J Infect Chemother 25 (2019) 388–391

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Note

Changing epidemiology of non-*albicans* candidemia in Korea☆

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ARTICLE INFO

Article history:
Received 6 July 2018
Received in revised form
28 August 2018
Accepted 30 September 2018
Available online 26 October 2018

Keywords:
Epidemiology
non-*albicans Candida*
Antifungal resistance
Candida glabrata
Candida parapsilosis

ABSTRACT

An epidemiologic surveillance of non-*albicans* candidemia for a 6-year period was conducted in Korea. Compared to the published epidemiologic data for the previous 6 years, an increase of *C. glabrata* (from 21.3% to 28.5%) and a decrease of *C. parapsilosis* (from 36.5% to 24.7%) were noticed. During the study period, *C. tropicalis* (36.4%) was most frequently isolated non-*albicans Candida*, followed by *C. glabrata* (28.5%), *C. parapsilosis* (24.7%), and *C. krusei* (2.6%). Replacement of primary amphotericin B treatment with echinocandins ($P < 0.001$) eliminated amphotericin B resistance (from 7.8% in 2011 to 0% in 2014).

Clinical infections caused by non-*albicans Candida* are increasing globally and now exceed those caused by *C. albicans* in the Asia-Pacific region [1–3]. Because non-*albicans Candida* infections are associated with poor outcome and species-specific antifungal susceptibility changes overtime, periodic epidemiologic surveillance is essential for proper management of candidiasis. In addition, as primary treatment with echinocandins for severe candidiasis has markedly increased in Korea since 2014 with the approval for primary administration by the National Health Insurance Service (NHIS), the impact of this change on species distribution and antifungal susceptibility need to be evaluated. We conducted a nation-wide multicenter surveillance of non-*albicans Candida* blood isolates between 2010 and 2016, and compared the epidemiologic changes with previous 6 years [4–7].

We reviewed microbiologic data and electronic medical records between January 2010 and February 2016 at seven university hospitals in Korea: Samsung Medical Center, a 1950-bed tertiary care center in Seoul; Dong-A University Hospital, a 962-bed tertiary care center in Busan; Keimyung University Dongsan Medical Center, a 909-bed tertiary care center in Daegu; Chonnam National University Hospital, a 1085-bed tertiary care center in Gwangju; Kangbuk Samsung Hospital, a 700-bed tertiary care center in Seoul; Chungnam National University Hospital, a 1354-bed tertiary care center in Daejeon; and Kyungpook National University Hospital, a 900-bed tertiary care center in Daegu. We collected data about antifungal susceptibility and primary antifungal agent of adult

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https://doi.org/10.1016/j.jiac.2018.09.016
1341-321X/

patients (age ≥ 16) with non-*albicans* candidemia. Only the first candidemia episode for each patient was included, and unidentified *Candida* spp. were excluded from the analysis. Candidemia cases from January-February 2016 were counted together with cases from 2015. For comparison of epidemiologic data, we searched PubMed database with the keywords of *candida* and Korea. This study was approved by the institutional review board of each hospital.

An episode of candidemia was defined as systemic manifestations and a positive culture in one or more sets of blood cultures. Echinocandin agents included caspofungin, micafungin, and anidulafungin; amphotericin B agents included conventional amphotericin B and liposomal amphotericin. Rare *Candida* species were defined as non-*albicans Candida* except *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei*.

A VITEK 2 automated system (bioMérieux Inc., Marcy l'Etoile, France) with a standard identification card and modified broth microdilution method was used for identification of *Candida* spp. and antimicrobial susceptibility testing. Minimum inhibitory concentration (MIC) breakpoints and quality control protocols were used according to Clinical and Laboratory Standards Institute (CLSI) standards [8], which are generally used in the participated hospitals. Since the breakpoint for amphotericin B resistance is not provided by CLSI, we used the EUCAST guideline (MIC > 1 μg/mL) (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/Antifungal_breakpoints_v_9.0_180212.pdf).

