BMC Infectious Diseases

Risk factors for fatal candidemia caused by *Candida albicans* and non-albicans *Candida* species

Ming-Fang Cheng[1,2,3,4], Yun-Liang Yang[5], Tzy-Jyun Yao[6], Chin-Yu Lin[6], Jih-Shin Liu[6], Ran-Bin Tang[2], Kwok-Woon Yu[3], Yu-Hua Fan[7], Kai-Sheng Hsieh[1], Monto Ho[8] and Hsiu-Jung Lo*[8]

Address: [1]Department of Pediatrics, Veterans General Hospital-Kaohsiung, Kaohsiung, Taiwan, [2]Section of Infection Disease, Department of Pediatrics, Taiwan, [3]Department of Microbiology, Veterans General Hospital-Taipei, Taiwan, [4]National Yang Ming University, Taipei, Taiwan, [5]Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan, [6]Division of Biostatistics and Bioinformatics, Miaoli, Taiwan, [7]Koahsiung Medical University, Kaohsiung, Taiwan and [8]Division of Clinical Research, National Health Research Institutes, Miaoli, Taiwan

Email: Ming-Fang Cheng - mfcheng@vghks.gov.tw; Yun-Liang Yang - yyang@mail.nctu.edu.tw; Tzy-Jyun Yao - tjyun_yao@yahoo.com; Chin-Yu Lin - lin09_1999@yahoo.com; Jih-Shin Liu - jihshin@nhri.org.tw; Ran-Bin Tang - rbtang@vghtpe.gov.tw; Kwok-Woon Yu - kwyu@vghtpe.gov.tw; Yu-Hua Fan - yhfan2@vghtpe.gov.tw; Kai-Sheng Hsieh - kshsieh@isca.vghks.gov.tw; Monto Ho - monto@imap.pitt.edu; Hsiu-Jung Lo* - hjlo@nhri.org.tw

* Corresponding author

Abstract

Background: Invasive fungal infections, such as candidemia, caused by *Candida* species have been increasing. Candidemia is not only associated with a high mortality (30% to 40%) but also extends the length of hospital stay and increases the costs of medical care. Sepsis caused by *Candida* species is clinically indistinguishable from bacterial infections. Although, the clinical presentations of the patients with candidemia caused by *Candida albicans* and non-albicans *Candida* species (NAC) are indistinguishable, the susceptibilities to antifungal agents of these species are different. In this study, we attempted to identify the risk factors for candidemia caused by *C. albicans* and NAC in the hope that this may guide initial empiric therapy.

Methods: A retrospective chart review was conducted during 1996 to 1999 at the Veterans General Hospital-Taipei.

Results: There were 130 fatal cases of candidemia, including 68 patients with *C. albicans* and 62 with NAC. Candidemia was the most likely cause of death in 55 of the 130 patients (42.3 %). There was no significant difference in the distribution of *Candida* species between those died of candidemia and those died of underlying conditions. Patients who had one of the following conditions were more likely to have *C. albicans*, age $\geqq$ 65 years, immunosuppression accounted to prior use of steroids, leukocytosis, in the intensive care unit (ICU), and intravascular and urinary catheters. Patients who had undergone cancer chemotherapy often appeared less critically ill and were more likely to have NAC.

Conclusion: Clinical and epidemiological differences in the risk factors between candidemia caused by *C. albicans* and NAC may provide helpful clues to initiate empiric therapy for patients infected with *C. albicans* versus NAC.

Background

Invasive fungal infections caused by *Candida* species have increased significantly. They now rank fourth as the most common cause of nosocomial bloodstream infections in the United Stated [1] and the most common one at one major hospital in Taiwan [2]. Candidemia is not only associated with a mortality of about 30% to 40% but also extends the duration of hospital stay [3,4] and increases the cost for medical care [5]. In recent years, *Candida* species associated with candidemia have shifted from *Candida albicans* to non-albicans *Candida* species (NAC) [6]. Approximately half of the reported cases of candidemia are now caused by NAC [7-10].

