Received: 30 April 2021 | Revised: 2 August 2021 | Accepted: 27 September 2021

DOI: 10.1111/myc.13376

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

Increasing morbidity and mortality of candidemia over one decade in a Swiss university hospital

Julien Battistolo[1] | Emmanouil Glampedakis[1,2] | Lauro Damonti[1,3] | Julien Poissy[1,4] | Bruno Grandbastien[2] | Laetitia Kalbermatter[2] | Jean-Luc Pagani[5] | Philippe Eggimann[6] | Pierre-Yves Bochud[1] | Thierry Calandra[1] | Oscar Marchetti[1,7] | Frederic Lamoth[1,8] | the Fungal Infection Network of Switzerland (FUNGINOS)

[1]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[2]Hospital Preventive Medicine Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[3]Department of Infectious Diseases, Bern University Hospital, Bern, Switzerland

[4]UMR 8576 - UGSF and Unit of Structural and Functional Glycobiology, University of Lille, Inserm U1285, CHU Lille, Pôle de médecine intensive-réanimation, CNRS, Lille, France

[5]Adult Intensive Care Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[6]Department of Orthopedics and Traumatology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[7]Department of Medicine, Ensemble Hospitalier de la Côte, Morges, Switzerland

[8]Institute of Microbiology, Department of Laboratories, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Correspondence
Frederic Lamoth, Infectious Diseases Service, Department of Medicine, Lausanne University Hospital (CHUV) and University of Lausanne, Rue du Bugnon 46, CH1011 Lausanne, Switzerland.
Email: frederic.lamoth@chuv.ch

Abstract

Background: The epidemiology of candidemia is evolving with raising concern about the emergence of intrinsically resistant non-*albicans Candida* species and acquisition of antifungal resistance. In addition to microbiological surveys, epidemiological studies including clinical data are needed to assess the impact of candidemia on morbidity and mortality.

Objectives: To assess the clinical and microbiological trends of candidemia in a Swiss university hospital.

Patients/Methods.

This single-centre retrospective study compared the incidence of candidemia, *Candida* species distribution, antifungal resistance profiles, clinical characteristics and outcomes between two periods separated by one decade.

Results: A total of 170 candidemic episodes were included (68 from period 1, 2004-2006, and 102 from period 2, 2014-2017). Incidence of candidemia (0.85 to 0.97 episode/10,000 patient-days), species distribution (55%–57% *C albicans*) and antifungal susceptibilities remained unchanged. During period 2, candidemia was more frequently observed in intensive care units (ICU, 38% vs 19% in period 1, $P = .01$) and amongst older patients (median age 68 vs 59 years old, $P < .01$) with more immunosuppressive conditions (24% vs 9%, $P = .01$). Candidemia in period 2 was more frequently followed by septic shock (23% vs 7% in period 1, $P = .01$) and ICU admission (42% vs 12%, $P < .01$) and was associated with higher mortality (34% vs 18%, $P = .03$). Overall, factors associated with mortality in multivariate analyses included cirrhosis, solid malignancies and ICU stay at the time of candidemia.

Conclusions: Despite stable incidence, species distribution and antifungal resistance of candidemia, an epidemiological shift of the disease towards older and more critically ill patients was observed, with higher mortality rates.

Julien Battistolo and Emmanouil Glampedakis are contributed equally to this work.

KEYWORDS
antifungal resistance, blood cultures, *Candida*, elderly, incidence, intensive care unit, invasive candidiasis, septic shock

1 | INTRODUCTION

Candidemia is one of the most frequent nosocomial bloodstream infections and is associated with important morbidity and mortality.[1,2] The epidemiology of candidemia is changing over time with a global trend towards increasing incidence, but important geographic variations are reported.[1,3-6] Whilst the parameters influencing this epidemiological diversity are unclear, the case-mix of candidemia is also evolving with some studies reporting a decreased incidence amongst neonates and a shift towards elder populations.[3,5] The distribution of *Candida* spp. is characterised by a decreasing proportion of *Candida albicans* and an increase of non-*albicans Candida* spp, such as *Candida glabrata*, that are less susceptible to azole drugs.[1,6] Emergence of acquired echinocandin resistance, notably amongst *C albicans* and *C glabrata*, is also a concern.[6,7] The widespread use of antifungal drugs, as well as the progressive shift from fluconazole to echinocandins for first-line therapy of candidemia according to the international guidelines,[8-10] may influence these trends of species distribution and antifungal susceptibility patterns. Whilst the majority of candidemia surveys rely on laboratory databases, epidemiological studies including both clinical and laboratory data are essential to assess the impact of candidemia on morbidity and mortality.

In this study, we compared the evolving clinical and microbiological characteristics of candidemia in a Swiss university hospital between two periods separated by one decade.