A linear regression model was used to evaluate changes in epidemiologic trends and initial antifungal agents, and a Chi-square test was used for comparison of species distribution. All *P*-values were two-tailed and $P < 0.05$ was considered statistically significant. IBM SPSS Statistics version 20.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Through PubMed search, we identified five relevant articles with epidemiologic data of candidemia in Korea [2,4–7]. After excluding one study that overlapped study period with the present surveillance [7], four multicenter studies with of 1122 non-*albicans Candida* blood isolates from 2004 to 2009 were included in the analysis [2,4–6], From the present surveillance, a total of 769 patients with non-*albicans* candidemia were identified: 99, 120, 151, 137, 143, and 119 patients annually for 2010–2015, respectively. Distribution of specific species of each year is presented in Supplementary Table 1. The decreased number of cases in 2015 was associated with the Korean MERS outbreak. Due to fear of in-hospital transmission of MERS, admission was decreased in overall hospitals and one of included hospital experienced partial closure for a month [9].

Overall distribution and changing epidemiology of non-*albicans* candidemia during a 6-year surveillance is presented in Fig. 1-(a), and compared with the published data of previous 6 years (Table 1 and Supplementary Figure 1). During the present 6-year surveillance, no significant changes of non-albicans *Candida* spp. were noticed. *C. tropicalis* was the most common non-*albicans* candidemia pathogen (n = 280, 36.4%), followed by *C. glabrata* (n = 219, 28.5%), *C. parapsilosis* (n = 190, 24.7%), and *C. krusei* (n = 20, 2.6%). Compared to the published data of previous 6 years, the proportion of *C. parapsilosis* decreased (from 36.5% to 24.7%), while that of *C. glabrata* increased (from 21.3% to 28.5%). Among rare *Candida* spp., *C. guilliermondii* (n = 18, 2.3%) was most frequently identified by VITEK 2 automated system, followed by *C. famata* (n = 13, 1.7%), *C. lusitaniae* (n = 9, 1.2%), *C. utilis* (n = 6, 0.8%), and *C. pelliculosa* (n = 6, 0.8%).

Primary antifungal agents and antifungal susceptibility were evaluated from January 2010 to February 2016. During the study period, use of amphotericin B agents decreased, as amphotericin B was replaced by echinocandins ($P < 0.001$, Fig. 1-b). Amphotericin B-resistant isolates also decreased, disappearing entirely in 2014 (Fig. 1-c). The proportion of fluconazole non-susceptible isolates did not change significantly (ranged from 24.4% to 38.6%), and caspofungin resistance was not observed. Previous studies also did not report echinocandin resistance [5], and amphotericin resistance was reported to be 0.5% in 2006 and 3.1% in 2007 [2,5]. Species-specific fluconazole susceptibility was applied from 2009 study, and the proportion of fluconazole non-susceptible isolates was 31.1% [6], which was within the range of the present surveillance.

Antifungal susceptibility by *Candida* species with applied clinical breakpoints is shown in Supplementary Table 2. Most of non-*albicans Candida* species except *C. krusei* were susceptible to flucytosine (>95%). Flucytosine-intermediate isolates were almost exclusively observed in *C. krusei* (83.3%). For fluconazole, small proportions of *C. parapsilosis*, *C. tropicalis*, and rare *Candida* spp. were non-susceptible (3.2%, 2.4%, and 6.9%, respectively); 95.1% of *C. glabrata* isolates were classified as susceptible-dose dependent (SDD) and 100% of *C. krusei* isolates as resistant according to the CLSI guideline [8]. Non-susceptibility to voriconazole was also highest in *C. glabrata* (7.3%). A total of 10 non-*albicans candida* isolates were resistance to amphotericin B, most of which were *C. glabrata* (80.0%). Caspofungin resistance was not observed, while micafungin resistance was reported in only one *C. glabrata* isolate (5.3%).

