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SIGNIFICANCE OF YEASTS IN BLOODSTREAM INFECTION: EPIDEMIOLOGY AND PREDISPOSING FACTORS OF CANDIDAEMIA IN ADULT PATIENTS AT A UNIVERSITY HOSPITAL (2010–2014)

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The incidence of *Candida* bloodstream infection (BSI) has increased during the past decades. Species distribution is changing worldwide, and non-*albicans Candida* spp. are becoming more prevalent. Acquired resistance to antifungal agents has been documented in several reports. The aim of our study was to assess the epidemiology and antifungal susceptibility of *Candida* isolates from BSI at our institute. The incidence of *Candida* BSI increased during the first four years of our investigation, from 1.7 to 3.5 episodes / 10 000 admissions, then dropped to 2.66 episodes / 10 000 admissions in the last year. The most frequently isolated species was *C. albicans* (63%), followed by *C. glabrata* (13%), *C. parapsilosis* (10.2%), *C. tropicalis* (9.3%), and *C. krusei* (3.7%). One isolate each of *C. kefyr*, *C. fabianii* and *C. inconspicua* were detected. The percentage of *C. albicans* remained stable throughout the study period. The most frequent risk factors of *Candida* BSI in our patient population were intensive care treatment (60.4%), abdominal surgery (52.5%), and solid malignancy (30.7%). All isolates were wild-type organisms, no acquired antifungal resistance was detected.

Keywords: *Candida* spp., bloodstream infection, epidemiology, antifungal susceptibility

Introduction

Candida spp. are a leading cause of bloodstream infection (BSI), associated with high mortality and increased hospital costs [1]. The annual incidence of *Candida* BSI varies greatly by region based on epidemiological studies from

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Europe and the USA: incidence ranges from 3.0 to 26.2 / 100 000 inhabitants. The incidence of *Candida* BSI in Denmark and Spain were similar (8.6 / 100 000 inhabitants, and 8.1 / 100 000 inhabitants, respectively), while a much higher incidence (26.2 / 100 000 inhabitants) was reported from Baltimore in the USA, and the incidence was the lowest in Norway (3.0 / 100 000 inhabitants) [2–6].

Risk factors of *Candida* BSI are well established, including treatment at the intensive care unit (ICU), broad-spectrum antibiotic therapy, abdominal surgery, malignancy, the administration of total parenteral nutrition (TPN), the presence of intravenous catheters, mechanical ventilation, acute renal failure, immunosuppressive treatment, neutropenia, and prior colonization with *Candida* spp. [7–12].

C. albicans remains the most frequently isolated species in most reports, but a shift towards non-albicans species has been detected [6, 13, 14]. The rise in the rate of fluconazole non-susceptible *Candida* spp., mainly *C. glabrata,* has been linked with prior fluconazole exposure [15, 16]. Reports of breakthrough *Candida* BSI and the isolation of multiresistant isolates, especially *C. glabrata* strains resistant to echinocandins, are alarming [17, 18].

The epidemiology of *Candida* BSIs varies greatly by region, therefore evaluation of local data is essential to assess local trends, identify patients at risk of infection, and to determine which antifungal drug is most adequate as empirical therapy. The aim of our study was to evaluate the epidemiology of *Candida* BSIs in the adult population at our institute, and to detect any strains with acquired antifungal resistance.

Materials and Methods

All episodes of candidaemia in patients over the age of 18 were analyzed during a five-year period, from January 2010 to December 2014, at Semmelweis University, a 2250-bed tertiary hospital with 105 000 admissions per year. An episode of candidaemia was defined as isolation of *Candida* from blood culture on at least one occasion. Episodes were considered separate if they occurred more than 30 days apart, or different *Candida* species were isolated.

Patient data was collected retrospectively using a standardized case report form which included demographic data, underlying diseases, comorbidities (diabetes mellitus, organ failure, malignancy, immunosuppression), presence of intravascular devices, mechanical ventilation, administration of parenteral nutrition, and isolate characteristics (*Candida* species, antifungal susceptibility profile). Microbiological data, such as previous colonization by *Candida* spp., and time to blood culture positivity were also recorded.

