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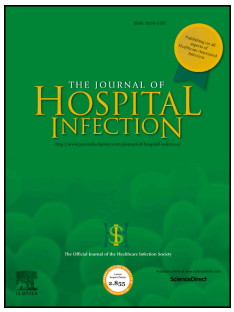

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Candidemia in an Irish intensive care unit (ICU) setting between 2004 and 2018 reflects increased incidence of *Candida glabrata*.

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Summary

The cumulative incidence of candidemia 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). *C. glabrata* (n=21: 28%) was the next most prevalent species; 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 fluconazole resistant, with 13% resistant to amphotericin B, highlighting need for prudent antifungal stewardship to impede development of multidrug-resistant *C. glabrata* in the ICU setting.

Introduction

Invasive candidiasis is a challenging complication in the intensive care unit (ICU) setting. A 2003 UK study reported incidence of candidemia at 7.4/1000 ICU admissions [1]. Predominantly nosocomial, *Candida* species represent the fourth most frequently isolated pathogens in blood stream infection (BSI) in the US [1].

Candidemia 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 candidemia in ICUs reported a mortality rate of 41% among patients with candidemia versus non-candidemia patients [3]. The study listed surgery as a major risk factor, with abdominal procedures most associated followed by sepsis and acute renal failure. Parenteral nutrition and administration of antimicrobials targeting anaerobic pathogens were also identified as risk factors [3].

ESCMID published guidelines in 2012 supporting clinical decisions regarding management of invasive candidiasis. The guidelines attempted to clarify 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 most useful for treatment of candidemia [4], but introduction of echinocandins (including anidulafungin, caspofungin and micafungin) reduced reliance on fluconazole. This is important as fluconazole efficacy against non-*C. albicans* species including *C. glabrata* and *C. krusei* is unreliable [5], and increasingly a limitation in the context of increased prevalence of non-*C. albicans* species.

Invasive candidiasis is caused typically by one of five *Candida* species (*C. albicans, C. glabrata, C. tropicalis, C. parapsilosis*, or *C. krusei*) [6]. The ARTEMIS DISK surveillance study compiled candidemia isolate data from 127 medical centres and found *C. albicans* to be the primary causative agent (62%) [7]. However, prevalence of *C. albicans* has decreased steadily [6], concomitant with an increase in *C. glabrata* and *C. parapsilosis* species. Factors determining species distribution include geography, antifungal therapy and patient factors [8]. In northern Europe and the US, 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 prevalence of fluconazole resistant strains of *C. glabrata* and *C. krusei* [9].

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

Methodology

Setting

University Hospital Limerick (UHL) in Ireland's mid-West has circa 480 inpatient beds for a catchment population of 400,000. At the time of writing, UHL ICU is an 8-bed facility with approximately 300 admissions per annum. ICU admissions are received from the Emergency department, other UHL departments and from five hospitals within the UL hospitals group.

Study Design

Analysis of data, including chart reviews, relevant to any patient in ICU with *Candida*-positive blood culture between January 2004 and August 2018. Patient demographics, clinical management & empirical therapy, duration of stay, presence of a Central Venous Catheter (CVC), outcomes, identification of *Candida* isolates and antifungal susceptibility were reviewed. The SOFA Score (sepsis-related organ failure assessment) was used a marker of predicted mortality.

Laboratory Methods

Biomerieux BacT/Alert 3D™ was used for blood culture incubation. Biomerieux API® Candida and Bruker MALDI-TOF™ mass spectrometry were used for *Candida* species identification. Sensititre YeastOne™ (TREK Diagnostic Systems) microbroth dilution was used to determine minimum inhibitory concentrations (MIC), and antifungal susceptibility was determined using Clinical Laboratory and Standards Institute (CLSI) guidelines.

Data Analysis

Data were stored and analysed using Microsoft Excel 2016. A two tailed T test assuming unequal variances was used to determine any statistical difference between means in *C. albicans* and *C. glabrata* groups where p=<0.05 was deemed statistically significant.

Results

Distribution of Candida species (2004-2018)

Between January 2004 and August 2018, 74 ICU patients developed candidemia. This represents an incidence rate of 17/1000 ICU admissions. Of the *Candida* species isolated, *C. albicans* was most prevalent accounting for 55% (n=41), with non-*C.albicans* accounting for 45% (n=33) (Table 1). Reduction in the incidence of *C. albicans* was observed from 2004-2018. In 2004, *C. albicans* accounted for 83% (n=5) of cases, while there was no case of *C. albicans* candidemia observed in the first eight months of 2018 (Table 1).

Reduction in *C. albicans* correlated with increase in non-*C. albicans* species namely *C. glabrata*, *C. parapsilosis* and *C. tropicalis*. Between 2004-2018, *C. glabrata* accounted for 28% (n=21) of candidemia with *C. parapsilosis* and *C. tropicalis* each accounting for 14% (n=10). In 2004, *C. glabrata* was not isolated while in 2018 (up to August) *C. glabrata* was implicated in both recorded cases (Table 1).