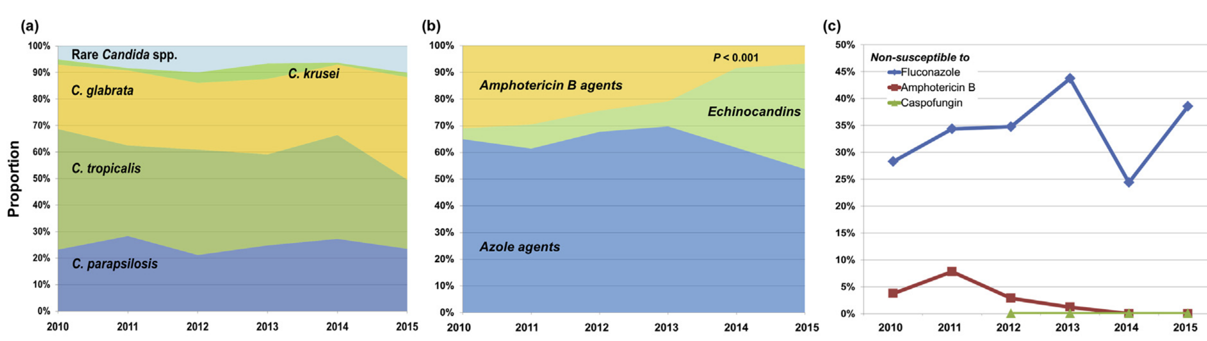

Fig. 1. Species distribution, primary antifungal agents, and antifungal resistance of non-*albicans* candidemia in Korea. A multicenter surveillance data from January 2010 to February 2016 were evaluated. For practical purposes, cases identified in 2016 were counted together with cases of 2015. Comparison with four published data of previous 6 years is presented as Supplementary Figure 1. During the 6-years surveillance, no significant changes of non-albicans *Candida* spp. were noticed (a). Primary use of amphotericin B agents decreased throughout the study period, being rapidly replaced by echinocandin agents since 2014 ($P < 0.001$ by linear regression; b). The proportion of fluconazole non-susceptible isolates did not significantly changed, and caspofungin resistance was not noticed. Amphotericin B-resistant isolates were decreased and disappeared in 2014 (c).

Table 1
Distribution of non-*albicans Candida* species.

Non-*albicans Candida* spp.	2004–2009 n = 1122	2010–2015 n = 769	*P* value	Total n = 1891
Candida parapsilosis	409 (36.5)	190 (24.7)	<0.001	599 (31.7)
Candida tropicalis	389 (34.7)	280 (36.4)	0.437	669 (35.4)
Candida glabrata	239 (21.3)	219 (28.5)	<0.001	458 (24.2)
Candida krusei	12 (1.1)	20 (2.6)	0.011	32 (1.7)
Rare Candida spp.	73 (6.5)	60 (7.8)	0.279	133 (7.0)
Candida guilliermondii	20 (1.8)	18 (2.3)	0.396	38 (2.0)
Candida famata	9 (0.8)	13 (1.7)	0.077	22 (1.2)
Candida lusitaniae	6 (0.5)	9 (1.2)	0.126	15 (0.8)
Candida utilis	5 (0.5)	6 (0.8)	0.347	11 (0.6)
Candida pelliculosa	5 (0.5)	6 (0.8)	0.347	11 (0.6)
Others	28 (2.5)[a]	8 (1.0)	n/a*	36 (1.9)

Data are expressed as number (%) of patients. A multicenter surveillance data from January 2010 to February 2016 were evaluated. For practical purposes, cases identified in 2016 were counted together with cases of 2015. Data from four previously reported epidemiologic studies were used for the 2004 to 2009 period [2,4–6].
Abbreviations: n/a, not available.
[a] Specific species of rare *Candida* spp. in 2009 was not presented [6].

