux, Marcy l'Etoile, France) was used for blood culture incubation. API Candida (bioMérieux) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker, Billerica, MA, USA) were used for *Candida* spp. identification. Sensititre YeastOne (Trek Diagnostic Systems, Thermo Fisher Scientific, Waltham, MA., USA) microbroth dilution was used to determine minimum inhibitory concentrations, and antifungal susceptibility was determined using the guidelines of the Clinical Laboratory and Standards Institute (CLSI).

Data analysis

Data were stored and analysed using Excel 2016 (Microsoft Corp., Redmond, WA, USA). A two tailed *t*-test assuming unequal variances was used to determine any statistical difference between means in the *C. albicans* and *C. glabrata* groups, where $P \leq 0.05$ was considered to indicate statistical significance.

Results

Distribution of Candida spp. (2004–2018)

Between January 2004 and August 2018, 74 ICU patients developed candidaemia. This represents an incidence rate of 17/1000 ICU admissions. Of the *Candida* spp. isolated, *C. albicans* was the most prevalent, accounting for 55% ($N=41$) of cases, with non-*C.albicans* spp. accounting for 45% ($N=33$) of cases (Table I). A reduction in the incidence of *C. albicans* was observed from 2004 to 2018. In 2004, *C. albicans* accounted for 83% ($N=5$) of cases, while no cases of *C. albicans* candidaemia were observed in the first eight months of 2018 (Table I).

The reduction in *C. albicans* correlated with an increase in non-*C. albicans* spp., namely *C. glabrata*, *C. parapsilosis* and *C. tropicalis*. Between 2004 and 2018, *C. glabrata* accounted for 28% ($N=21$) of cases of candidaemia, with *C. parapsilosis* and *C. tropicalis* each accounting for 14% ($N=10$) of cases. In 2004, no cases of *C. glabrata* were observed, while *C. glabrata* was implicated in both recorded cases in 2018 (up to August) (Table I).

Determinants of C. albicans and C. Glabrata candidaemia patient groups 2004–2018

Patient ages ranged from 22 to 88 years (mean 66 years) (Table A, see online supplementary material). Those infected with *C. albicans* ($N=41$) and *C. glabrata* ($N=21$) had mean ages of 65 and 69 years, respectively ($P=0.26$). SOFA scores were found to be independent of causative *Candida* spp., with a mean score of 9 across all groups (Table A, see online supplementary material) ($P=0.52$). The mean time from ICU admission to diagnosis of candidaemia was seven days for patients with *C. albicans* and four days for patients with *C. glabrata* (Table A, see online supplementary material) ($P=0.26$). The mean ICU LOS was 21 days for patients with *C. albicans* and 18 days for patients with *C. glabrata* ($P=0.38$). CVC lines were *in situ* for 80% of candidaemias. The overall 30-day mortality rate (2004–2018) for all candidaemias was 39% ($N=29$), although it varied between patients infected with *C. albicans* (29%; $N=12$) and *C. glabrata* (57%; $N=12$).

Table I
Candida spp. encountered between January 2004 and August 2018

Year	*C. albicans*	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*	Other[a]	Total
2004	5	0	1	0	0	6
2005	2	2	0	0	0	4
2006	4	0	0	1	0	5
2007	3	1	0	0	0	4
2008	7	3	0	2	0	12
2009	3	0	2	0	0	5
2010	2	3	0	0	0	5
2011	1	0	1	0	0	2
2012	2	3	0	1	0	6
2013	4	3	1	0	0	8
2014	2	1	1	0	1	5
2015	2	2	0	0	0	4
2016	0	2	0	0	0	2
2017	4	0	0	0	1	5
2018	0	1	0	0	0	1
Total	*N*=41 (55%)	*N*=21 (28%)	*N*=6 (8%)	*N*=4 (6%)	*N*=2 (3%)	*N*=74 (100%)

[a] Other *Candida* spp. identified included *C. krusei* and *C. dubliniensis*.