Blood samples were collected and processed using either the Bactec™ 9120 (Beckton Dickinson) or BacT/ALERT® 3D (BioMérieux) automated blood culture systems. Isolates were identified by phenotypic methods [carbohydrate assimilation profile obtained by the API 20C AUX system (BioMérieux), and morphology of pseudohyphae on malt agar] and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS, Bruker) analysis. Routine antifungal susceptibility testing was performed by E-test® (BioMérieux) method, according to the manufacturer's instructions. Minimal inhibitory concentration (MIC) results were interpreted according to EUCAST clinical breakpoints [19].

Fisher's exact test was used to assess if any of the risk factors of candidaemia had any connection with 30-day mortality and to describe changes in isolate incidence. A p value of <0.05 was considered significant.

Results

Incidence

Candidaemia was detected in 129 cases in adult patients between 2010–2014. The number of episodes per year and their incidence is presented in Table I. More than half (62%, n = 80) of the 129 episodes occurred in the ICU. Figure 1 shows the distribution of candidaemia in the different departments.

Patient demographics and clinical characteristics

The mean age of patients was 62.8 years overall, and 60.1% were male. Eighty-three (64.8%) patients were admitted with a surgical diagnosis, and 55.5% of the patients had major abdominal surgery before the detection of candidaemia.

Table I. Candidaemia in adult patients at Semmelweis University, 2010–2014

	Number of episodes / 10 000 admissions
2010	1.8
2011	1.8
2012	2.57
2013	3.50
2014	2.66

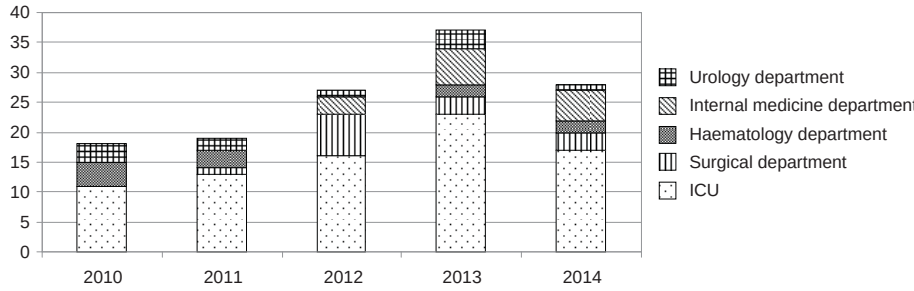

Figure 1. Incidence of candidaemia (number of episodes per department) at Semmelweis University, 2010–2014

Among underlying diseases of *Candida* BSI, solid malignancy was the most prevalent (30.5%), followed by diabetes mellitus (24.2%), and immunosuppression (19.5%).

The mean time to blood culture positivity was 1.41 days overall (range 0.37–5.64 days), with blood cultures containing *C. glabrata* requiring longer incubation time to positivity (2.67 days on average, range 0.43–5.64) than the other species.

Previous colonization in at least one site by the same *Candida* sp. that was isolated from the bloodstream was detected in 99 episodes (77.3%). The sites of colonization were the respiratory tract (46.9%), the urinary tract (22.6%), an intravascular device (35.9%), and wounds (23.4%). The source of *Candida* BSI was identified in 74 cases: four bloodstream isolates originated from the urinary tract, 17 from an abdominal abscess or peritoneal infection, three from deep skin infections, three from the mediastinum, and one case of endocarditis was identified. Forty-six (35.9%) episodes were associated with a central venous line. Demographic data and clinical characteristics are summarized in Table II.

Overall 30-day mortality was 50.8%, whereas 30-day mortality the highest (90.9%) with *C. tropicalis* BSI and the lowest with *C. krusei* (25%) and *C. parapsilosis* (27.3%).

