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ORIGINAL ARTICLE

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The epidemiology of non-*Candida* yeast isolated from blood: The Asia Surveillance Study

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Summary

Background: Current guidelines recommend echinocandins as first-line therapy for candidemia. However, several non-*Candida* yeast are non-susceptible to echinocandins (echinocandin non-susceptible yeast, ENSY), including *Cryptococcus*, *Geotrichum*, *Malassezia*, *Pseudozyma*, *Rhodotorula*, *Saprochaete*, *Sporobolomyces* and *Trichosporon*. In laboratories that are not equipped with rapid diagnostic tools, it often takes several days to identify yeast, and this may lead to inappropriate presumptive use of echinocandins in patients with ENSY fungemia. The aim of this study was to determine the distribution of ENSY species during a 1-year, laboratory surveillance programme in Asia.

*Other members of the study network are listed in the Appendix 1.

Methods: Non-duplicate yeast isolated from blood or bone marrow cultures at 25 hospitals in China, Hong Kong, India, Singapore, Taiwan and Thailand were analysed. Isolates were considered to be duplicative if they were obtained within 7 days from the same patient.

Results: Of 2155 yeast isolates evaluated, 175 (8.1%) were non-*Candida* yeast. The majority of non-*Candida* yeast were ENSY (146/175, 83.4%). These included *Cryptococcus* (109 isolates), *Trichosporon* (23), *Rhodotorula* (10) and *Malassezia* (4). The proportion of ENSY isolates (146/2155, 6.7%) differed between tropical (India, Thailand and Singapore; 51/593, 8.6%) and non-tropical countries/regions (China, Hong Kong and Taiwan; 95/1562, 6.1%, $P = 0.038$). ENSY was common in outpatient clinics (25.0%) and emergency departments (17.8%) but rare in intensive care units (4.7%) and in haematology-oncology units (2.9%). *Cryptococcus* accounted for the majority of the non-*Candida* species in emergency departments (21/24, 87.5%) and outpatient clinics (4/5, 80.0%).

Conclusions: Isolation of non-*Candida* yeast from blood cultures was not rare, and the frequency varied among medical units and countries.

KEYWORDS
candidemia, echinocandin, fungemia, presumptive therapy, yeast

1 | INTRODUCTION

The epidemiology of yeast infections and fungemia continues to evolve throughout the world, in parallel with advances in medical care for critically ill and immunocompromised patients and the extensive use of antifungal agents.[1-5] Among human fungal pathogens, *Candida* species are the most common yeast that cause bloodstream infections. In the majority of guidelines, echinocandins are the recommended first-line therapy for candidemia, due to their clinical efficacy, fungicidal activity, favourable safety profile, and limited drug interactions, and concerns about fluconazole resistance.[6-11]

Among non-*Candida* yeast, *Cryptococcus* is the most common fungal pathogen that causes community-acquired invasive fungal disease and is intrinsically resistant to echinocandins.[4,12,13] In Taiwan, the proportion of *Cryptococcus neoformans* from blood or bone marrow increased from 14% (8/59) between 1957 and 1972 to 33% (29/87) between 1982 and 1997.[14] In addition, the emergence of rare yeast species such as *Trichosporon* and *Rhodotorula* poses a major threat because of their low susceptibility and potential to develop resistance to one or more antifungal agents.[4,12,13,15] Overall, common human yeast pathogens known to be intrinsically resistant or non-susceptible to echinocandins (echinocandin non-susceptible yeast, ENSY), including *Cryptococcus*, *Geotrichum*, *Malassezia*, *Pseudozyma*, *Rhodotorula*, *Saprochaete*, *Sporobolomyces* and *Trichosporon*.[4,12,15-17]

Species identification is therefore important in order to target echinocandin therapy only at patients with susceptible yeast infections. However, it usually takes an additional 1-3 days to identify yeast to species level using either manual methods or commercially available API ID32C, AuxaColor and Vitek 2 systems.[18,19] This delay in identification means that, in some cases, inappropriate echinocandin therapy may be initiated in patients with reported yeast isolation from blood. This underlines the limits of presumptive treatment for fungemia and stresses the necessity to introduce rapid identification methods for yeast species identification.[19]

However, it is concerning that in a recent survey of mycology laboratory practice across seven Asian countries, rapid identification methods such as matrix-assisted laser desorption ionisation-time of flight mass spectrometry, and molecular identification methods such as PCR and sequencing were available only in 27 laboratories (12.3%) and 37 (16.9%) among 219 respondents, respectively.[20] Most laboratories that perform identification with MALDI still require a subculture, which delays identification by 1 to 3 days (especially for slower growing basidiomycetous yeast). The potential impact of presumptive treatment with echinocandins for fungemia remains uncertain.