2 | MATERIALS AND METHODS

2.1 | Study design and data collection

This was a retrospective single-centre study conducted at the Lausanne University Hospital, a 1500-bed tertiary care centre, including 35 intensive care units (ICU) beds. The microbiology laboratory database was screened for all positive blood cultures for *Candida* spp. from adult patients (≥18 years old) over two periods that were 10 years apart, period 1 (2004-2006) and period 2 (2014-2017). Data of period 1 were collected from a prospective national survey of the Fungal Infection Network of Switzerland (FUNGINOS).[11,12] Data of period 2 included cases of a prospective FUNGINOS cohort[13] and were completed by a screening of all positive blood cultures for *Candida* spp. not included in this existing cohort. Clinical data were extracted from these databases or directly from the electronic medical records, including demographic characteristics of patients, underlying diseases, risk factors for invasive candidiasis, site of *Candida* infection, service of hospitalisation at the time of candidemia, severity of infection according to sepsis and septic shock definitions,[14] duration of hospital stay, antifungal treatment and clinical outcome. Microbiological data, such as *Candida* species identification and antifungal susceptibility testing results (Sensititre YeastOne™, Trek Diagnostics Systems, ThermoFisher Scientific, Cleveland, OH), were collected from the microbiology laboratory database. All data were reviewed by two investigators (JB and EG).

Data on the number of admissions and patient-days were obtained from the institutional statistical registries. Data about fluconazole and echinocandins (caspofungin and anidulafungin) consumption were collected from the pharmacy database. The consumption data were converted to defined daily doses (DDD), indexed per 1000 patient-days (https://www.whocc.no/filearchive/publications/2021_guidelines_web.pdf).

2.2 | Statistical analyses

Fisher's exact test and Mann-Whitney U test were used for comparisons of dichotomous and continuous variables, respectively. A two-sided *P*-value ≤.05 was considered as statistically significant. Factors associated with in-hospital mortality in the pooled population of both periods were assessed by univariate analyses. A multivariate logistic regression model with backward elimination (cut-off *P*-value of .1) was created having in-hospital mortality as the dependent variable. Baseline conditions with *P*-value≤.1 in the univariate analyses were used as independent variables. Results of this model were presented as odds ratios (OR), adjusted odds ratios (aOR) and their 95% confidence intervals (CI). Analyses were performed using SPSS software ver. 23.0 (IBM, Armonk, NY, USA) and R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

2.3 | Ethics statement

The study was approved by the institutional ethics review board (Swissethics Project 2019-00367) for the retrospective use of clinical data.

3 | RESULTS

3.1 | Analysis of global hospital trends

A comparison of the hospital case-mix between period 1 (2004-2006) and period 2 (2014-2017) showed that the total number of admissions/year and patient-days/year increased (98 010 vs 174 704 and 831 593 vs 1 369 859, in periods 1 and 2, respectively). However, the mean duration of hospital stay decreased (8.5 days vs 7.8 days in periods 1 and 2, respectively).

The proportion of ICU admissions related to the entire hospital admissions decreased (5.1% vs 3.3% in periods 1 and 2, respectively), but the proportion of ICU patient-days was stable (3.2% for both periods), as a consequence of the extension of ICU stay (mean 5.4 vs 7.6 days in periods 1 and 2, respectively). Similar trends were observed at the oncology and haematology wards regarding the proportion of patients admissions and patient-days (2.9% vs 2.2% and 2.9% vs 2.6% for periods 1 and 2, respectively) and hospital stay duration (mean 8.6 vs 9.4 days in periods 1 and 2, respectively).

A slight increase of the mean age of the overall hospital population was observed (56.9- vs 58.7-year-old for periods 1 and 2, respectively), as it was the case for the ICU (60.3- vs 62.9-year-old, respectively).

3.2 | Candidemia incidence

170 candidemic episodes in 168 patients were included in the study: 68 episodes (68 patients) for period 1 (2004-2006) and 102 episodes (100 patients) for period 2 (2014-2017). Incidences of candidemia were 0.85 (95% CI [0.65-1.05]) and 0.97 (95% CI [0.80-1.13]) per 10'000 patients-days for periods 1 and 2, respectively (P =.38). Incidences calculated per hospital admissions were also similar over the two periods: 7.24 (95% CI 5.55-8.92) and 7.61 (95% CI 6.31-8.90) per 10,000 admissions for periods 1 and 2, respectively (P =.73). Analyses limited to the ICU setting showed a trend towards increased incidence of candidemia (6.77 vs 10.68 per 10,000 patient-days for period 1 and 2, respectively, P =.11). Fluconazole and caspofungin were available at our institution during the entire duration of both periods. Anidulafungin was introduced in 2012. The antifungal drug consumption showed a significant increase from period 1 to period 2 for both fluconazole (from 12.6 to 22.3 DDD per 1000 patient-days, P <.01) and echinocandins (from 1.2 to 4.8 DDD per 1000 patient-days, P <.01).