Changing epidemiology of candidiasis is observed globally in association with increasing use of antifungal agents, while specific proportion of each *Candida* spp. is different among countries [1,10]. Since specific non-*albicans Candida* spp. show different antifungal susceptibility and clinical outcome, periodic epidemiologic study is essential for proper management of candidiasis. We evaluated epidemiologic trend of non-*albicans* candidemia over a 12-year period in Korea with four previously reported studies, and noticed an increase of *C. glabrata* (from 21.3% to 28.5%) and a decrease of *C. parapsilosis* (from 36.5% to 24.7%).

Increasing trend of *C. glabrata* was also globally observed, and has clinical importance in that *C. glabrat*a has a strong association with antifungal resistance [10]. In addition to intrinsically decreased susceptibility to azole agents [11], emergence and disappearance of amphotericin B resistance were mainly observed in *C. glabrata* isolates in our study (among 10 amphotericin B-resistant *candida* isolates, eight were *C. glabrata*). Although amphotericin B resistance is infrequent among clinical isolates of common *Candida* spp., induction of resistance after amphotericin B treatment has been reported [12]. Molecular mechanisms responsible for amphotericin B resistance in pathogenic yeasts have not been clearly discovered, while changes in sterol content in association with the ERG6 gene mutation were reported in *C. glabrata* isolates [13]. Also, although only one micafungin-resistant *C. glabrata* was observed in the present surveillance, FKS mutation-associated echinocandin resistance of *C. glabrata* has been reported globally [10]. Considering continuously increasing echinocandin use in Korea, emergence of echinocandin-resistant isolates should be closely monitored, especially among *C. glabrata*. Although *C. parapsilosis* was reported to increase in association with echinocandin use [14], the proportion of *C. parapsilosis* decreased before the wide-use of echinocandins and did not show marked changes thereafter. We think other various factors including burden of immunocompromised hosts or use of central venous catheters might affect the proportion of non-albicans *Candida* spp., in addition to the overall use of antifungal agents.

This changing epidemiology of antifungal resistance closely correlated with transition of primary antifungal agents. Clinical practice in Korea is largely influenced by NHIS, which covers the entire population without allowance of any private health insurance. NHIS approval of echinocandin agents as the primary antifungal treatment for severe candidiasis in 2014 caused a rapid shift from amphotericin B to echinocandin use. Since primary echinocandin use for mild to moderately ill patients is not approved yet, increase of echinocandin use for candidiasis would not far exceed that of 2015. Further changes in NHIS approval may bring consequent changes in distribution and resistance of candidiasis, and following surveillance should be followed.

Since we used published data for the period of 2004–2009, antifungal susceptibility data was limited and included centers were not identical during that period. Although we presented *P* values in Table 1, these values have limited meaning as simple comparisons between the present surveillance and the previous published data. For major *Candida* spp., species identification using VITEK 2 system is relatively reliable [15], but rare *Candida* spp., including *C. famata*, *C. lusitaniae*, or *C. guilliermondii* are frequently misidentified [16]. Although we presented specific species of rare *Candida* spp. in the tables, it should be cautiously interpreted. For accurate evaluation, epidemiologic studies for rare *Candida* spp. need to be performed with gene analyses methods [16]. Lastly, epidemiologic change of *C. albicans* was not evaluated in the present analysis. Despite these limitations, we reviewed epidemiologic changes of non-*albicans* candidemia over a 12 year period, and noticed changing epidemiology and antifungal resistance of non-*albicans* candidemia.

In conclusion, in an epidemiologic surveillance of a 6-year period and review of the published data for the previous 6 years in Korea, an increase of *C. glabrata* and a decrease of *C. parapsilosis* were noticed. Replacement of amphotericin B with echinocandins for primary treatment eliminated amphotericin B resistance, most of which were observed among *C. glabrata* isolates.

Funding

This work was supported by Astellas Pharma Korea, Inc. (AKR-MYC-2015-01).

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2018.09.016.

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