Univariate analysis was performed to assess if any risk factors of candidaemia could be associated with a higher mortality rate. No such connection was detected; p values are presented in Table III.

Isolate characteristics

A total of 136 isolates were collected. The most frequently isolated species was *C. albicans* (63%), followed by *C. glabrata* (13%), *C. parapsilosis* (10.2%), *C. tropicalis* (9.3%), and *C. krusei* (3.7%). *C. kefyr* caused one episode

in 2013, and *C. fabianii* and *C. inconspicua* caused one episode each in 2014. Seven cases (6.9%) of BSI with multiple *Candida* spp. were recorded. *C. albicans* and *C. glabrata* were isolated in four cases, *C. albicans* and *C. parapsilosis* in one case, *C. albicans* and *C. tropicalis* in one case, and *C. parapsilosis* and *C. glabrata* in one case.

There was no significant change in the percentage of *C. albicans* per year (63% of all isolates) during the study period, but the rate of species with decreased susceptibility or resistance to fluconazole increased from 10.5% in 2010 to 39.3% in 2014 ($p < 0.005$). Figure 2 shows species distribution between 2010 and 2014.

All isolates were wild-type organisms and no acquired resistance was detected based on EUCAST breakpoints and available epidemiological cut-off values. The antifungal MIC range, MIC 50 and MIC 90 values are presented in Table IV.

Discussion

The incidence of *Candida* BSI at our institute increased between 2010 and 2013 ($R^2 = 0.9$) from 1.7 to 3.5 episodes / 10 000 admissions, in agreement with worldwide trends, but dropped back to 2.66 episodes / 10 000 admissions in 2014. The incidence rate is similar to previous Hungarian data and results from other European centers [20, 21, 22]. The decrease in incidence during the last study year may be explained by the administration of prophylactic antifungal therapy by clinicians after the problem of increasing rates of *Candida* BSI was detected.

C. albicans was the most frequently isolated species (63%), and the percentage of *C. albicans* isolates per year did not change significantly during the study period. Several studies have detected a shift towards non-*albicans Candida* spp., especially *C. glabrata*, causing BSI [23]. This trend was observed at our institute as well, with the number of non-*albicans* isolates increasing steadily from 2010 to 2014. The number of *C. glabrata* isolates increased from 2 isolates in 2010 to 9 isolates in 2014.

Candidaemia was especially prevalent in patients in the ICU after abdominal surgery: the majority of our cases (60.9%) occurred in the ICU, and over half (55.5%) following major abdominal surgery. These findings mirror the results of Kuhns et al., who in a survey of 47 707 cases determined that 20.7% of BSI in the ICU following abdominal surgery were caused by *Candida* spp. [24].

Solid malignancy was a major risk factor of candidaemia, present in 30.5% of the patients. Surveillance cultures are recommended in patients at risk to detect colonization by *Candida* spp. [25], which precluded *Candida* BSI at our institute in 77.3% of cases.

Table II. Clinical and demographic characteristics of patients with *Candida* bloodstream infection at Semmelweis University, Hungary, 2010–2014. Values are indicated as number (%)