The aim of the current collaborative study was to determine the frequency of isolation from blood of yeast species that are intrinsically resistant or non-susceptible to echinocandins. The study was based on laboratory-based surveillance at 25 hospitals located in six Asian countries/regions.[21] We also reviewed and compared published data around the world.

2 | MATERIALS AND METHODS

2.1 | Study design and mycology data collection

This was a 1-year, cross-sectional, laboratory-based surveillance study conducted between July 1, 2010 and June 30, 2011. It was designed

by the Asia Fungal Working Group (AFWG) under the auspices of the International Society for Human and Animal Mycology. A total of 25 hospitals participated in the study, located in China (10 hospitals), Hong Kong (1), India (4), Singapore (1), Taiwan (6) and Thailand (3). Details of the background of these hospitals, the capacity and practice of their mycology laboratories, and the incidence and distribution of candidemia have been published elsewhere.[21] The study was approved by the Institutional Review Board or Research Ethics Committee at 21 of the hospitals; approval for research was waived at the other four centres.

Fungi were identified by the local microbiology or mycology laboratories at each study site. Blood culture systems and methods for fungal identification were as previously described.[21] Microbiology laboratories in the participating hospitals identify the yeast by morphology (17 of 25 hospitals), CHROMagar (15), API20C of ID32C (17), manual assimilation/fermentation tests (6) and automatic methods (such as Vitek) (12). Only four hospitals provided the molecular identification methods such as PCR and sequencing in routine practice during the study period.

The data recorded for each isolate included the date of collection, hospital service, genus and species, whenever available. Duplicates were removed from the analysis. Yeast isolates were considered to be duplicate if they came from the same source type in the same patient, within 7 days of each other, and the final identifications were the same.[22] The frequencies of ENSY among non-duplicate yeast isolated from blood cultures were analysed; these included *Cryptococcus*, *Geotrichum*, *Malassezia*, *Pseudozyma*, *Rhodotorula*, *Saprochaete*, *Sporobolomyces* and *Trichosporon*.[4,12,15-17]

2.2 | Statistical analysis

Statistical analyses were performed using SPSS v19 (SPSS Inc., Chicago, IL, USA). Categorical variables were analysed using the chi-square test, and continuous variables were compared by Student's *t*-test. A *P*-value < 0.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Fungal isolates

From 51 254 clinical isolates submitted across the 25 participating hospitals, 2155 non-duplicate yeast isolates from blood, and bone marrow specimens were included in the present analysis. Of these, 1980 (91.9%) isolates were *Candida* species and 175 (8.1%) were other, non-*Candida* yeast (Table 1). Among the 175 non-*Candida* yeast isolates, the majority were ENSY (146/175, 83.4%) which included *Cryptococcus* (109), *Trichosporon* (23), *Rhodotorula* (10) and *Malassezia* (4). In this study cohort, there were no *Geotrichum*, *Pseudozyma*, *Saprochaete* or *Sporobolomyces* which are intrinsically resistant to echinocandins.

3.2 | Genus distribution by country/region

The proportions of ENSY among yeast-in-blood isolates (overall, 146/2155, 6.7%) from each country/region are shown in Figure 1. ENSY proportions in most country/region are below 10%, except for Thailand, which ENSY proportions >20% were observed. The proportion of ENSY isolates in tropical countries/regions (India, Thailand and Singapore) is higher than that in non-tropical countries/regions (China, Hong Kong and Taiwan) (8.6% [51/593] vs 6.1% [95/1562], $P = 0.038$). However, the higher rate of *Cryptococcus* spp. in Thailand when compared with the rates in other countries is the main reason for the above-mentioned difference because, after excluding *Cryptococcus* spp., no significant difference was observed (1.6% [9/551] vs 1.9% [28/1495], $P = 0.852$).

Cryptococcus spp. were most frequently observed in Thailand (20.2% of 173 yeast-in-blood isolates) but were rare in India (0.6% of 341 isolates) (Figure 1). A total of 23 *Trichosporon* isolates were reported, of which 11 were from Taiwan and four were from China. Among 10 *Rhodotorula* isolates, eight were reported from Taiwan.