3.3 | Patient demographics and characteristics

Demographic and baseline characteristics of candidemic patients from the two periods are compared in Table 1. The patients of period 2 were older (median 68 years, range 52-75, vs 59, 39-71, for period 1, P <.01) and were more frequently receiving immunosuppressive therapies (24% vs 9%, P =.01), in particular corticosteroid therapy. HIV infection was, however, less prevalent in period 2 compared to period 1 (4% vs 13%, P =.04), and there was also a trend towards a decreased proportion of intravenous drug abusers in period 2 (7% vs 16%, P =.08).

3.4 | Clinical and microbiological characteristics of candidemia

The characteristics of the candidemic episodes are shown in Table 2. During period 2, a higher proportion of candidemia occurred in the ICU (38% vs 19% for period 1, P =.01) and septic shock at presentation was more frequent (23% vs 7%, P =.01). Bacterial co-infections were also more frequent in period 2 (78% vs 59%, P =.01).

There were no differences regarding *Candida* species distribution with *C albicans* being the predominant species in both periods

TABLE 1 Demographic and baseline characteristics of patients with candidemia

	Period 1 2004–2006) n = 68	Period 2 (2014–2017) n = 100	P-value
Demographic characteristics			
Female sex	31 (46)	40 (40)	.52
Age, years	59 (39-71)	68 (52-75)	**<.01**
Baseline conditions			
Solid tumour	14 (21)	34 (34)	.08
Hematologic cancer	8 (12)	7 (7)	.41
Diabetes	6 (9)	18 (18)	.12
Liver cirrhosis	9 (13)	9 (9)	.44
Kidney failure (acute of chronic)	23 (34)	45 (45)	.20
Renal replacement therapy	9 (13)	22 (22)	.16
Pancreatitis	4 (6)	5 (5)	1.00
HIV infection	9 (13)	4 (4)	**.04**
Solid-organ transplantation	2 (3)	5 (5)	.70
Antifungal prophylaxis (within 4 weeks)	4 (6)	6 (6)	1.00
Risk factors for candidemia			
Previous ICU stay	28 (41)	52 (52)	.20
Previous antibiotic exposure (within 4 weeks)	59 (87)	91 (91)	.44
Previous surgery (within 2 weeks)	39 (57)	49 (49)	.35
Central venous catheter	61 (90)	83 (83)	.19
Total parenteral nutrition	21 (31)	30 (30)	1.00
Intravenous drug use	11 (16)	7 (7)	.08
Neutropenia (neutrophil count <500 cells/μl)	7 (10)	10 (10)	1.00
Immunosuppressive therapy	6 (9)	24 (24)	**.01**
Corticosteroids	5 (7)	22 (22)	**.01**
Calcineurin inhibitors	2 (3)	2 (2)	1.00
Other	1 (1)	6 (6)	.24

Note: Numbers are total number (percentage) for proportions or median (interquartile range) for continuous variables. Significant p-value (≤0.05) is in bold characters.

Abbreviations: HIV: human immunodeficiency virus;ICU: intensive care unit.

TABLE 2 Characteristics of the candidemic episodes

	Period 1 (2004-2006) n = 68	Period 2 (2014-2017) n = 102	*p*-value
Primary site of infection			
Primary bloodstream or intravascular catheter infection	48 (71)	68 (67)	.62
Abdominal	13 (19)	19 (19)	1.00
Other	7 (10)	15 (15)	.49
Candida species			
C albicans	39 (57)	56 (55)	.87
C glabrata	14 (21)	30 (29)	.21
C tropicalis	7 (10)	6 (6)	.38
C parapsilosis	2 (3)	4 (4)	1.00
C krusei	1 (1)	3 (3)	.65
Other *Candida* spp.[a]	3 (5)	2 (2)	.40
More than one species[b]	2 (3)	1 (1)	.56
Characteristics at presentation			
Timing from hospital admission to candidemia, days	12 (5-22)	15 (7-32)	.20
Timing from blood culture sampling to positivity, days	1 (1-3)	1 (1-3)	.47
ICU stay at the time of candidemia	13 (19)	39 (38)	**.01**
Sepsis at diagnosis[c]	48 (71)	80 (78)	.28
Septic shock at diagnosis[c]	5 (7)	23 (23)	**.01**
Bacterial co-infections during hospital stay	40 (59)	80 (78)	**.01**

Notes: Numbers are total number (percentage) for proportions or median (interquartile range) for continuous variables. Significant p-value (≤0.05) are in bold characters.

Abbreviations: CVC: central venous catheter; ICU: intensive care unit.

[a]*Candida pelliculosa* (2), *Candida kefyr* (2), *Candida norvegensis* (1).

[b]*C albicans* and *C glabrata*.

[c]Sepsis and septic shock were defined according to consensus of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP / SCCM).[14]

(57% and 55% for period 1 and 2, respectively). Antifungal susceptibility results are presented in Table 3. There were no significant differences in minimal inhibitory concentrations (MIC) values over time. According to the updated criteria of the Clinical and Laboratory Standards Institute (CLSI),[15] the overall resistance rates for fluconazole and echinocandin (at least one drug of the class) were 3% and 2% for period 1 and 0% and 2% for period 2, respectively.