		All (n = 128)	*Candida albicans* (n = 75)	*Candida parapsilosis* (n = 11)	*Candida tropicalis* (n = 11)	*Candida glabrata* (n = 17)	*Candida krusei* (n = 4)	*>1 Candida sp.* (n = 8)
Demographics								
	Median age (range)	63.2 (22–86)	62.3 (22–86)	53.5 (22–72)	66.9 (48–81)	69.5 (50–84)	54.2 (49–59)	64.7 (28–86)
	Male sex	77 (60.1%)	45 (60%)	4 (36.4%)	7 (63.6%)	13 (76.5%)	3 (75%)	4 (50%)
	Treatment at ICU	78 (60.9%)	45 (60%)	7 (63.6%)	7 (63.6%)	13 (76.5%)	2 (50%)	3 (37.5%)
Underlying disease								
	Solid malignancy	39 (30.5%)	25 (33%)	2 (18.2%)	2 (18.2%)	6 (35.3%)	1 (25%)	3 (37.5%)
	Diabetes mellitus	31 (24.2%)	21 (28%)	2 (18.2%)	1 (9%)	5 (29.4%)	1 (25%)	1 (12.5%)
	Immunosuppression	25 (19.5%)	13 (17.3%)	5 (45%)	1 (9%)	1 (5.9%)	2 (50%)	3 (37.5%)
	Acute hematologic malignancy	8 (6.25%)	4 (5.3%)	3 (27.3%)	1 (9%)	0	0	0
	Neutropenia	11 (8.6%)	5 (6.7%)	3 (27.3%)	1 (9%)	0	1 (11%)	1 (12.5%)
	Previous renal failure	13 (10.16%)	9 (12%)	1 (9%)	1 (9%)	1 (5.9%)	0	1 (12.5%)
	Moderate to severe liver disease	8 (6.25%)	6 (8%)	0	2 (18.2%)	0	0	0
	Transplant recipient	2 (1.6%)	0	0	0	0	2 (50%)	0

Table II. (cont.)

		All (n = 128)	*Candida albicans* (n = 75)	*Candida parapsilosis* (n = 11)	*Candida tropicalis* (n = 11)	*Candida glabrata* (n = 17)	*Candida krusei* (n = 4)	*>1 Candida sp.* (n = 8)
Clinical characteristics								
	Major abdominal surgery	71 (55.5%)	42 (56%)	5 (45%)	6 (54.5%)	12 (70.6%)	2 (50%)	3 (37.5%)
	Total parenteral nutrition	32 (25%)	14 (18.7%)	4 (36.4%)	2 (18.2%)	5 (29.4%)	2 (50%)	5 (62.5%)
	Prolonged broad-spectrum antibiotic therapy	91 (71.1%)	59 (78.7%)	7 (63.6%)	5 (55%)	12 (70.6%)	3 (75%)	5 (62.5%)
	Prior antifungal therapy	9 (7%)	6 (8%)	0	0	2 (11.8%)	1 (25%)	0
	Immunosuppressive therapy	14 (10.9%)	8 (10.7%)	2 (18.2%)	0	1 (5.9%)	1 (11%)	2 (25%)
	Chemotherapy in the past 30 days	10 (7.8%)	7 (9.3%)	1 (9%)	1 (9%)	1 (5.9%)	0	0
Source of infection								
	Abdominal	28 (21.9%)	18 (24%)	0	1 (9%)	6 (35.3%)	1 (25%)	2 (25%)
	Central venous line associated	46 (35.9%)	30 (40%)	4 (36.4%)	3 (27.3%)	3 (17.6%)	2 (50%)	4 (50%)
	Urinary tract	5 (3.9%)	4 (5.3%)	0	0	1 (5.9%)	0	0
30 day mortality		65 (50.8%)	38 (50.7%)	3 (27.3%)	10 (90.9%)	7 (41.2%)	1 (25%)	4 (50%)

Table III. Risk factors of candidaemia vs. mortality (2010–2014, Semmelweis University, Hungary)

	Recovered patient	Fatal outcome	p value
Abdominal surgery	27	24	0.2
Treatment at ICU	31	27	0.088
Solid malignancy	11	15	0.652
Acute leukaemia	4	3	0.7
Immunosuppression	8	12	0.617
Parenteral nutrition	11	11	0.808
Presence of an endovascular catheter	27	36	0.656