TABLE 1 Distribution of non-duplicate yeast isolates in blood or bone marrow specimens

Fungus	Number of isolates	(%)
Total yeast isolates	2155	100
Candida species	1980	91.9
Non-*Candida* spp.	175	8.1
Cryptococcus species[a,b]	109	5.1
Trichosporon species[a,c]	23	1.1
Rhodotorula species[a]	10	0.5
Kodamaea (Pichia) ohmeri[d]	7	0.3
Malassezia species[a,d]	4	0.2
Hansenula anomala (*Pichia anomala*)[d]	4	0.2
Hansenula polymorpha[d]	2	0.1
Yarrowia lipolytica[d]	2	0.1
Other non-*Candida* yeast[e]	14	0.6

[a]Yeast that are intrinsically resistant or with high probability of non-susceptibility to echinocandins and ESCMID, and ECMM support a recommendation against use of echinocandins.[12]
[b]*Cryptococcus neoformans* (102 isolates), *Cryptococcus laurentii* (2) and *Cryptococcus* spp. (5).
[c]*Trichosporon asahii* accounted for 9 of these isolates.
[d]*Kodamaea* (*Pichia*) *ohmeri* (7 isolates; 4 from Taiwan and 3 from China), *Hansenula anomala* (*Pichia anomala*) (4 isolates; 2 from Taiwan and 2 from India), *Hansenula polymorpha* (2 isolates; both from China), *Malassezia* species (4 isolates; 2 from Taiwan, 1 from Hong Kong and 1 from Thailand), *Yarrowia lipolytica* (2 isolates; both from Taiwan).
[e]Fourteen isolates were not reported to a genus level.

3.3 | Species distribution according to medical services

Among the 2155 yeast-in-blood isolates included in this analysis, information on the type of medical service from which they came were available for 2144 isolates. Of the 11 isolates for which medical service information was not available, three were ENSY. Thus, 143 ENSY were analysed according to medical service.

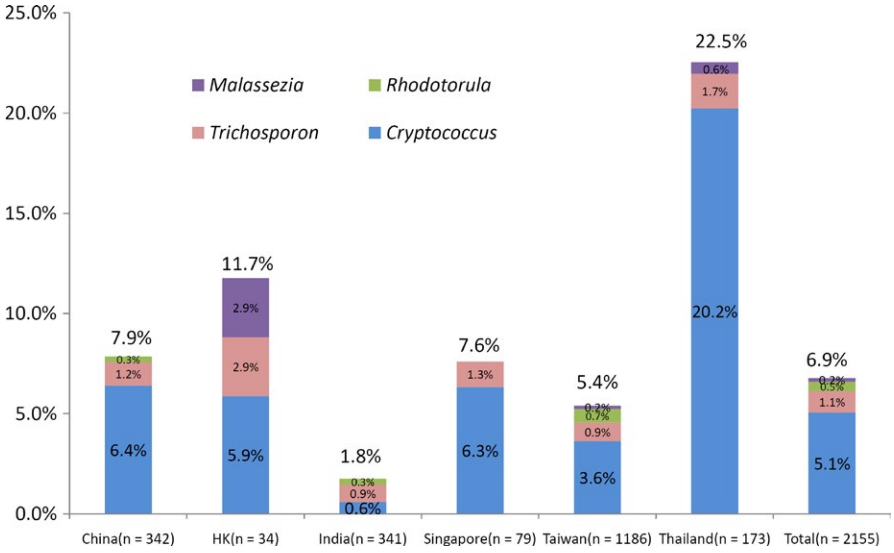

FIGURE 1 Distribution within each country/region of 146 yeast isolated from blood and bone marrow specimens that were intrinsically resistant or had a high probability of non-susceptibility to echinocandins. HK, Hong Kong

