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Diabetes, malignancy and age as predictors of *Candida glabrata* bloodstream infection: A re-evaluation of the risk factors☆

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ABSTRACT

Objective. – Echinocandins and azoles are widely used in the treatment of candidaemia. Guidelines of the Infectious Diseases Society of America recommend commencing treatment with an echinocandin in candidaemic patients with risk factors for *Candida glabrata* i.e. patients who are elderly, or who have diabetes or malignancy, or those with recent prescription of azoles. We attempted to validate whether age, diabetes and malignancy are associated with *C. glabrata* candidaemia.
Patients, materials and methods. – Information in relation to demographics, patient associated risk factors, and laboratory parameters were collected from the casenotes and the laboratory information system. We then analysed the distribution of the risk factors (age, diabetes, and malignancy) in candidaemic patients with *C. glabrata* and patients with species other than *C. glabrata* (excluding *Candida krusei*).
Results. – Over a 42-month period (April 2011–September 2017), 124 patients had candidaemia. We analysed data for 119 patients of whom 33 (27.7%) had *C. glabrata* and the remaining 86 (72.2%) were infected with other species. Sixty-five patients were elderly (age $\geq$ 65), 40 had some form of malignancy, 34 had diabetes, and 4 patients were prescribed azoles in the 30 days prior to candidaemia (many patients had multiple risk factors). Comparing patients with *C. glabrata* to patients infected with other species, we found no association with diabetes (39.3% vs. 24.4%, $P = 0.1$), malignancy (36.3 vs. 32.5%, $P = 0.69$), and age (54.5% vs. 54.6%, $P = 0.99$).
Conclusions. – Diabetes, malignancy and age are not reliable predictors of candidaemia due to *C. glabrata*.

1. Introduction

Candidaemia is the most common invasive fungal infection in hospitalised patients Invasive candidiasis is associated with significant mortality [1]. There has been a shift in the epidemiology of *Candida* species leading to emergence of *Candida glabrata* as a significant cause of candidaemia [2]. A majority of isolates of *C. glabrata* are non-susceptible (intermediate/susceptible dose-dependent or resistant) to fluconazole [3]. Echinocandins have reliable activity against most *Candida* species but they are expensive compared to fluconazole and are available for parenteral use only. Widespread use of echinocandins may also lead to emergence of resistance [4]. Timely and effective antifungal therapy is associated with superior outcomes highlighting the importance of choosing optimal therapy early in illness [5]. In order to balance the drawbacks and benefits of using echinocandins as initial therapy compared to fluconazole, the clinical practice guidelines of the Infectious Diseases Society of America (IDSA) have suggested certain risk factors that should predict *C. glabrata* infection in patients with candidaemia. These include increasing age, diabetes mellitus (DM), malignancy, and recent use of azole antifungal agents [6]. In addition, commencement of therapy with an echinocandin is also recommended in those who are haemodynamically unstable to avoid suboptimal therapy in critically ill patients. However, data in relation to the association of these risk factors with *C. glabrata* bloodstream infection are limited. Also, with the diagnosis of DM and cancer occurring at earlier stages in their development, the relationship between these risk factors and the nature of the infecting species may have

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changed and so revisiting the strength of association of risk factors with a given infection is relevant. We retrospectively interrogated our database to ascertain whether advanced age, DM, or malignancy or a combination of these risk factors conferred a significantly higher risk of *C. glabrata* bloodstream infection in patients with candidaemia.

2. Patients and methods

2.1. Patients and setting

The study was conducted in the acute hospitals within NHS Ayrshire and Arran, Scotland, with total bed strength of 1200. Adult patients with candidaemia from April 2011 to September 2017 were identified with the help of Laboratory Information Systems (LIS). Patient demographics, risk factors including a diagnosis of DM or malignancy, prior use of azole antifungal agents (i.e. in the 30 days prior to the onset of candidaemia), details of antifungal treatment, and information on survival were obtained from the patient management system, LIS, electronic medicines management system and from the casenotes. We defined elderly patients as those aged $\geq$ 65 years, very elderly as those $\geq$ 75 years [7], and haemodynamic instability as systolic blood pressure $\leq$ 90 mm Hg with requirement for vasoconstrictor agents [8]. Organ system involvement was ascertained on the basis of clinical findings and results of the laboratory investigations.

2.2. Microbiological investigations

Blood cultures were processed using the BacT/Alert 3D system (bioMerieux, Marcy-l'Étoile, France) with five days incubation period. Positive blood culture bottles were subjected to microscopy and the broth was subjected to culture methods as described previously [9]. Identification of the growth on culture plates was carried out using API 20C Aux yeast identification system (bioMerieux, Marcy-l'Étoile, France) until 2013 and Matrix-Assisted Laser Desorption Ionisation-Time of Flight Mass Spectrometry (MALDI-TOF-MS) (Bruker Daltonik GmbH, Germany) from 2014 onwards. For MALDI-TOF-MS, the identification of species was considered valid when the log score was $>$ 1.7. Antifungal susceptibility testing was carried out using the Sensititre Yeast One (YO10) colourimetric microdilution test (Thermo Scientific, Trek Diagnostic Systems, West Sussex, United Kingdom) and the interpretation was based on the breakpoints established by the Clinical & Laboratory Standards Institute. Repeat cultures with identical species were regarded as one episode if within 30 days of the first positive culture. Data were stored in Excel file format in the NHS server.