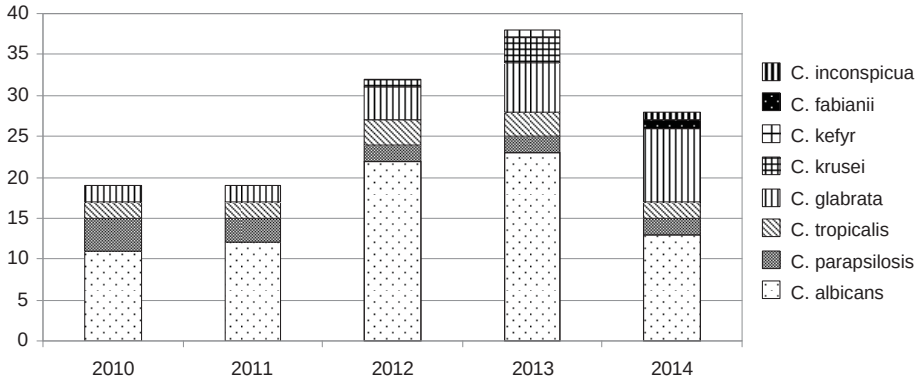

Figure 2. Species distribution of *Candida* bloodstream isolates at Semmelweis University, Hungary, 2010–2014

Table IV. Antifungal MIC range, MIC50 and MIC90 values of *Candida* bloodstream isolates at Semmelweis University, Hungary, 2010–2014

Species	Antifungal agent	MIC range (μg/ml)	MIC50 (μg/ml)	MIC90 (μg/ml)
Candida albicans (n = 75)	Fluconazole	0.064–1	0.25	0.5
	Itraconazole	0.016–0.125	0.032	0.125
	Voriconazole	0.004–0.064	0.008	0.064
	Posaconazole	0.008–0.016	0.008	0.016
	Anidulafungin	0.008–0.032	0.016	0.032
	Micafungin	0.004–0.016	0.008	0.016
	Caspofungin	0.004–0.032	0.008	0.032
	Amphotericin B	0.064–0.5	0.25	0.5

Table IV. (cont.)

Species	Antifungal agent	MIC range (μg/ml)	MIC50 (μg/ml)	MIC90 (μg/ml)
Candida parapsilosis (n = 11)	Fluconazole	0.064–1	0.125	0.5
	Itraconazole	0.03–0.125	0.125	0.125
	Voriconazole	0.004–0.064	0.016	0.032
	Posaconazole	0.008–0.032	0.016	0.032
	Anidulafungin	0.5–1.0	1	1
	Micafungin	0.25–0.5	0.25	0.5
	Caspofungin	0.064–0.25	0.125	0.25
	Amphotericin B	0.125–0.5	0.25	0.5
Candida tropicalis (n = 11)	Fluconazole	0.125–1	0.25	0.5
	Itraconazole	0.016–0.125	0.064	0.125
	Voriconazole	0.008–0.064	0.016	0.064
	Posaconazole	0.008–0.032	0.016	0.032
	Anidulafungin	0.008–0.016	0.016	0.016
	Micafungin	0.008–0.032	0.016	0.032
	Caspofungin	0.016–0.032	0.032	0.032
	Amphotericin B	0.125–0.5	0.25	0.5
Candida glabrata (n = 17)	Fluconazole	2.0–16	4	8
	Itraconazole	0.064–0.25	0.125	0.25
	Voriconazole	0.125–0.5	0.25	0.5
	Posaconazole	0.5–1.0	1	1
	Anidulafungin	0.016–0.03	0.03	0.03
	Micafungin	0.004–0.016	0.08	0.016
	Caspofungin	0.004–0.03	0.016	0.03
	Amphotericin B	0.25–1.0	0.5	1
Candida krusei (n = 4)	Fluconazole	16–32	32	32
	Itraconazole	0.03–1.0	1	1
	Voriconazole	0.032–1.0	0.064	1
	Posaconazole	0.032–0.125	0.032	0.125
	Anidulafungin	0.008–0.03	0.016	0.03
	Micafungin	0.004–0.03	0.008	0.03
	Caspofungin	0.016–0.03	0.016	0.03
	Amphotericin B	0.25–0.5	0.25	0.5

Eight cases (6.25%) of BSI caused by more than one *Candida* spp. were detected. Polyfungal candidaemia is uncommon and has been associated with severe underlying disease, use of intravascular catheter, treatment at ICU, prior antibiotic exposure and heavy colonization with *Candida* spp. [26]. Significant statistical results could not be achieved due to the small sample size, but patients with multiple *Candida* isolates suffered from solid malignant disease (37.5%), and received TPN more frequently (62.5%) compared with overall rates.