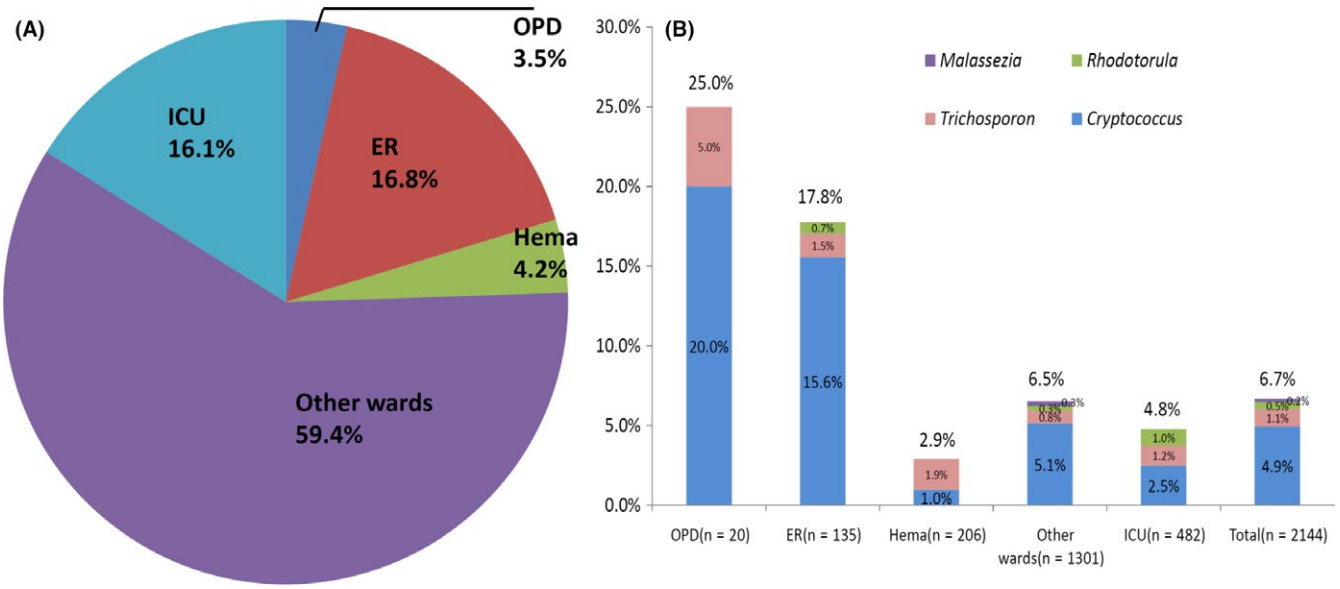

FIGURE 2 Proportion of the total number of 143 yeast isolated from blood and bone marrow specimens that were intrinsically resistant or had a high probability of non-susceptibility to echinocandins coming from each hospital service (A). Distribution within each medical service of yeast that were intrinsically resistant or had a high probability of non-susceptibility to echinocandins (B). "Other wards" included general wards other than those specialising in haematology-oncology. ER, emergency rooms; Hema, haematology-oncology ward; ICU, intensive care unit; OPD, outpatient clinic

Overall, almost two-thirds (59.4%) of ENSY came from general wards other than haematology-oncology units (Figure 2A). However, this was largely because most yeast isolates overall came from these wards. When analysed according to each different type of medical service, the proportion of total isolates that were ENSY varied substantially, ranging from 2.9% in haematology-oncology wards to 25.0% in outpatient clinics (Figure 2B). The proportions of ENSY in outpatient clinics is higher than haematology-oncology wards and intensive care units (ICUs) (25.0% [5/20] vs 2.9% [6/206], $P = 0.001$; 25.0% [5/20] vs 4.8% [23/482], $P = 0.003$). The proportions of ENSY in emergency rooms (ERs) are higher than haematology-oncology wards and ICUs (17.8% [24/135] vs 2.9% [6/206], $P = 0.001$; 17.8% [24/135] vs 4.8% [23/482], $P = 0.003$).

Cryptococcus accounted for 87.5% (21/24) of non-*Candida* species isolated from ERs and 80.0% (4/5) from outpatient clinics. The proportion of *Cryptococcus* among non-*Candida* species in ERs was significantly higher than in ICUs (52.1% [12/23], $P = 0.008$) and haematology-oncology wards (33.3% [2/6], $P = 0.016$).