3.5 | Clinical management and outcome

Data about management and outcome of candidemia are shown in Table 4. Significant differences regarding antifungal therapy were observed, with fluconazole being the most frequent first-line treatment in period 1 (75% vs 24% in period 2, P <.01) and an echinocandin (caspofungin or anidulafungin) being the predominant first-line treatment in period 2 (56% vs 10% in period 1, P <.01). The delay from blood cultures sampling to antifungal therapy initiation was similar between the two periods (median of 2 days). Duration of antifungal therapy was significantly reduced in period 2 (median 16 days vs 19 days in period 1, P =.02). Removal of intravascular catheter was less frequent in period 2 (67% vs 93% in period 1, P <.01).

Analysis of overall outcome during the hospital stay showed that more candidemic patients required subsequent ICU admission (ie for any reason from the time of candidemia diagnosis and until hospital discharge) in period 2 (41% vs 12% in period 1, P <.01). Candidemic patients of period 2 also presented a trend towards longer ICU stay (median 14 vs 7 days in period 1, P =.07) and exhibited a significantly higher mortality rate (34% vs 18%, P =.03).

3.6 | In-hospital mortality risk factors

For the entire study population (periods 1 and 2), baseline conditions associated with a significant increased mortality during hospitalisation are shown in Table 5. These variables were used

TABLE 3 Results of antifungal susceptibility testing of *Candida* isolates from the two study periods (period 1:2004-2006, and period 2:2014-2017)

		Antifungal drug MIC_{50}/MIC_{90} (μg/ml) (range) % resistant (R) isolates[a]						
***Candida* species**	**Period**	**Fluconazole**	**Voriconazole**	**Posaconazole**	**Amphotericin B**	**Caspofungin**	**Anidulafungin**	**Micafungin**
Candida albicans	Period 1	0.25 / 0.50 (0.06-1) R : 0%	0.01 / 0.02 (0.01-0.06) R : 0%		0.5 / 0.5 (0.13-1) ND	0.032 / 0.13 (<0.03-0.25) R : 0%		
	Period 2	0.25 / 0.50 (<0.06-2) R : 0%	/ 0.03 (<0.008-0.12) R : 0%	0.015 / 0.042 (0.015-0.50) ND	0.5 / 1 (0.05-1) ND	0.03 / 0.06 (<0.03-1) R :2%	0.03 / 0.06 (<0.03-0.25) R : 0%	0.01 / 0.03 (<0.01 - 0.5) R : 0%
Candida glabrata	Period 1	16 / 64 (4-128) R : 12%	0.25 / 0.5 (0.06-2) ND		0.5 / 1 (0.13-1) ND	0.06 / 0.13 (0.02-0.25) R :0%		
	Period 2	8 / 16 (1-32) R :0%	0.25 / 0.5 (0.06-4) ND	0.5 / 2 (0.05-2) ND	1 / 1 (0.06-1) ND	0.06 / 0.13 (0.03-0.25) R : 0%	0.03 / 0.06 (<0.03-1) R : 6%	0.015 / 0.015 (<0.01-0.12) R : 0%
Candida tropicalis	Period 1	1 / 2 (0.5-4) R : 0%	0.03 / 0.25 (0.01-0.25) R : 0%		0.25 / 0.5 (0.13-0.5) ND	0.03 / 0.5 (0.03-0.5) R : 0%		
	Period 2	2 / 2 (0.25-2) R : 0%	0.12 / 0.25 (0.01-0.25) R : 0%	0.12 / 0.5 (0.02-0.5) ND	0.5 / 1 (0.5-1) ND	0.03 / 0.12 (0.02-0.12) R : 0%	0.03 / 0.12 (0.02 - 0.12) R : 0%	0.02 / 0.06 (0.02-0.12) R : 0%
Candida parapsilosis	Period 1	2 / 2 (2-2) R : 0%	0.03 / 0.03 (0.03) R : 0%		0.25 / 0.5 (0.25 / 0.5) ND	0.25 / 0.5 (0.25-0.5) R : 0%		
	Period 2	0.5 / 0.5 (0.5) R : 0%	0.008 / 0.01 (0.008-0.02) R : 0%	0.015 / 0.026 (<0.015 - 0.026) ND	0.5 / 0.5 (0.25-0.5) ND	0.5 / 0.5 (0.25-0.5) R : 0%	1 / 2 (1-2) R : 0%	1 / 2 (1 −2) R : 0%
Candida krusei	Period 1	64 ND	0.25 R : 0%		1 ND	1 R :100%		
	Period 2	32 ND	0.5 /0.5 (0.25-0.5) R : 0%	0.25 / 0.25 (0.25) ND	0.5 / 1 (0.5 - 1) ND	0.25 / 0.5 (0.25 −0.5) R : 0%	0.06 / 0.06 (0.03-0.06) R : 0%	0.12 / 0.12 (0.12) R : 0%

Note: $MIC_{50}/MIC_{90:}$ Minimum inhibitory concentration encompassing 50% and 90% of isolates, respectively. R: resistant isolates according to the Clinical and Laboratory Standards Institute (CLSI) criteria.[15]
ND: no defined criteria.

