Epidemiology of Candida Infections in HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University

Woraphot Tantisiriwat MD, MPH*,
Somchai Santiwattanakul PhD**

** Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand*
*** Department of Pathology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand*

Objective: *To identify the epidemiology of candida isolations in HRH Princess Maha Chakri Sirindhorn Medical Center and the sensitivity of all candida species to fluconazole.*
Material and Method: *Two hundred of Candida albicans and other Candida species from clinical specimens were collected from microbiological department between January 2010 and April 2012. All Candida were identified by standard methods and the sensitivity of fluconazole was tested by using fluconazole E test test.*
Results: *There were 8 species of Candida in this study including: C. albicans (n = 94), C. tropicalis (n = 66), C. glabrata (n = 11), C. guilliermondii (n = 10), C. parapsilosis (n = 9), C. zeylanoides (n = 4), C. keyfr (C. pseudotropicalis) (n = 2), C. lusitaniae (n = 1), Candida species (n = 3). The percentage of non-albicans Candida spp. was slightly higher than C. albicans (53% vs. 47%). C. tropicalis was identified as the highest percentage of all non-albicans Candida spp. Fluconazole resistant strains were detected among C. albicans (35.71%), C. tropicalis (13.85%), C. guilliermondii (20.0%), and C. zeylanoides (50.0%). The common spp. with highest percentage of resistant strain was C. albicans.*
Conclusion: *Fluconazole could be used as the first-line antifungal for candidiasis at HRH Princess Maha Chakri Sirindhorn Medical Center. Empirical treatment with amphotericin B and stepping down to fluconazole when sensitivity suggested might be the recommendation for severe cases in our setting.*

Keywords: *Candida, Fluconazole, Epidemiology, Sensitivity, HRH Princess Maha Chakri Siridhorn Medical Center*

J Med Assoc Thai 2015; 98 (Suppl. 9): S66-S70
Full text. e-Journal: *http://www.jmatonline.com*

Less azole-susceptible *Candida* spp. was frequently detected among tertiary care centers. These resistant strains are related with increasing in azole usage[1,2]. The consequent result is increasing in echinocandin prescribing in many hospitals[3]. There was limited information about the impact on antifungal susceptibility and *Candida* species distribution from increased echinocandin use[4]. However, treatment with echinocandin has higher cost when compared with azole. Azole prophylaxis was considered as a potential risk factor for emergence of resistant *Candida* species. It was commonly used among neutropenic patients especially in patients with hematologic malignancies. Antifungal prophylaxis is recommended for these patients in order to eliminate the risk of developing invasive fungal disease in hemato-oncology setting[5]. Hence, selection pressure from exposure to azoles plays as an important role in the emergence of resistance to fluconazole among *Candida* spp.[6-8].

Candidemia was reported with high mortality rate in University Hospital of Thailand. Non-albicans *Candida* spp. was identified in higher percentage than *Candida albicans*[9,10]. Early appropriate antifungal usage could improve treatment outcome[10]. Individual setting has different *Candida* species distribution and antifungal susceptibility, thus epidemiological review is required to develop the appropriate antifungal usage guideline. The cost of treatment could be saved from proper antifungal drug prescription[11].

HRH Princess Maha Chakri Sirindhorn Medical Center is a 350 bed tertiary care hospital in Nakhon Nayok, Thailand. It's setting and medical practice is different from the other University Hospital.

Correspondence to:
Tantisiriwat W, Department of Preventive and Social Medicine, HRH Princess Maha Chakri Sirindhorn Medical Center, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok 26120, Thailand.
Phone: +66-37-395258 ext. 10657
E-mail: photmd@gmail.com

Patients with hematologic malignancies in HRH Maha Chakri Princess Sirindhorn Medical Center were not many. Azole prophylaxis is not routinely used in HRH Maha Chakri Princess Sirindhorn Medical Center hence the authors hypothesized that azole was still sensitive to most of the *Candida* spp. The authors aimed to review epidemiology of *Candida* spp. as well as the susceptibility to azole in order to reveal the response of all *Candida* spp. to azole. This data would be important for the practice and the development of practice guideline for treatment of candidemia and candida infections in HRH Princess Maha Chakri Sirindhorn Medical Center.