3.4 | Species distribution by season

Based on the date provided, the season of collection could be assigned to each isolate. The proportion of ENSY varied from 4.2% in

TABLE 2 The proportions of non-*Candida* yeast in blood specimens by region/country or patient population[a]

Region/country	Setting/population	Study period	Patients (inpatients, outpatients or both)	Number of yeast isolates	Proportion of non-*Candida* yeast	Proportion of *Cryptococcus* spp. in non-*Candida* yeast	Remark	References
Global								
Artemis study	Multinational, multicentre, general	1997-2007	both	11 240, non-*Candida* yeast		32.2%	*Saccharomyces* (11.7%), *Trichosporon* (10.6%), and *Rhodotorula* (4.1%) were the leading three non-*Candida* fungi.	22
Americas								
US	Single hospital	1998-2010	both	2984	3.1%	NA	*Rhodotorula* spp. (21 isolates), *Saccharomyces* (8) and *Trichosporon* (8) were the leading three non-*Candida* fungi.	31
Mexico	Single hospital	2005-2014	both	91	34.1%	93.9%	Underlying disease was HIV/AIDS in 63% of cases	23
Argentina	Multicentre	2007-2008	inpatients	461	8.9%	78.0%	*C. neoformans* was mainly associated with HIV/AIDS	28
	Paediatric patients (<15 y)			177	3.4%	0%	2 isolates (33.3%) were *Trichosporon* spp.	
Brazil	Single hospital	1996-2004	both	1195	14.6%	45.4%	*Pichia anomala* (18.4%) and *Rhodotorula* spp (16.1%) were also common.	24
Brazil	Single hospital	2001-2003	both	229	2.6%	100%		25
		2011-2013		288	5.9%	100%		
Europe								
Europe	Multicentre, cancer patients	2005-2009	both	279	7.5%	19.0%	8 *Trichosporon* spp. (38.1%) were the most common isolates in non-*Candida* yeast	32
Sweden	Nationwide	2005-2006	both	403	1.0%	0%		33
Belgium	Multicentre	2005-2006	both	412	7.8%	12.5%	21 *Saccharomyces cerevisiae* (65.6%) were the most common isolates in non-*Candida* yeast	26
Denmark	Nationwide	2004-2009	both	3982	1.1%	31.8%	22 *S. cerevisiae* (50%) were the most common isolates in non-*Candida* yeast	27
France	Regional, Paris	NA		3668	5.1%	73.3%	19 *Geotrichum* (10.1%) were the second common non-*Candida* yeast	12
Italy	Single hospital	2005-2013	both	1250	1.9%	29.2%	Non-*Candida* yeast were dominated by *Rhodotorula* spp. (n = 9) and *C. neoformans*, which together accounted for 1.3% of all bloodstream isolates and 66.6% of all non-*Candida* yeast	34
Portugal	Multicentre	2011-2012	inpatients	240	3.8%	88.9%	*C. neoformans* was the most common isolate in non-*Candida* yeast	29
Spain	Multicentre	2009-2010	both	1374	1.9%	38.5%	*C. neoformans* was the most common isolate in non-*Candida* yeast	35

Region/ country	Setting/ population	Study period	Patients (inpatients, outpatients or both)	Number of yeast isolates	Proportion of non-*Candida* yeast	Proportion of *Cryptococcus* spp. in non-*Candida* yeast	Remark	References
Spain	Multicentre paediatric patients (<15 y)	2009-2010	inpatients	203	1.0%	0%	Only two isolates were non-*Candida* yeast; one was *Trichosporon asahii*, the other was *Rhodotorula glutinis*	36
Spain	Multicentre	2010-2011	both	781	2.4%	26.3%	*C. neoformans* was the most common non-*Candida* yeast isolate, followed by *Trichosporon asahii* (15.8%)	37
Asia								
Asia	25 hospitals	2010-2011	both	2071	7.8%	67.7%		This study
China	10 hospitals	2010-2011	both	325	9.8%	68.8%		This study
China	Single hospital	2010-2012	inpatients	141	7.8%	45.5%	*C. neoformans* was the most common isolate in non-*Candida* yeast	38
China	4 hospitals	2012-2013	both	137	8.0%	9%	*Pichia* spp. were the most common isolates in non-*Candida* yeast (45%)	39
Hong Kong	Single hospital	2010-2011	both	34	11.8%	50%		This study
India	Single hospital, paediatric patients	2007	inpatients	102	21%	0%	*P. anomala* was the most common isolate (85.7%), followed by *Trichosporon asahii* (14.3%)	40
India	4 hospitals	2010-2011	inpatients	305	2.6%	25%		This study
Singapore	Single hospital	2010-2011	inpatients	78	7.7%	83.3%		This study
Taiwan	6 hospitals	2010-2011	both	1160	6.2%	59.7%		This study
Thailand	3 hospitals	2010-2011	both	169	23.1%	89.7%		This study