Acquired resistance to at least one group of antifungals has been detected in case of several *Candida* spp. Reports of multi-resistant *C. glabrata* isolates resistant to azoles, echinocandins and amphotericin B are especially alarming [27, 28]. All the isolates in our study were wild-type organisms, indicating that acquired antifungal resistance of *Candida* spp. is not an issue in Hungary yet. The emergence of resistant isolates has been linked with prior antifungal treatment. Echinocandin treatment has only recently been implemented in Hungarian routine clinical care, explaining why resistant isolates have not been detected yet. What is especially daunting is the fact that isolates resistant to echinocandins are frequently resistant to amphotericin B as well, posing a serious therapeutic challenge to clinicians.

The overall 30-day mortality rate at our institute was higher (50.8%) than figures reported in other European and US centers (22–37%) [29, 30]. Mortality rate by species was the highest for *C. tropicalis* (90.9%) and *C. albicans* (50.7%); these two species are the most virulent compared with other species and have been associated with higher mortality rates in BSI [31], though the mortality rate for *C. tropicalis* may be falsely high due to the small sample size.

No risk factors of *Candida* BSI were found to be significantly associated with patient mortality.

This study describes the local epidemiology and antifungal susceptibility at a university hospital. The incidence of *Candida* BSI increased during the study period, and fluconazole non-susceptible species became more prevalent. Rare *Candida* spp., such as *C. fabianii* and *C. inconspicua* were identified as cause of BSI. No isolates with acquired antifungal resistance were detected. Surveillance of *Candida* BSI should be continued in the future to assess changes in epidemiology and to monitor antifungal resistance.

Authors' Contributions

PJ and KK conceived and designed the study. PJ collected and analysed the data. PJ and KK wrote and corrected the manuscript. JE and IM contributed in collecting the isolates and in correction of the manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Kett, D. H., Azoulay, E., Echeverria, P. M., Vincent, J. L., and for the Extended Prevalence of Infection in the ICU Study (EPIC II) Group of Investigators: *Candida* bloodstream infections in intensive care units: Analysis of the extended prevalence of infection in intensive care unit study. Crit Care Med **39,** 665–670 (2011).
2. Arendrup, M. C., Bruun, B., Christensen, J. J., Fuursted, K., Johansen, H. K., Kjaeldgaard, P., Knudsen, J. D., Kristensen, L., Møller, J., Nielsen, L., Rosenvinge, F. S., Røder, B., Schønheyder, H. C., Thomsen, M. K., Truberg, K.: National surveillance of fungemia in Denmark (2004 to 2009). J Clin Microbiol **49,** 325–334 (2011).
3. Puig-Asensio, M., Padilla, B., Garnacho-Montero, J., Zaragoza, O., Aguado, J. M., Zaragoza, R., Montejo, M., Muñoz, P., Ruiz-Camps, I., Cuenca-Estrella, M., Almirante, B.; CANDIPOP Project; GEIH-GEMICOMED (SEIMC); REIPI: Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: A population-based surveillance in Spain. Clin Microbiol Infect **20,** 245–254 (2014).
4. Sandven, P., Bevanger, L., Digranes, A., Haukland, H. H., Mannsåker, T., Gaustad, P., and the Norwegian Yeast Study Group: Candidemia in Norway (1991 to 2003): Results from a nationwide study. J Clin Microbiol **44,** 1977–1981 (2006).
5. Cleveland, A. A., Farley, M. M., Harrison, L. H., Stein, B., Hollick, R., Lockhart, S. R., Magill, S. S., Derado, G., Park, B. J., Chiller, T. M.: Changes in incidence and antifungal drug resistance in candidemia: Results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011. Clin Infect Dis **55,** 1352–1361 (2012).
6. Wisplinghoff, H., Ebbersa, J., Geurtza, L., Stefanik, D., Major, Y., Edmond, M. B., Wenzel, P., Seifert, H.: Nosocomial bloodstream infections due to Candida spp. in the USA: Species distribution, clinical features and antifungal susceptibilities. Int J Antimicrob Agents **43,** 78–81 (2014).
7. Tapia, G. G., Razonable, R. R., Eckel-Passow, J. E., Lahr, B. D., Afessa, B., Keegan, M. T., Catania, J., Baddour, L. M.: A scoring model of factors associated with Candida glabrata candidemia among critically ill patients. Mycoses **55,** 228–236 (2012).
8. Chi, H. W., Yang, Y. S., Shang, S. T., Chen, K. H., Yeh, K. M., Chang, F. Y., Lin, J. C.: Candida albicans versus non-albicans bloodstream infections: The comparison of risk factors and outcome. J Microbiol Immunol Infect **44,** 369–375 (2011).
9. Leenders, N. H., Oosterheert, J. J., Ekkelenkamp, M. B., De Lange, D. W., Hoepelman, A. I., Peters, E. J.: Candidemic complications in patients with intravascular catheters colonized with Candida species: An indication for preemptive antifungal therapy? Int J Infect Dis **15,** 453–458 (2011).
10. Pfaller, M., Neofytos, D., Diekema, D., Azie, N., Meier-Kriesche, H. U., Quan, S. P., Horn, D.: Epidemiology and outcomes of candidemia in 3648 patients: Data from the Prospective Antifungal Therapy (PATH Alliance®) registry, 2004–2008. Diagn Microbiol Infect Dis **74,** 323–331 (2012).