TABLE 4 Management and outcome of the candidemic episodes

	Period 1 (2004-2006) n = 68	Period 2 (2014-2017) n = 102	*p*-value
First line antifungal treatment[a]			
Fluconazole	51 (75)	25 (24)	**<.01**
Echinocandin	7 (10)	57 (56)	**<.01**
Other / unspecified	4 (6)	9 (9)	.56
None	6 (9)	11 (11)	.80
Characteristics of treatment/interventions			
Delay from blood culture sampling to start antifungal therapy, days	2 (1-3)	2 (2-3)	.89
Duration of antifungal therapy, days	19 (14-36)	16 (14-24)	**.02**
Change of CVC[b]	57 (93)	56 (67)	**<.01**
Surgical drainage	9 (13)	21 (21)	.30
Infectious diseases consultation	59 (87)	74 (73)	.11
Outcome			
ICU admission after candidemia[c]	8 (12)	42 (41)	**<.01**
Duration of ICU stay after candidemia, days	7 (5-14)	14 (8-42)	.07
Duration of hospitalisation, days	39 (28-72)	44 (19-83)	.92
Timing from candidemia to discharge, days	26 (16-58)	35 (16-57)	.72
Death during hospitalisation[d]	12 (18)	33 (34)	**.03**

Notes: Numbers are total number (percentage) for proportions or median (interquartile range) for continuous variables. Significant *p*-value (≤0.05) is in bold characters.

Abbreviations: CVC, central venous catheter; ICU, intensive care unit.

[a]First antifungal drug received for at least 48 hours after candidemia diagnosis.

[b]Percentages are reported for the number of patients having a central venous catheter.

[c]ICU admission for any reason following the date of candidemia diagnosis and until hospital discharge.

[d]Data available for 166/170 episodes, percentages calculated accordingly.

TABLE 5 Independent risk factors associated with increased mortality (*n* = 166 patients)[a]

Univariate				Multivariate	
Factor	**Mortality**	**OR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Period 2 (2014-2017)	33/98 (34)	2.35 (1.06 - 5.51)	**.03**	2.02 (0.86 - 4.73)	.11
Age >65 years	29/80 (36)	2.47 (1.16 - 5.43)	**.01**	1.42 (0.60 - 3.34)	.43
Kidney failure[b]	24/66 (36)	2.14 (1.01 - 4.57)	**.03**	1.50 (0.63 - 3.55)	.36
Liver cirrhosis	10/18 (56)	3.99 (1.31 - 12.65)	**<.01**	6.49 (2.14 - 19.67)	**<.01**
Solid tumour	20/44 (46)	3.21 (1.44 - 7.19)	**<.01**	4.94 (2.10 - 11.64)	**<.01**
Diagnosis at the ICU	21/52 (40)	2.52 (1.16 - 5.50)	**.01**	3.29 (1.42 - 7.67)	**<.01**

Note: Hosmer and Lemeshow test for the model: *P* =.78.

Abbreviations: aOR: adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR: odds ratio.

[a]Mortality data missing for 4 patients.

[b]Acute or chronic kidney failure.

for the multivariate logistic regression model. Period 2 was forced into the model as a baseline factor in order to assess whether the higher mortality rate of this period was related to the other factors. In the multivariate regression model, only the presence of cirrhosis (aOR 6.49, 95% CI 2.14-19.67), solid tumour (4.94, 2.10-11.64) and diagnosis of candidemia in the ICU (3.29, 1.42-7.67) were all factors associated with significantly increased mortality (*P* <.01). The presence of any of these three conditions was

significantly more prevalent in period 2 compared to period 1 (69% vs 47%, respectively, $P < .01$).

Of note, there was no significant difference in overall mortality rate between patients who received an echinocandin vs another antifungal drug as first-line therapy (33% vs 24%, $P = .21$). The timing from blood culture sampling to initiation of antifungal therapy was somewhat longer amongst non-survivors vs survivors, but this difference was not statistically significant (mean 2.5 vs 2.1 days, respectively, $P = .21$).

4 | DISCUSSION

Candidemia remains a major nosocomial threat and monitoring of local epidemiological trends is important for improved patients care. This monocentric analysis comparing the incidence and characteristics of candidemic episodes of two periods separated by a 10-year interval showed some important demographic and clinical changes of candidemia.