The Chi^2 (or Fisher exact test where a cell value was 0) was used to compare the variables and *P*-values of $\leq$ 0.05 were considered to be significant.

3. Results

A total of 126 *Candida* isolates were obtained from 124 patients (67 females and 57 males). Two patients had mixed infection: one had *Candida albicans* and *C. glabrata* and the other had *C. albicans* and *Candida dubliniensis*. The species distribution was as follows: *C. albicans* (62), *C. glabrata* (34), *Candida parapsilosis* (18), *Candida krusei* (4), *C. dubliniensis* (3), *Candida lusitaniae* (2), *Candida guilliermondii* (1), *Candida kefyr* (1) and *Candida tropicalis* (1). The age range of the patients was from 26–93 years. We then looked at the distribution of risk factors in patients with and without *C. glabrata*. For this, we excluded the patient with mixed *C. glabrata* and *C. albicans* infection and the four patients with *C. krusei*, which is intrinsically resistant to fluconazole. The remaining 119 patients were included in the analysis. Sixty-five patients were aged 65 or above, 40 had some form of malignancy, 34 had diabetes, and 4 patients had been on an azole in the 30 days prior to candidaemia. Several patients had more than one risk factor. The epidemiological characteristics, organ system involvement, and the details of antifungal therapy in patients with *C. glabrata* and *Candida* other than *C. glabrata* (excluding *C. krusei*) are shown in Table 1. Significantly more patients with *C. glabrata* were treated with an echinocandin as expected. None of the risk factors were predictive of *C. glabrata* either individually or in combination (Table 2).

4. Discussion

Recent epidemiologic studies have demonstrated that infections due to *Candida* species other than *C. albicans* have been increasing in prevalence in Europe [10]. Our analysis confirms that species other than *C. albicans* significantly contribute to the burden of candidaemia. Prior investigations have compared risk factors between *C. albicans* and non-*C. albicans* species [11,12] while

Table 1
Comparison of demographic, laboratory, and therapeutic variables in patients with candidaemia caused by *C. glabrata* and *Candida* species other than *C. glabrata* (excluding *C. krusei*).

Parameters	*C. glabrata* (*n* = 33)	Non-*C. glabrata* (*n* = 86)	*P*-value
Demographics			
Mean age (years)	62	64.8	–
Gender (males/females)	11/22	42/44	–
Outcome			
Survival day 30, *n* (%)	26 (78.7)	57 (66.2)	0.18
Survival day 90, *n* (%)	19 (57.5)	50 (58.1)	0.95
Definitive treatment			
Echinocandin, *n* (%)	20 (60.6)	33 (38.3)	0.02*
Fluconazole, *n* (%)	7 (21.2)	46 (53.4)	0.001*
Others, *n* (%)	3 (9)	1 (1.3)	0.03*
None, *n* (%)	3 (9)	6 (6.9)	0.69
Organ system involvement			
Renal tract, *n* (%)	6 (18.1)	23 (26.7)	0.33
Unknown, *n* (%)	8 (24.2)	21 (24.4)	0.98
Intra-abdominal, *n* (%)	10 (30.3)	13 (15.1)	0.06
Skin & Soft tissue, *n* (%)	0 (0)	4 (4.6)	0.57
Gastrointestinal system, *n* (%)	3 (9)	3 (3.4)	0.21
Cardiac, *n* (%)	2 (6)	1 (1.3)	0.12
Genital tract, *n* (%)	0 (0)	1 (1.3)	1
Central venous catheter infection, *n* (%)	4 (12.1)	20 (23.2)	0.17

* *P*-value $\leq$ 0.05 indicates statistical significance.

Table 2
Comparison of the risk factors for *C. glabrata* and *Candida* species other than *C. glabrata* (excluding *C. krusei*).

Risk factors	*C. glabrata* (*n* = 33), *n* (%)	Non-*C. glabrata* (*n* = 86), *n* (%)	*P*-value
Age $\geq$ 65 years	18 (54.5)	47 (54.6)	0.99
Age $\geq$ 75 years	11 (33.3)	25 (29)	0.65
Malignancy	12 (36.3)	28 (32.5)	0.69
Diabetes	13 (39.3)	21 (24.4)	0.1
Azole within previous 30 days	1 (3)	3 (3.4)	0.9
Hemodynamic instability	3 (9)	8 (9.3)	0.97
Age $\geq$ 65 or malignancy	20 (60.6)	57 (66.2)	0.56
Age $\geq$ 65 or diabetes	25 (75.7)	59 (68.6)	0.44
Malignancy or diabetes	21 (63.6)	44 (51.1)	0.22
Age $\geq$ 65 or malignancy or diabetes	27 (81.8)	68 (79)	0.73
Any of the above risk factors	29 (87.8)	71 (82.5)	0.47
Age $\geq$ 65 years and malignancy	10 (30.3)	19 (22)	0.35
Age $\geq$ 65 years and diabetes	6 (18.1)	9 (10.4)	0.25
Malignancy and diabetes	4 (12.1)	6 (6.9)	0.36
Age $\geq$ 65, malignancy, and diabetes	4 (12.1)	5 (5.8)	0.24

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