11. Jordá-Marcos, R., Álvarez-Lerma, F., Jurado, M., Palomar, M., Nolla-Salas, J., León, M. A., León, C.; EPCAN Study Group: Risk factors for candidaemia in critically ill patients: A prospective surveillance study. Mycoses **50,** 302–310 (2007).
12. Labelle, A. J., Micek, S. T., Roubinian, N., Kollef, M. H.: Treatment-related risk factors for hospital mortality in Candida bloodstream infections. Crit Care Med **36,** 2967–2972 (2008).
13. Hii, I. M., Chang, H. L., Lin, L. C., Lee, Y. L., Liu, Y. M., Liu, C. E., Chen, C. H., Cheng, Y. R., Chang, C. Y.: Changing epidemiology of candidemia in a medical center in middle Taiwan. J Microbiol Immunol Infect, http://dx.doi.org/10.1016/j.jmii.2013.08.017 (2013).
14. Ma, C. F., Li, F. Q., Shi, L. N., Hu, Y. A., Wang, Y., Huang, M., Kong, Q. Q.: Surveillance study of species distribution, antifungal susceptibility and mortality of nosocomial candidemia in a tertiary care hospital in China. BMC Infect Dis **13,** 337 (2013).
15. Bassetti, M., Ansaldi, F., Nicolini, L., Malfatto, E., Molinari, M. P., Mussap, M., Rebesco, B., Bobbio Pallavicini, F., Icardi, G., Viscoli, C.: Incidence of candidaemia and relationship with fluconazole use in an intensive care unit. J Antimicrob Chemother **64,** 625–629 (2009).
16. Lee, I., Fishman, N. O., Zaoutis, T. E., Morales, K. H., Weiner, M. G., Synnestvedt, M., Nachamkin, I., Lautenbach, E.: Risk factors for fluconazole-resistant Candida glabrata bloodstream infections. Arch Intern Med **169,** 379–383 (2009).
17. Pfeiffer, C. D., Garcia-Effron, G., Zaas, A. K., Perfect, J. R., Perlin, D. S., Alexander, B. D.: Breakthrough invasive Candidiasis in patients on micafungin. J Clin Microbiol **48,** 2373–2380 (2010).
18. Cho, E. J., Shin, J. H., Kim, S. H., Kim, H. K., Park, J. S., Sung, H., Kim, M. N., Im, H. J.: Emergence of multiple resistance profiles involving azoles, echinocandins and amphotericin B in Candida glabrata isolates from a neutropenia patient with prolonged fungaemia. J Antimicrob Chemother **70,** 1268–1270 (2015).
19. The European Committee on Antimicrobial Susceptibility Testing. Antifungal Agents. Breakpoint tables for interpretation of MICs. Version 7.0, 2014. http://www.eucast.org.
20. Wille, M. P., Guimarães, T., Furtado, G. H., Colombo, A. L.: Historical trends in the epidemiology of candidaemia: Analysis of an 11-year period in a tertiary care hospital in Brazil. Mem Inst Oswaldo Cruz **108**(3), 288–292 (2013).
21. Dóczi, I., Dósa, E., Hajdú, E., Nagy, E.: Aetology and antifungal susceptibility of yeast bloodstream infections in a Hungarian university hospital between 1996 and 2000. I Med Microbiol **51**(8), 677–681 (2002).
22. Tortorano, A. M., Peman, J., Bernhardt, H., Klingspor, L., Kibbler, C. C., Faure, O., Biraghi, E., Canton, E., Zimmermann, K., Seaton, S., Grillot, R.; ECMM Working Group on Candidaemia: Epidemiology of candidaemiain Europe: Results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis **23**(4), 317–322 (2004).
23. Moretti, M. L., Trabasso, P., Lyra, L., Fagnani, R., Resende, M. R., de Oliveira Cardoso, L. G., Schreiber, A. Z.: Is the incidence of candidemia caused by Candida glabrata increasing in Brazil? Five-year surveillance of Candida bloodstream infection in a university reference hospital in southeast Brazil. Med Mycol **51**(3), 225–230 (2013).
24. Kuhns, M., Rosenberger, A., Bader, O., Reichard, U., Gross, U., Weig, M.: Incidence of Candidaemia following abdominal surgery in German hospitals. Zentralbl Chir 2013 Nov 15. [in German]