Empirical treatment of suspected candidaemia (2004–2018)

Empirical treatment was administered to 78% (*N*=58) of patients with subsequent candida-positive blood culture. Azoles were administered in 59% (*N*=34) of cases, with fluconazole accounting for 55% of all empirical treatments (Table B, see online supplementary material). Amphotericin B was given in 7% (*N*=5) of cases, with its last recorded use in 2007. The first recorded use of an echinocandin (caspofungin) was in 2008, and this accounted for 33% (*N*=19) of empirical treatments overall (Table B, see online supplementary material). The most recent use of fluconazole as an empirical therapy was in 2014.

Antifungal agent susceptibility of Candida spp. isolates (2004–2018)

Candida antifungal susceptibility testing was performed using the CLSI guidelines. From 2004 to 2018, the antifungal susceptibility panel evolved significantly. Caspofungin was not included in the susceptibility panel prior to 2009, despite being used as an empirical therapy in 2008. 5-Flucytosine was removed from the antifungal susceptibility panel in 2016. Susceptibility testing revealed that all tested isolates were susceptible to caspofungin. Azole resistance was encountered frequently, with 37% of *C. glabrata* isolates being resistant to fluconazole. This contrasts with just 2% of *C. albicans* being resistant to fluconazole. Amphotericin B resistance was not uncommon among *C. glabrata* isolates (14%), whereas all tested *C. albicans* isolates were susceptible to amphotericin B (Table II). Mean and median susceptibility data are shown in Table C (see online supplementary material).

Discussion

This study provided comprehensive insight regarding the changing epidemiology of candidaemia in Ireland, which at 17/1000 ICU admissions was considerably more prevalent than the rate of 7.4/1000 ICU admissions reported previously in the UK [1] and Northern Ireland [10].

Candida spp. isolated in Limerick over the 15-year study period comprised *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*. Several studies have demonstrated that these few *Candida* spp. account for the majority of candidaemias, with the present study providing further evidence [6]. *C. albicans* is the most frequently isolated species in invasive candidiasis globally [6,7]. Similarly, in the present

Table II
Antifungal agent susceptibility data (2004–2018) determined using the guidelines of the Clinical Laboratory and Standards Institute[a]

Antifungal agent	All *Candida* spp.	*C. albicans*	*C. glabrata*
5-Flucytosine	*N*=66	*N*=37	*N*=19
Susceptible	*N*=63 (95%)	*N*=36 (97%)	*N*=19 (100%)
Intermediate	*N*=1 (2%)	*N*=0 (0%)	*N*=0 (0%)
Resistant	*N*=2 (3%)	*N*=1 (3%)	*N*=0 (0%)
Amphotericin B	*N*=72	*N*=41	*N*=21
Susceptible	*N*=67 (93%)	*N*=41 (100%)	*N*=18 (86%)
Intermediate	*N*=0 (0%)	*N*=0 (0%)	*N*=0 (0%)
Resistant	*N*=5 (7%)	*N*=0 (0%)	*N*=3 (14%)
Fluconazole	*N*=70	*N*=41	*N*=19
Susceptible	*N*=61 (87%)	*N*=40 (98%)	*N*=12 (65%)
Intermediate	*N*=0 (0%)	*N*=0 (0%)	*N*=0 (0%)
Resistant	*N*=9 (13%)	*N*=1 (2%)	*N*=7 (37%)
Itraconazole	*N*=71	*N*=41	*N*=19
Susceptible	*N*=63 (89%)	*N*=39 (95%)	*N*=14 (74%)
Intermediate	*N*=2 (3%)	*N*=0 (0%)	*N*=1 (5%)
Resistant	*N*=6 (8%)	*N*=2 (5%)	*N*=4 (21%)
Caspofungin	*N*=41	*N*=19	*N*=15
Susceptible	*N*=41 (100%)	*N*=19 (100%)	*N*=15 (100%)
Intermediate	*N*=0 (0%)	*N*=0 (0%)	*N*=0 (0%)
Resistant	*N*=0 (0%)	*N*=0 (0%)	*N*=0 (0%)