Patients with candidemia usually present an acute septic syndrome that is indistinguishable from bacteremia, but they may also exhibit a more indolent course manifested by fever of unknown origin. Major risk factors for candidemia include intravascular catheters, parenteral hyperalimentation, and broad-spectrum antibiotics. Empirical antifungal agents may be administrated to patients manifested with fever of unknown origin and have above mentioned risk factors, particularly those who have been treated with broad-spectrum antibiotics. The clinical presentation of the patients with sepsis caused by *C. albicans* and NAC are indistinguishable. However, NAC are often less susceptible to fluconazole than *C. albicans* is [7,11,12] and may require greater dosage to cure clinically [13,14].

We have conducted a retrospective chart review of patients whose death was associated with candidemia. The goal was to assist decisions to select the most appropriate empirical therapy for patients suspected to have candidemia. The objective was to determine whether specific risk factors could be identified to help selecting those patients who are more likely infected with *C. albicans* versus NAC.

Methods

This study was conducted at the Veterans General Hospital-Taipei. This is a 2800-bed teaching hospital with about 69,000 admissions annually [7]. A total of 415 blood isolates of *Candida* species (one strain per species per patient) were collected from April 1996 to December 1999. During this period 130 patients met the inclusion criteria of having at least one positive blood culture for *Candida* species within one month prior to the fatal outcome. There were 68 patients infected with *C. albicans* and 62 with NAC.

Candida species were isolated from blood using BACTEC 860 system (Becton Dickinson, INC, Sparks, MD). The species were identified using API-32C system (bioMerieux Vitek, Inc, St. Louis, MI).

Clinical data

Clinical data of 130 patients were recorded on standardized forms and analyzed according to age at the time of diagnosis, gender and underlying illnesses. These included cancer, diabetes, immunosuppression accounted to prior use of steroids, systemic antifungal agents, cancer chemotherapy, parenteral nutrition, the presence of central or arterial line, endotracheal tube, and urinary catheter, admission to an intensive care unit (ICU), history of infection or gastrointestinal surgery, hemogram, antifungal management, and cause of death. The predisposing events within one month prior to diagnosis and the laboratory data within seven days prior to obtaining the first positive blood culture were analyzed. To decide that a patient died directly of candidemia or underlying illness, we recoded the causes of death according to the death certificate of the patients.

Statistical analysis

The statistical significance of association between categorical variables was assessed using the Fisher's Exact Test. The risk factors with p values < 0.1 in the univariate analysis were placed in a multivariate analysis using the multiple logistic regression package in the SAS System for Windows V8. Confidence limit of 95% means that the confidence limit contains the true value of odds ratio with probability of 0.95. The narrower the confidence limit is, the more accurate the estimate is.

Results

The population consisted of 130 patients whose death was associated with candidemia. Fifty-five (42.3 %) of these deaths were considered to be directly caused by *Candida* species. The remaining died of complications of their underlying illness. The distribution of species of the total deaths and those causally related to candidemia is shown in Table 1. There were no significant differences in causation of death according to species. Interestingly, of the four major species related to candidemia, 61.5% of the isolated *Candida glabrata* contributed to mortality, followed by 50% of *Candida parapsilosis*, 41.2% of *C. albicans*, and 31.3% of *Candida tropicalis*.

The demographic and clinical characteristics of the study population categorized according to the presence of *C. albicans* or NAC in the blood are summarized in Table 2. The significant ($p \leq 0.05$) risk factors on univariate analysis for *C. albicans* candidemia were age $\geq$ 65 years, prior bacterial urinary tract infection, central venous catheter, parenteral nutrition and leucocytosis with white blood cell counts (WBC) $\geq$ 15000/mm³, without significant neutropenia with absolute neutrophil counts (ANC) $\geq$ 100000/mm³. The significant risk factors for NAC were age < 65 years, cancer chemotherapy, neutropenia (WBC < 3000/mm³) and severe thrombocytopenia (platelet

Table 1: Distribution of *Candida species* of fatal outcome attributed to disseminated candidemia

species	Blood isolates (N = 130)		Death directly related to candidemia (N = 55)		
		% in Number 130 isolates		% in Number 55 isolates	% in species of blood isolates
C. albicans	68	52.3	28	50.9	41.2
non-albicans *Candida* species	62	47.7	27	49.1	43.5
C. tropicalis	32	24.7	10	18.2	31.3
C. glabrata	13	10.0	8	14.5	61.5
C. parapsilosis	12	9.2	6	10.9	50.0
C. guilliermondii	2	1.5	1	1.8	50.0
C. peniculosa	2	1.5	2	3.6	100.0
C. famata	1	0.8	0	0	0