[a]Pubmed search using the following phrase: (fungemia [Title/Abstract]) OR yeast in blood cultures [Title/Abstract])) AND ("2007/1/1"[Date - Publication]: "2015/11/31"[Date - Publication]), accessed on 30 November 2015, limited to English literature. The publications that were most representative of the country/region or the most up-to-date were selected when more than one was found.

autumn to 8.2% in winter, but these differences were not statistically significant. The proportions of individual species (*Cryptococcus*, *Trichosporon* and *Rhodotorula*) also did not vary substantially according to season, which was either due to small sample sizes or variations between countries (Figure S1).

4 | DISCUSSION

In this 1-year surveillance study conducted in 25 hospitals across Asia, yeast that were intrinsically resistant or non-susceptible to echinocandins accounted for 6.7% of 2155 non-duplicate isolates from the blood. The frequency varied from 2.9% in haematology-oncology wards to 25.0% in outpatient clinics.

Most non-*Candida* yeast are known to be resistant to echinocandins;[4] and indeed, this study showed that 83.4% of such isolates were ENSY. Hence, it is clinically significant that non-*Candida* yeast accounted for 8.1% of all yeast-in-blood isolates (Table 1). Moreover, proportions varied substantially between the six countries/regions included in the survey, with non-*Candida* species making up 24.9% of isolates from Thailand but only 2.3% of those from India. This wide variation in the proportion of non-*Candida* species accords with other reports from around the world (summarised in Table 2). Overall, frequencies were higher in tropical countries, such as Mexico, Brazil and Thailand.[23-25] Our study also showed similar results. (Figure 2)

In the present study, *Cryptococcus* was the predominant ENSY species. *Cryptococcus* is the leading ENSY pathogen in many countries worldwide (Table 2), although there are exceptions. For example, in Belgium and Denmark, *Saccharomyces cerevisiae* were the predominant non-*Candida* isolates.[26,27] Higher proportions of *Cryptococcus* in blood are closely related to human immunodeficiency diseases.[23,28,29] The proportions of non-*Candida* yeast varied from 1.0% to 34% in different countries, patient papulations and medical settings (Table 2). In our study, almost a quarter of non-*Candida* yeast occurred in the outpatient clinics or ERs, which may explain the difference between hospital-based studies and inpatient-only studies (Table 2).

Not all yeast are susceptible to echinocandins.[4,12,13,15,17] Furthermore, there are currently no guidelines or recommendations that explicitly describe how to select appropriate presumptive therapy for fungemia in regions where rapid identification systems are not available and non-*Candida* yeast-in-blood is common. Physicians in these countries should be familiar with common presentations and risk factors associated with *Cryptococcus* and other non-*Candida* infections (Table S1). For example, in Asia, cryptococcemia may be a possibility in a cirrhotic patient presenting at an ER, with altered mental status and community-acquired sepsis of unknown source. Rapid microbiological evidence can be obtained by examining spinal fluid with India ink and detecting antigens in serum. These additional clues and tests may help physicians to select the most appropriate antifungal agent.[12]

This study has several limitations. First, this laboratory-based surveillance study is limited by the overall lack of clinical, outcome, and epidemiologic data, and was unable to assess the impact among patients with ENSY fungemia treated with echinocandins. Second, although patient isolates were deduplicated if within 7 days, this study did not provide the numbers of patients with these 2155 yeast isolates represent. Third, we did not collect isolates for identification at a central reference laboratory. Among 175 non-*Candida* isolates, fourteen isolates were not identified to a genus level. Therefore, we probably underestimated the frequency and impact of rare and emerging yeast.[4,12,16] Forth, antifungal susceptibility testing for these ENSY were not performed during this surveillance; and hence, we are unable to comment on the emergence of resistance to echinocandins.