25. Posteraro, B., De Pascale, G., Tumbarello, M., Torelli, R., Pennisi, M. A., Bello, G., Maviglia, R., Fadda, G., Sanguinetti, M., Antonelli, M.: Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1-3)-β-D-glucan assay, Candida score, and colonization index. Crit Care **15**(5), R249 (2011).
26. Pulimood, S., Ganesan, L., Alangaden, G., Chandrasekar, P.: Polymicrobial candidemia. Diagn Microbiol Infect Dis **44**(4), 353–357 (2002)
27. Cho, E. J., Shin, J. H., Kim, S. H., Kim, H. K., Park, J. S., Sung, H., Kim, M. N., Im, H. J.: Emergence of multiple resistance profiles involving azoles, echinocandins and amphotericin B in Candida glabrata isolates from a neutropenia patient with prolonged fungaemia. J Antimicrob Chemother **70**(4), 1268–1270 (2015).
28. Cleveland, A. A., Harrison, L. H., Farley, M. M., Hollick, R., Stein, B., Chiller, T. M., Lockhart, S. R., Park, B. J.: 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 **10**(3), e0120452 (2015).
29. Pfaller, M., Neofytos, D., Diekema, D., Azie, N., Meier-Kriesche, H. U., Quan, S. P., Horn, D.: Epidemiology and outcomes of candidemia in 3648 patients: Data from the Prospective Antifungal Therapy (PATH Alliance®) registry, 2004–2008. Diagn Microbiol Infect Dis **74,** 323–331 (2012).
30. Das, I., Nightingale, P., Patel, M., Jumaa, P.: Epidemiology, clinical characteristics, and outcome of candidemia: Experiencein a tertiary referral center in the UK. Int J Infect Dis **15**(11), 759–763 (2011).
31. Arendrup, M., Horn, T., Frimodt-Møller, N.: In vivo pathogenicity of eight medically relevant *Candida* species in an animal model. Infection **30**(5), 286–291 (2002).