Table 2: Characteristics of 130 patients who died in association with candidemia

Characteristic	*C. albicans* (N = 68)		NAC (N = 62)		Fisher's Exact Test
	No.	%	No.	%	Two-sided P-value
Age $\geqq$ 65 years old	56	82.4	36	58.1	**0.004***
MICU	6	8.8	10	16.1	0.286
Medical ward stay	24	35.3	32	51.6	0.077*
Cancer	24	35.3	32	51.6	0.077*
Immunosuppressive therapy	17	25	7	11.3	0.069*
Bacteremia	25	36.8	15	24.2	0.133
Bacterial urinary tract infection	23	33.8	10	16.1	**0.026***
Prior antifungal administration	5	7.4	9	14.5	0.259
Catheters within 30 days	65	95.6	56	90.3	0.309
ETT	35	51.5	23	37.1	0.114
CVC	57	83.8	41	66.1	**0.025***
AL	21	30.9	14	22.6	0.326
Urinary catheter	49	72.1	39	62.9	0.348
PPN	50	73.5	34	54.8	**0.029***
Cancer chemotherapy	5	7.4	12	19.4	0.066*
Corticosteroids	26	38.2	18	29	0.354
ANC	(N = 44)		(N = 40)		1
ANC $\leqq$ 1500/mm^3	2	4.5	2	5	
WBC	(N = 67)		(N = 61)		**0.0004***
$\leqq$ 3000/mm^3	4	6	14	23	
3000/mm^3 to 5000/mm3	35	52.2	38	62.3	
> 15000/mm^3	28	41.8	9	14.8	
Platelet	(N = 66)		(N = 61)		**0.011***
$\leqq$ 20000/mm^3	5	7.6	10	16.4	
20000/mm^3 to 100000/mm^3	20	30.3	29	47.5	
> 100000/mm^3	41	62.1	22	36.1	

* Factors selected for multivariate analysis. AL, arterial line; ANC, absolute neutrophil count; CVC, central venous catheter; ETT, endo trachial tube; ICU, Intensive care unit; PN, parenteral nutrition; WBC, white blood cell

count $\leqq$ 20000 /mm^3). NAC patients were more likely to have cancers and to be located on the medical wards (p = 0.08). When multivariate analysis was employed, the significant risk factors for *C. albicans* were age $\geqq$ 65 years, immunosuppressive therapy, and leucocytosis. Significant risk factors for NAC were age < 65 years and location on medical wards, which are shown in Table 3.

Discussion
Candida albicans remains the most common species causing candidemia, but the proportion caused by NAC is

Table 3: Multiple regression analysis of risk factors for candidemia caused by *Candida albicans* vs. non-albicans Candida species

Effect	Odds Ratio	95% confidence Limits		P-value
White Blood Cell (WBC)				0.0202
> 15000/mm^3 vs. ≦ 3000/ mm^3	5.89	1.35	25.7	0.0184
3001 − 15000/mm^3 vs. ≦ 3000/ mm^3	1.66	0.44	6.26	0.4549
> 15000/mm^3 vs. 3001 − 15000/mm^3	3.55	1.29	9.79	0.0144
Age65 (≧ 65 vs. < 65)	6.73	2.37	19.1	0.0003
Immunosuppressive therapy	4.39	1.26	15.32	0.0201
Located on a medical ward	0.37	0.16	0.88	0.025

increasing [7-10]. Patients with NAC are more likely to require greater dosage of fluconazole to cure clinically [13,14]. Thus there is a need to identify patients at risk of NAC candidemia to initiate empirical amphotericin B therapy or high-dose fluconazole.