[a] *Candida* spp. isolates were often not tested against the same panel of antifungal agents due to changes in the guidelines of the Clinical Laboratory and Standards Institute between 2004 and 2018.

study, *C. albicans* was the causative agent of most cases (55%), although this was lower than reported in other major studies; for example, a 2014 study by ARTEMIS DISK reported that *C. albicans* accounted for 62% of invasive candidiasis [7]. More recent work has shown a global reduction in the prevalence of *C. albicans* [6]. Although clear, the decline of *C. albicans* observed in this study has been gradual, with fluctuations, but correlated with an increase in non-*C. albicans* isolates. Notably, *C. albicans* was not isolated in the first eight months of 2018, representing a marked decline. Conversely, other *Candida* spp. have elevated incidence, with *C. glabrata* accounting for the greatest proportion of non-*C. albicans* cases (28%). Should this trend persist, *C. glabrata* will likely replace *C. albicans* as the primary cause of invasive candidiasis in this setting.

It is likely that patient characteristics influence candidaemia. The SENTRY study highlighted *C. albicans*-induced candidaemia in younger patients compared with *C. glabrata*; specifically, *C. glabrata* was isolated in 23% of those cases involving patients aged ≥65 years in contrast to 3% of candidaemias in those aged ≤15 years [8]. The apparent association between age and *Candida* spp. was less clear in the present study as there was no significant age difference between *C. albicans* and *C. glabrata* patient groups.

The SOFA score is considered to be a useful predictor of mortality in ICU patients, with a score ≤9 representing predicted mortality of 33% while a score ≥11 equates to predicted mortality of 95%. The mean SOFA score of 9 for all candidaemia admissions to UHL correlated with the 30-day mortality rate of 39%. Remarkably, patients with *C. glabrata* candidaemia (57%) were found to have a significantly higher mortality rate than patients with *C. albicans* candidaemia (29%). Clearly, this raises concerns in light of the increasing prevalence of *C. glabrata*.

This study found that empirical therapy was administered in the majority of cases of candidaemia (78%) and the choice of therapy was informed by ESCMID guidelines. Overall, azoles accounted for 58% of treatments, of which fluconazole was most frequently prescribed (55%), albeit prior to 2014. Since then, empirical therapy has included caspofungin, with the initial recorded use in 2008. Indeed, all isolates tested in this study were susceptible to caspofungin, thus providing assurance for its continued use as first-line treatment for candidaemia. In stark relief, susceptibility to fluconazole was less pertinent, with 37% of *C. glabrata* isolates resistant to fluconazole. This supports ESCMID recommendations reconsidering fluconazole as the drug of choice in an era of non-*C. albicans* candidaemia. With regard to potential development of resistance, widespread fluconazole dosage has been known to increase the prevalence of *C. glabrata* secondary to selection pressure [9]. This may partly explain the increase in *C. glabrata* in this Irish setting given the predominant use of fluconazole as an empirical therapy prior to 2012. Alarmingly, 14% of the *C. glabrata* isolates in this study were resistant to amphotericin B, whereas typical clinical isolates seldom exhibit such resistance. It may be pertinent that this hospital has consistently recorded lower use of antifungals than the median for Irish tertiary hospitals since 2007.

These data reiterate the risk of candidaemia for immunosuppressed patients, such as in ICU settings, with *C. glabrata* candidaemia seen to have a particularly poor prognosis. All *Candida* spp. isolates were susceptible to caspofungin, but *C. glabrata* was found to be significantly more resistant than *C. albicans* to fluconazole and amphotericin B. In the context of effective antifungal stewardship, this study suggests a need to evolve quickly from empirical and prophylactic use of antifungals that are currently effective, towards adoption of rapid molecular diagnosis of candidaemia and vigilance specific to the enhanced risks of drug-resistant *C. glabrata*.

Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.01.017.

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