The main strength of this study is an Asian multicentre laboratory-based data analysis that the frequency of isolation from the blood of yeast species that are ENSY. The ENSY identified in this study were mainly belonged to Basidiomycetes (*Cryptococcus*, *Trichosporon* and *Rhodotorula*), a group well known intrinsically resistant to echinocandins. On the other hand, the non-*Candida* Ascomycetes (such as *Pichia*, *Hansenula* and *Saccharomyces*) were rarely identified. A recent large-scale study involving 1698 yeast isolates showed that Basidiomycetes are less susceptible all antifungal drugs tested compared to Ascomycetes.[17]

In conclusion, this study revealed that yeast that are intrinsically resistant or non-susceptibility to echinocandins are not uncommonly isolated from blood cultures in representative countries in Asia. These data suggest that an operational algorithm for management of patients when yeast are detected in blood specimens is warranted in areas where non-*Candida* yeast-in-blood is common and in hospitals that do not possess the latest diagnostic technology. Improved communication among physicians and laboratories, as well as the acquisition of modern, rapid laboratory equipment that can provide results to the species level (and/or in vitro susceptibilities) are needed to guide antifungal therapy for yeast isolated from blood cultures.[30]

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AUTHOR CONTRIBUTIONS

This study was coordinated by the principal investigators, YC Chen and BH Tan. YC Chen initiated the project and core AFWG members (YC Chen, BH Tan, A Chakrabarti, RY Li, A Chindamporn, AL Tan, Z Liu, AK Patel, SP Watcharananan and PL Sun) designed the protocol together. YC Chen supervised SY Lin, LY Hsu and UI Wu for data analyses. SY Lin, PL Lu, JH Yang and YC Chen prepared the manuscript. The authors had full access to all the data in the study, critical review and comments during preparation, and had final responsibility for the decision to submit for publication.

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REFERENCES

1. Patterson TF. Advances and challenges in management of invasive mycoses. *Lancet*. 2005;366:1013-1015.
2. Maschmeyer G. The changing epidemiology of invasive fungal infections: new threats. *Int J Antimicrob Agents*. 2006;27(Suppl 1):3-6.
3. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis*. 2010;50:1101-1111.
4. Miceli MH, Diaz JA, Lee SA. Emerging opportunistic yeast infections. *Lancet Infect Dis*. 2011;11:142-151.
5. Chen PY, Chuang YC, Wang JT, et al. Comparison of epidemiology and treatment outcome of patients with candidemia at a teaching hospital in Northern Taiwan, in 2002 and 2010. *J Microbiol Immunol Infect*. 2014;47:95-103.
6. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;347:2020-2029.
7. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidiasis: a phase III randomised double-blind trial. *Lancet*. 2007;369:1519-1527.
8. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med*. 2007;356:2472-2482.
9. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis*. 2012;54:1110-1122.
10. 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.
11. 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-e50.
12. Arendrup MC, Boekhout T, Akova M, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect*. 2014;20(Suppl 3):76-98.
13. Castanheira M, Messer SA, Jones RN, et al. Activity of echinocandins and triazoles against a contemporary (2012) worldwide collection of yeast and moulds collected from invasive infections. *Int J Antimicrob Agents*. 2014;44:320-326.
14. Chen YC, Chang SC, Shih CC, et al. Clinical features and in vitro susceptibilities of two varieties of *Cryptococcus neoformans* in Taiwan. *Diagn Microbiol Infect Dis*. 2000;36:175-183.
15. Colombo AL, Padovan AC, Chaves GM. Current knowledge of *Trichosporon* spp. and trichosporonosis. *Clin Microbiol Rev*. 2011;24:682-700.
16. Farmakiotis D, Kontoyiannis DP. Epidemiology of antifungal resistance in human pathogenic yeasts: current viewpoint and practical recommendations for management. *Int J Antimicrob Agents*. 2017;50:318-324.
17. Desnos-Ollivier M, Robert V, Raoux-Barbot D, et al. Antifungal susceptibility profiles of 1698 yeast reference strains revealing potential emerging human pathogens. *PLoS ONE*. 2012;7:e32278.
18. Paugam A, Ancelle T, Lortholary O, et al. Longer incubation times for yeast fungemia: importance for presumptive treatment. *Diagn Microbiol Infect Dis*. 2014;80:119-121.
19. Posteraro B, Efremov L, Leoncini E, et al. Are the conventional commercial yeast identification methods still helpful in the era of new clinical microbiology diagnostics? a meta-analysis of their accuracy. *J Clin Microbiol*. 2015;53:2439-2450.
20. Chindamporn A, Chakrabarti A, Li RY, et al. Survey of laboratory practices for diagnosis of fungal infection in seven Asian countries – an Asia Fungal Working Group (AFWG) initiative. *Med Mycol*. 2017;56(4):416-425.
21. Tan BH, Chakrabarti A, Li RY, et al. Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study. *Clin Microbiol Infect*. 2015;21:946-953.
22. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: 10.5-year analysis of susceptibilities of noncandidal yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. *J Clin Microbiol*. 2009;47:117-123.
23. Gaona-Flores VA, Campos-Navarro LA, Cervantes-Tovar RM, et al. The epidemiology of fungemia in an infectious diseases hospital in Mexico city: a 10-year retrospective review. *Med Mycol*. 2016;54:600-604.
24. De Almeida GM, Costa SF, Melhem M, et al. *Rhodotorula* spp. isolated from blood cultures: clinical and microbiological aspects. *Med Mycol*. 2008;46:547-556.
25. Castro LL, Schutze M, Bucker DH, et al. Prevalence of fungemia in a tertiary hospital: analysis of the last decade. *Rev Assoc Med Bras*. 1992;2016(62):315-319.
26. Costa-de-Oliveira S, Pina-Vaz C, Mendonca D, et al. A first Portuguese epidemiological survey of fungaemia in a university hospital. *Eur J Clin Microbiol Infect Dis*. 2008;27:365-374.
27. Arendrup MC, Bruun B, Christensen JJ, et al. National surveillance of fungemia in Denmark (2004 to 2009). *J Clin Microbiol*. 2011;49:325-334.
28. Cordoba S, Vivot W, Bosco-Borgeat ME, et al. Species distribution and susceptibility profile of yeasts isolated from blood cultures: results of a multicenter active laboratory-based surveillance study in Argentina. *Rev Argent Microbiol*. 2011;43:176-185.
29. Faria-Ramos I, Neves-Maia J, Ricardo E, et al. Species distribution and in vitro antifungal susceptibility profiles of yeast isolates from invasive infections during a Portuguese multicenter survey. *Eur J Clin Microbiol Infect Dis*. 2014;33:2241-2247.
30. Kothari A, Morgan M, Haake DA. Emerging technologies for rapid identification of bloodstream pathogens. *Clin Infect Dis*. 2014;59:272-278.
31. Chitasombat MN, Kofteridis DP, Jiang Y, et al. Rare opportunistic (non-*Candida*, non-*Cryptococcus*) yeast bloodstream infections in patients with cancer. *J Infect*. 2012;64:68-75.
32. Cornely OA, Gachot B, Akan H, et al. Epidemiology and outcome of fungemia in a cancer cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). *Clin Infect Dis*. 2015;61:324-331.
33. Ericsson J, Chryssanthou E, Klingspor L, et al. Candidaemia in Sweden: a nationwide prospective observational survey. *Clin Microbiol Infect*. 2013;19:E218-E221.