In contrast to reports from other European countries,[1,5,16,17] we did not observe an increased incidence of candidemia in our institution. The *Candida* species distribution, as well as antifungal resistance rates, remained stable despite a significant increase of antifungal drug consumption and a class shift for first-line antifungal therapy of candidemia from fluconazole to echinocandins. It is noteworthy that the overall use of antifungals remained lower when compared to other European and US centres that reported changes in *Candida* species distribution and/or antifungal resistance profiles.[18-21] Despite non-significant changes, we could observe a slight trend towards increased proportion of *C glabrata* amongst the non-*albicans Candida* spp., which should be carefully monitored in the future.

Despite the stability of incidence and microbiological parameters, our analysis of the demographic and clinical data revealed notable trends over time in the case-mix, clinical characteristics and outcome of candidemia. Our results suggest that candidemia is shifting to more frail populations, such as the elderly and ICU patients. In contrast, it tended to be less frequently observed in younger populations with usually better prognosis, such as HIV patients and intravenous drug abusers. Similar observations with higher occurrence of candidemia amongst older and/or ICU patients with higher comorbidity scores have been reported.[1,3,17,22] Ageing and more severe conditions in the ICU population may explain this epidemiological evolution.[23] Indeed, we observed that the mean age of our entire hospital population and mean duration of ICU stay were higher in period 2 in comparison with period 1.

As a probable consequence of this epidemiological shift, we found a significantly higher mortality rate in period 2 compared to period 1. In order to demonstrate the role of the more severe baseline conditions in this excess mortality rate of period 2, we performed univariate and multivariate analyses of factors associated with candidemia mortality for the entire study population. Our multivariate logistic regression model including baseline conditions, as well as period 2, found that only liver cirrhosis, solid tumours, and ICU stay at the time of candidemia were independent risk factors for in-hospital deaths. Indeed, the presence of any of these conditions was more frequent in period 2, whilst the period itself was not recovered as an independent risk factor of mortality. The impact of ageing, ICU stay, liver cirrhosis and cancer on mortality rates of candidemia has been highlighted in previous reports.[24-27]

Regarding the management of candidemia, the most notable change consisted in the shift from fluconazole to echinocandins as first-line antifungal therapy, which is in line with the updated European guidelines.[8,10] However, it is noteworthy that fluconazole still remained the first-line antifungal therapy for about one fourth (24%) of episodes in period 2. Whilst results of clinical trials suggested a superior efficacy of echinocandins compared to fluconazole for the treatment of invasive candidiasis, in particular in severely ill patients,[28,29] our data could not demonstrate a beneficial impact of echinocandins on candidemia outcomes because of multiple confounding factors. Indeed, echinocandins were more frequently administered in period 2, where patients were more severely ill, and, according to our institutional practices, were favoured amongst ICU patients and/or in case of septic shock.

Interestingly, removal of central venous catheter was less frequent in period 2. The benefit of such intervention is controversial and has not been clearly demonstrated.[30,31] One recent study suggested that the association between catheter retention and unfavourable outcome was actually the consequence of limited therapeutic management plans in more critically ill patients with poor prognosis rather than the cause of their increased mortality.[11] Albeit not demonstrated in the present study, this hypothesis is plausible considering the higher age and overall morbidity of patients in period 2.

We also noticed a significant shorter duration of antifungal therapy in the second period, which probably results from increased awareness about risk of emerging antifungal resistance and may reflect improved antifungal stewardship strategies. Involvement of infectious diseases consultants for the management of candidemia remained high (>70%) in both periods, but tended to decrease in period 2. As demonstrated by a recent study, such specialised interventions may increase adherence to guidelines for management of candidemia and contribute to improve clinical outcome.[32]

A limitation of the present study consists of its monocentric design. Previous epidemiological studies on trends of candidemia have highlighted important differences across centres and countries.[1,3-5,33] Analyses of pooled data are characterised by important heterogeneity and cannot be extrapolated for individual centres.[1] Institutional antifungal stewardship programmes should therefore include constant monitoring of the epidemiology of candidemia at a local level for improving diagnostic and management strategies.

In conclusion, this analysis of the epidemiological trends of candidemia over one decade showed that, despite stable incidence, species distribution and antifungal resistance rates, the severity and mortality of candidemia are increasing with a progressive shift towards older and more critically ill patients' populations. These

observations may rise a concern about the growing impact of candidemia and invasive fungal diseases in general amongst an increasingly frail and debilitated patients population.

ACKNOWLEDGMENTS

We acknowledge Prof. Nina Khanna, Dr Anna Conen, Dr Stefan Zimmerli, Dr Dionysios Neofytos and Dr Peter Werner Schreiber, from the Fungal Infection Network of Switzerland (FUNGINOS).