Determinants of C. albicans and C. glabrata candidemia patient groups 2004-2018

Patient ages ranged from 22-88 years (mean 66 years) (Supplementary Material Table 1). Those infected with *C. albicans* (n=41) and *C. glabrata* (n=21) had a mean age of 65 years and 69 years, respectively (p=0.26). SOFA scores were found to be independent of causative *Candida* species, with a mean score of 9 across all groups (Supplementary Material Table 1) (p=0.52). Mean time from ICU admission to diagnosis of candidemia varied between those with *C. albicans* (7 days) and *C. glabrata* (4 days) (Supplementary Material Table 1) (p=0.26). The mean ICU LOS varied between those with *C. albicans* (21 days) and *C. glabrata* (18 days) (p=0.38). CVC lines were *in situ* for 80% of the candidemias. The overall 30-day mortality rate (2004-2018) for all candidemia was 39% (n=29), although varying between those infected with *C. albicans* (29%; n=12) and *C. glabrata* (57%; n=12).

Empirical treatment of suspected candidemia (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 (Supplementary Material Table 2). 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 2008 and has accounted overall for 33% (n=19) of empirical treatments (Supplementary Material Table 2). The most recent use of fluconazole as an empirical therapy was 2014.

Anti-fungal agent susceptibility of Candida isolates (2004-2018)

Candida antifungal susceptibility testing was performed using 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 anti-fungal susceptibility panel in 2016. Susceptibility testing revealed all tested isolates were sensitive to caspofungin. Azole resistance was encountered frequently, with 37% of *C. glabrata* isolates being fluconazole resistant. This contrasts with just 2% of *C. albicans* being fluconazole-resistant. Amphotericin B resistance was not uncommon among *C. glabrata* isolates with 14% resistant in comparison to all tested *C. albicans* isolates being sensitive (Table 2). Mean and median susceptibility data are shown in Supplementary Material Table 3.

Discussion

This study provided comprehensive insight regarding the changing epidemiology of candidemia 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 for Northern Ireland [10].

Candida species isolated in Limerick over the 15-year study period comprised *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. parapsilosis* and *C. krusei*. Several studies have demonstrated that these few *Candida* species account for the majority of candidemias, with our study providing further evidence [6]. *C. albicans* is the most frequently isolated species in invasive candidiasis globally [6] [7]. Similarly, in our study, *C. albicans* was the causative agent of most cases (55%), although lower than described in other major studies, including a 2014 study by ARTEMIS DISK that reported *C. albicans* accounting for 62% of invasive candidiasis [7]. More recent work has shown a reduction globally in *C. albicans* prevalence [6]. Although clear, the decline of *C. albicans* observed in this study has been gradual, with fluctuations, but correlated with 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* species 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 candidemia. The SENTRY study highlighted *C. albicans*-induced candidemia in younger patients compared to *C. glabrata*; specifically, *C. glabrata* was isolated in 23% of those cases involving patients ≥65 in contrast to 3% of candidemias in those ≤15 [8]. The apparent association between age and *Candida* species was less clear in our study as there was no statistically significant age difference between *C. albicans* and *C. glabrata* patient groups.

SOFA score is considered a useful predictor of mortality in ICU patients, with a score ≤9 representing a predicted mortality of 33% while scoring ≥11 equates to predicted mortality of 95%. The mean SOFA score of 9 for all candidemia admissions to UHL correlated with the 30-day mortality rate of 39%. Remarkably, those with *C. glabrata*

candidemia (57%) were found to have a significantly higher mortality rate than those with a *C. albicans* candidemia (29%). Clearly, this is raising concerns in light of increasing *C. glabrata* prevalence.

We found that empirical therapy was administered in the majority of candidemia cases (78%) and the choice of therapy 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 caspofungin sensitive, thus providing assurance for its continued use as first line candidemia therapy. In stark relief, fluconazole susceptibility was less pertinent, with 37% of *C. glabrata* isolates resistant. This supports ESCMID recommendations reconsidering fluconazole as the drug of choice in an era of non-*C. albicans* candidemia. With regard to potential resistance development, widespread fluconazole dosage has been known to increase *C. glabrata* prevalence secondary to selection pressure [9]. This may partly explain the rise of *C. glabrata* in this Irish setting given predominant use of fluconazole as an empirical therapy prior to 2012. Alarmingly, 14% of our *C. glabrata* isolates were amphotericin B resistant, whereas typical clinical isolates seldom exhibit amphotericin B resistance. It may be pertinent that since 2007, this hospital has consistently recorded less use of antifungals than the median for Irish tertiary hospitals.

Our data reiterate the risk of candidemia for immunosuppressed patients, such as in ICU settings, with *C. glabrata* candidemia seen to have a particularly poor prognosis. All *Candida* 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, our study suggests a need to evolve quickly from empirical and prophylactic use of antifungals that are currently effective, and towards adoption of rapid molecular diagnosis of candidemia and vigilance specific to the enhanced risks of drug-resistant *C. glabrata.*

Conflict of interest statement

None declared.

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Table 1
Candida species encountered between January 2004 and August 2018

Year	*C. albicans*	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*	Other*	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%)	2(3%)	n=74(100%)

* Other *Candida* species identified included *C. krusei* and *C. dubliniensis.*

Table 2

Anti-fungal agent susceptibility data (2004-2018) determined using CLSI guidelines*

Anti-Fungal Agent	All *Candida* Species	*C. albicans*	*C. glabrata*
5-Flucytosine	n=66	n=37	n=19
Sensitive	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
Sensitive	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
Sensitive	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
Sensitive	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
Sensitive	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%)

*Candida isolates were often not tested against the same panel of anti-fungal agents due to changing CLSI guidelines between 2004-2018.