34. Posteraro B, Spanu T, Fiori B, et al. Antifungal susceptibility profiles of bloodstream yeast isolates by Sensititre YeastOne over nine years at a large Italian teaching hospital. *Antimicrob Agents Chemother*. 2015;59:3944-3955.
35. Peman J, Canton E, Quindos G, et al. Epidemiology, species distribution and in vitro antifungal susceptibility of fungaemia in a Spanish multicentre prospective survey. *J Antimicrob Chemother*. 2012;67:1181-1187.
36. Peman J, Canton E, Linares-Sicilia MJ, et al. Epidemiology and antifungal susceptibility of bloodstream fungal isolates in pediatric patients: a Spanish multicenter prospective survey. *J Clin Microbiol*. 2011;49:4158-4163.
37. Guinea J, Zaragoza O, Escribano P, et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. *Antimicrob Agents Chemother*. 2014;58:1529-1537.
38. Li W, Hu YA, Li FQ, et al. Distribution of yeast isolates from invasive infections and their in vitro susceptibility to antifungal agents: evidence from 299 cases in a 3-year (2010 to 2012) surveillance study. *Mycopathologia*. 2015;179:397-405.
39. Dong D, Li Z, Zhang L, et al. Clinical and microbiological investigation of fungemia from four hospitals in China. *Mycopathologia*. 2015;179:407-414.
40. Chakrabarti A, Chatterjee SS, Rao KL, et al. Recent experience with fungaemia: change in species distribution and azole resistance. *Scand J Infect Dis*. 2009;41:275-284.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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