The authors and the FUNGINOS Group warmly thank Mrs Isabel Cobos, Mrs Aurélie Guillet, Mrs Corine Guyaz, Mrs Monika Ochsner and Mrs Annie Savoie of the Infectious Diseases Service, Department of Medicine, Lausanne University Hospital, for outstanding assistance in collecting and managing clinical data from candidemic patients as well as Mr Christian Durussel, Mrs Dominique Pilloud, Dr Philippe Hauser and colleagues for outstanding technical support in collecting *Candida* bloodstream isolates and performing species identification and antifungal susceptibility testing at the FUNGINOS reference mycology laboratory, Institute of Microbiology, Lausanne University Hospital. The authors also warmly thank Mr Nicolas Larque of the Information Systems Division of the University Hospital of Lausanne for data collection about the hospital case-mix.

The Fungal Infection Network of Switzerland Foundation (FUNGINOS) received unrestricted grant support from (in alphabetical order): Essex Schering-Plough, Gilead, Merck, Sharp and Dohme-Chibret, Novartis, and Pfizer. None of the above funding sources has been involved in study design and conduct, patient recruitment, data collection, analysis, and interpretation; writing of the article; or decision to submit the article for publication.

In addition, the present project received unrestricted grant support from the Foundation for the Advancement in Medical Microbiology and Infectious Diseases (FAMMID), Lausanne, Switzerland. Open Access funding provided by Universite de Lausanne. [Correction added on 20 May 2022, after first online publication: Funding statement has been added.]

CONFLICT OF INTEREST

Julien Battistolo, Emmanouil Glampedakis, Lauro Damonti, Bruno Grandbastien,[2] Laetitia Kalbermatter and Jean-Luc Pagani have no conflict of interests to declare.

Julien Poissy declares speaker honoraria from Gilead, personal fees from Pfizer and Eumédica. PhE invited speaker at industry-sponsorised symposia and meetings for Pfizer, MSD, Gilead over the study period. TC advisory boards or consulted for Menarini, Shinogi, Cytosorbent, ThermoFisher and GE Healthcare for projects unrelated to the submitted work and on data safety monitoring boards for Cidara and Novartis. All contracts were made with and fees paid to his institution (CHUV). Pierre-Yves Bochud served as a recipient of a research award from the Leenaards Foundation, Lausanne, Switzerland. Grants from the Swiss national science foundation (SNF). Support from the Santos-Suarez foundation. Participant in the European Union's Seventh Framework Program (FP7/2007-2013) under grant agreement number HEALTH-2010-260 338 (ALLFUN). No conflict of interest. Oscar Marchetti served as a recipient of a research award from the Leenaards Foundation, Lausanne, Switzerland. Participant in the European Union's Seventh Framework Program (FP7/2007-2013) under grant agreement number HEALTH-2010-260 338 (ALLFUN). No other conflict of interests to declare. Frederic Lamoth declares research grants from Funginos, Novartis, Pfizer and Merck, and speaker honoraria from Gilead. All contracts were made with and fees paid to his institution (CHUV).

AUTHOR CONTRIBUTIONS

Julien Battistolo: Data curation (equal); Formal analysis (equal); Writing-original draft (equal). **Emmanouil Glampedakis:** Data curation (equal); Formal analysis (equal); Writing-original draft (equal). **Lauro Damonti:** Data curation (supporting); Writing-review & editing (supporting). **Julien Poissy:** Data curation (supporting); Writing-review & editing (supporting). **Bruno Grandbastien:** Data curation (supporting); Writing-review & editing (supporting). **Laetitia Kalbermatter:** Data curation (supporting); Writing-review & editing (supporting). **Jean-Luc Pagani:** Data curation (supporting); Writing-review & editing (supporting). **P Eggimann:** Data curation (supporting); Writing-review & editing (supporting). **Pierre-Yves Bochud:** Data curation (supporting); Writing-review & editing (supporting). **Thierry Calandra:** Conceptualization (supporting); Writing-review & editing (supporting). **Oscar Marchetti:** Conceptualization (equal); Data curation (supporting); Formal analysis (supporting); Writing-review & editing (supporting). **Frederic Lamoth:** Conceptualization (equal); Formal analysis (equal); Methodology (lead); Supervision (lead); Writing-review & editing (lead).

ORCID

Frederic Lamoth https://orcid.org/0000-0002-1023-5597

REFERENCES

1. Koehler P, Stecher M, Cornely OA, et al. Morbidity and mortality of candidaemia in Europe: an epidemiologic meta-analysis. *Clin Microbiol Infect*. 2019;25:1200-1212.
2. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198-1208.
3. Cleveland AA, Farley MM, Harrison LH, et al. Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011. *Clin Infect Dis*. 2012;55:1352-1361.
4. Cleveland AA, Harrison LH, Farley MM, et al. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008–2013: results from population-based surveillance. *PLoS One*. 2015;10:e0120452.
5. Hesstvedt L, Gaustad P, Andersen CT, et al. Twenty-two years of candidaemia surveillance: results from a Norwegian national study. *Clin Microbiol Infect*. 2015;21:938-945.
6. Lamoth F, Lockhart SR, Berkow EL, Calandra T. Changes in the epidemiological landscape of invasive candidiasis. *J Antimicrob Chemother*. 2018;73:i4-i13.
7. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in Candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. *Clin Infect Dis*. 2013;56:1724-1732.

8. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18(Suppl 7):19-37.
9. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1-50.
10. Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). *Clin Microbiol Infect*. 2012;18(Suppl 7):53-67.
11. Damonti L, Erard V, Garbino J, et al. Catheter retention as a consequence rather than a cause of unfavorable outcome in candidemia. *Intensive Care Med*. 2017;43:935-939.
12. Orasch C, Marchetti O, Garbino J, et al. Candida species distribution and antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing and new vs old Clinical and Laboratory Standards Institute clinical breakpoints: a 6-year prospective candidaemia survey from the fungal infection network of Switzerland. *Clin Microbiol Infect*. 2014;20:698-705.
13. Poissy J, Damonti L, Bignon A, et al. Risk factors for candidemia: a prospective matched case-control study. *Crit Care*. 2020;24:109.
14. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644-1655.
15. Clinical and Laboratory Standards Institute (CLSI). *Reference method for broth dilution antifungal susceptibility testing of yeasts*. , 4th ed. CLSI: 2017.
16. Goemaere B, Becker P, Van Wijngaerden E, et al. Increasing candidaemia incidence from 2004 to 2015 with a shift in epidemiology in patients preexposed to antifungals. *Mycoses*. 2018;61:127-133.
17. Mohr A, Simon M, Joha T, Hanses F, Salzberger B, Hitzenbichler F. Epidemiology of candidemia and impact of infectious disease consultation on survival and care. *Infection*. 2020;48:275-284.
18. Bailly S, Maubon D, Fournier P, et al. Impact of antifungal prescription on relative distribution and susceptibility of Candida spp. - Trends over 10 years. *J Infect*. 2016;72:103-111.
19. Bitterman R, Hussein K, Leibovici L, Carmeli Y, Paul M. Systematic review of antibiotic consumption in acute care hospitals. *Clin Microbiol Infect*. 2016;22(561):pp. e567–561 e519.
20. Siopi M, Tarpatzi A, Kalogeropoulou E, et al. Epidemiological trends of Fungemia in Greece with a focus on Candidemia during the recent financial crisis: a 10-year survey in a tertiary care academic hospital and review of literature. *Antimicrob Agents Chemother*. 2020;64.
21. Vallabhaneni S, Baggs J, Tsay S, Srinivasan AR, Jernigan JA, Jackson BR. Trends in antifungal use in US hospitals, 2006–12. *J Antimicrob Chemother*. 2018;73:2867-2875.
22. Tsay SV, Mu Y, Williams S, et al. Burden of Candidemia in the United States, 2017. *Clin Infect Dis*. 2020;71:e449-e453.
23. Mullins PM, Goyal M, Pines JM. National growth in intensive care unit admissions from emergency departments in the United States from 2002 to 2009. *Acad Emerg Med*. 2013;20:479-486.
24. Barchiesi F, Orsetti E, Mazzanti S, et al. Candidemia in the elderly: What does it change? *PLoS One*. 2017;12:e0176576.
25. Schroeder M, Weber T, Denker T, et al. Epidemiology, clinical characteristics, and outcome of candidemia in critically ill patients in Germany: a single-center retrospective 10-year analysis. *Ann Intensive Care*. 2020;10:142.
26. Tang HJ, Liu WL, Lin HL, Lai CC. Epidemiology and prognostic factors of candidemia in cancer patients. *PLoS One*. 2014;9:e99103.
27. Zhang W, Song X, Wu H, Zheng R. Epidemiology, species distribution, and predictive factors for mortality of candidemia in adult surgical patients. *BMC Infect Dis*. 2020;20:506.
28. Kett DH, Shorr AF, Reboli AC, Reisman AL, Biswas P, Schlamm HT. Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: support for the 2009 IDSA treatment guidelines for candidiasis. *Crit Care*. 2011;15:R253.
29. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med*. 2007;356:2472-2482.
30. Janum S, Afshari A. Central venous catheter (CVC) removal for patients of all ages with candidaemia. *Cochrane Database Syst Rev*. 2016;7:CD011195.
31. Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. *Clin Infect Dis*. 2010;51:295-303.
32. Mejia-Chew C, O'Halloran JA, Olsen MA, et al. Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study. *Lancet Infect Dis*. 2019;19:1336-1344.
33. Chapman B, Slavin M, Marriott D, et al. Changing epidemiology of candidaemia in Australia. *J Antimicrob Chemother*. 2017;72:1103-1108.

How to cite this article: Battistolo J, Glampedakis E, Damonti L, et al; the Fungal Infection Network of Switzerland (FUNGINOS). Increasing morbidity and mortality of candidemia over one decade in a Swiss university hospital. *Mycoses*. 2021;64:1512–1520. https://doi.org/10.1111/myc.13376