Krcmery and Barnes have identified the following risk factors for NAC [15]. These include prophylaxis with azole compounds as a risk factor for *C. krusei* and *C. glabrata*, neutropenia and bone marrow transplantation for *C. tropicalis*, and insertion of foreign bodies, neonates, and hyperalimentation for *C. parapsilosis* [15-18]. In this study we have identified additional risk factors that help distinguish candidemia caused by *C. albicans* and NAC. The most important risk factors for *C. albicans* are the old age, procedures associated with intensive care, and an acute sepsis. The most important risk factors for NAC are cancer chemotherapy in association with leukopenia and thrombocytopenia.

It has been reported that *Candida* species exhibit a spectrum in the extent of adherence to tissues, which correlates with the pathogenicity in humans and animals [19]. *Candida albicans* exhibit the greatest capacity to adhere to gingival epithelial cells, followed by *C. tropicalis* and *C. glabrata* [19]. The capacity of yeasts to attach to a wide range inanimate surfaces appears to protect them from immune responses and antimicrobial agents [20]. This may explain why *C. albicans* is more likely to be associated with central venous catheters in this study.

Conventional methods to eradicate *C. albicans* rely upon the use of antifungal drugs designed to kill the yeast or arrest its growth. However, removal of intravascular catheters is in fact the most simple and effective method [21,22]. Another approach is to design new agents that disrupt adherence of the yeasts to host tissues and catheters.

Conclusion

It is customary to administer amphotericin B for critically ill patients suspected of having candidemia. More often than not, azoles are used for relatively stable patients. NAC tend to be less susceptible to fluconazole than *C. albicans* is [7,11,23]. Thus, greater dosage is needed till the causative microorganism is isolated and identified, particularly with patients at high risk for NAC candidemia. Though, a large, prospective study is needed to validate this concept, the risk factors identified in this study may help, in clinical practice, to differentiate fatal candidemia caused by *C. albicans* versus NAC.

Abbreviations used

NAC, non-albicans *Candida* species; VGH-TPE, Veterans General Hospital-Taipei; ICU, intensive care unit; AL, arterial line; ANC, absolute neutrophil count; CVC, central venous catheter; ETT, endo trachial tube; WBC, white blood cell.

Competing interests

The author(s) declared that they have no competing interests.

Authors' contributions

MFC conceived the study and designed it together with, YLY, MH, and HJL. MFC conducted the experiments with contribution from RBT, YHF, and KSH. KWY collected clinical isolates. JSL performed the statistical study with contributions from CYL and TJY. MFC drafted the manuscript with contribution from YLY and HJL.

References

1. Jarvis WR: **Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species.** *Clin Infect Dis* 1995, **20**:1526-1530.
2. Chen YC, Chang SC, Sun CC, Yang LS, Hsieh WC, Luh KT: **Secular trends in the epidemiology of nosocomial fungal infections at a teaching hospital in Taiwan, 1981 to 1993.** *Infect Control Hosp Epidemiol* 1997, **18**:369-375.

3. Leleu G, Aegerter P, Guidet B: **Systemic candidiasis in intensive care units: a multicenter, matched-cohort study.** *J Crit Care* 2002, **17:**168-175.
4. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP: **Hospital-acquired candidemia: The attributable mortality and excess length of stay.** *Arch Intern Med* 1988, **148:**2642-2645.
5. Tortorano AM, Caspani L, Rigoni AL, Biraghi E, Sicignano A, Viviani MA: **Candidosis in the intensive care unit: a 20-year survey.** *J Hosp Infect* 2004, **57:**8-13.
6. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, Doyen C, Lebeau B, Spence D, Krcmery V, De Pauw B, Meunier F: **Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC).** *Clin Infect Dis* 1999, **28:**1071-1079.
7. Cheng MF, Yu KW, Tang RB, Fan YH, Yang YL, Hsieh KS, Ho M, Lo HJ: **Distribution and antifungal susceptibility of *Candida* species causing candidemia from 1996 to 1999.** *Diagn Microbiol Infect Dis* 2004, **48:**33-37.
8. Colombo AL, Nucci M, Salomao R, Branchini ML, Richtmann R, Derossi A, Wey SB: **High rate of non-albicans candidemia in Brazilian tertiary care hospitals.** *Diagn Microbiol Infect Dis* 1999, **34:**281-286.
9. Kao AS, Brandt ME, Pruitt WR, Conn LA, Perkins BA, Stephens DS, Baughman WS, Reingold AL, Rothrock GA, Pfaller MA, Pinner RW, Hajjeh RA: **The epidemiology of candidemia in two United States cities: results of a population-based active surveillance.** *Clin Infect Dis* 1999, **29:**1164-1170.
10. Pfaller MA, Jones RN, Doern GV, Sader HS, Messer SA, Houston A, Coffman S, Hollis RJ: **Bloodstream infections due to *Candida* species: SENTRY antimicrobial surveillance program in North America and Latin America, 1997–1998.** *Antimicrob Agents Chemother* 2000, **44:**747-751.
11. Yang YL, Ho YA, Cheng HH, Ho M, Lo HJ: **Susceptibilities of *Candida* species to amphotericin B and fluconazole: the emergence of fluconazole resistance in *Candida tropicalis*.** *Infect Control Hosp Epidemiol* 2004, **25:**60-64.
12. Yang YL, Cheng HH, Lo HJ: **In vitro activity of voriconazole against *Candida* species isolated in Taiwan.** *Int J Antimicrob Agents* 2004, **24:**294-296.
13. Nguyen MH, Peacock JE Jr, Morris AJ, Tanner DC, Nguyen ML, Snydman DR, Wagener MM, Rinaldi MG, Yu VL: **The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance.** *Am J Med* 1996, **100:**617-623.
14. Redding SW, Kirkpatrick WR, Dib O, Fothergill AW, Rinaldi MG, Patterson TF: **The epidemiology of non-albicans Candida in oropharyngeal candidiasis in HIV patients.** *Spec Care Dentist* 2000, **20:**178-181.
15. Krcmery V, Barnes AJ: **Non-albicans *Candida* spp. causing fungaemia: pathogenicity and antifungal resistance.** *J Hosp Infect* 2002, **50:**243-260.
16. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S: **The epidemiology of hematogenous candidiasis caused by different *Candida* species.** *Clin Infect Dis* 1997, **24:**1122-1128.
17. Kralovicova K, Spanik S, Oravcova E, Mrazova M, Morova E, Gulikova V, Kukuckova E, Koren P, Pichna P, Nogova J, Kunova A, Trupl J, Krcmery V Jr: **Fungemia in cancer patients undergoing chemotherapy versus surgery: risk factors, etiology and outcome.** *Scand J Infect Dis* 1997, **29:**301-304.
18. Wingard JR: **Importance of Candida species other than *C. albicans* as pathogens in oncology patients.** *Clin Infect Dis* 1995, **20:**115-125.
19. Nikawa H, Egusa H, Makihira S, Nishimura M, Ishida K, Furukawa M, Hamada T: **A novel technique to evaluate the adhesion of *Candida* species to gingival epithelial cells.** *Mycoses* 2003, **46:**384-389.
20. Yang YL, Cheng HH, Ho YA, Hsiao CF, Lo HJ: **Fluconazole resistance rate of *Candida* species from different regions and hospital types in Taiwan.** *J Microbiol Immunol Infect* 2003, **36:**187-191.
21. Fatkenheuer G, Buchheidt D, Cornely OA, Fuhr HG, Karthaus M, Kisro J, Leithauser M, Salwender H, Sudhoff T, Szelenyi H, Weissinger F: **Central venous catheter (CVC)-related infections in neutropenic patients – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO).** *Ann Hematol* 2003, **82(Suppl 2):**S149-57. Epub@2003 Sep 9.: S149-S157.
22. Salvaggio MR, Pappas PG: **Current Concepts in the Management of Fungal Peritonitis.** *Curr Infect Dis Rep* 2003, **5:**120-124.
23. Pfaller MA, Messer SA, Boyken L, Hollis RJ, Rice C, Tendolkar S, Diekema DJ: **In vitro activities of voriconazole, posaconazole, and fluconazole against 4,169 clinical isolates of *Candida* spp. and *Cryptococcus neoformans* collected during 2001 and 2002 in the ARTEMIS global antifungal surveillance program.** *Diagn Microbiol Infect Dis* 2004, **48:**201-205.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2334/5/22/prepub