Material and Method

The prospective study was conducted at HRH Princess Maha Chakri Sirindhorn Medical Center between January 2010 and April 2012. Specimens that were positive for *Candida* spp. were collected. The identification of *Candida* spp. was performed. Two hundred of *Candida albicans* and other *Candida* species from clinical specimens were collected from clinical microbiology division, Department of Pathology, HRH Princess Maha Chakri Sirindhorn Medical Center, Faculty of Medicine, Srinakharinwirot University. All *Candida* were identified by standard methods[12]. The sensitivity to fluconazole was tested by using fluconazole E test test. The sterile 90 mm diameter plastic plates containing Mueller-Hinton agar added with 2% glucose and 0.5 μg/mL methylene blue dye at 4.0 mm depth were used. The 0.5 McFarland standard of each *Candida* was plated all over the surface of agar. After completely dry, an E test strip was applied to each plate and incubated at 35°C for 24-48 hours. The lowest concentration at the border of the elliptical inhibition zone was read. The MIC for fluconazole was $\leq$8 considered as sensitive, 16-32 considered as intermediate and $\geq$64 considered as resistance. The QC was also performed by testing *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019 and *C. albicans* ATCC 90028. The data were analyzed by using SPSS program version 17.0.

Results

There were 200 specimens which were positive for *Candida* spp. There were 8 species of *Candida* in this study including: *C. albicans* (n = 94), *C. tropicalis* (n = 66), *C. glabrata* (n = 11), *C. guilliermondii* (n = 10), *C. parapsilosis* (n = 9), *C. zeylanoides* (n = 4), *C. keyfr* (*C. pseudotropicalis*) (n = 2) and *C. lusitaniae* (n = 1). There were 3 specimens which could not be identified. The specimens mostly came from urine specimens (61.5%) followed by sputum (20.5%) and blood (7%). The other specimens with *Candida* spp. were detected with percentage less than 5% were stool (4%), genital tract (3%), pus and body fluid (2%) and catheter (2%), respectively. The percentage of non-albicans *Candida* spp. was slightly higher than *C. albicans* (53% vs. 47%). *C. tropicalis* was identified as the highest percentage of all non-albicans *Candida* spp. which was 33%. The other non-albicans *Candida* spp. had lower frequency than 10%. These other non-albicans *Candida* spp. were *C. glabrata* (5.5%), *C. guilliermondii* (5.0%), *C. parapsilosis* (4.5%), *C. zeylanoides* (2.0%), *C. pseudotropicalis* (1.0%) and *C. lusitaniae* (0.5%).

Fluconazole susceptibility testing data is presented in Table 1. Fluconazole resistant strains were detected among *C. albicans*, *C. tropicalis*, *C. guilliermondii* and *C. zeylanoides*. The common species with highest percentage of resistant strain was *C. albicans*. Of all *Candida* spp. isolates detected from blood specimen were two isolates that were resistant to fluconazole. These strains were *C. tropicalis* (2 isolates) as shown in Table 2.

Discussion

From epidemiologic data of candida infections in HRH Maha Chakri Princess Sirindhorn Medical Center, there were less cases of candidemia (14 cases in 2 years and 4 months) as compared to data from Songklanagarind Hospital (206 cases in 6 years) and Chiang Mai University Hospital (138 cases in 6 years)[9,10]. Most cases of candida isolations came from urine specimens that was similar to data from Thammasat University Hospital[11]. Similar to Thammasat University Hospital, *C. albicans* was the most frequent species found[11]. *C. tropicalis* was the most common non-albican species found in HRH Princess Maha Chakri Sirindhorn Medical Center as compared to *C. glabrata* in Thammasat University Hospital[11].

Most of *Candida* spp. detected in HRH Princess Maha Chakri Sirindhorn Medical Center was susceptible to fluconazole. Hence fluconazole could be used as the empirical treatment for candidiasis. However about 36% of *C. albicans* was resistant to fluconazole, thus fluconazole could not provide the best outcome for infection caused by *C. albicans* especially in the setting of candidemia in HRH Princess Maha Chakri Sirindhorn Medical Center. Although there was no candidemia cases caused by *C. albicans* during

Table 1. Fluconazole susceptibility of *Candida* spp. isolates from clinical specimens (urine 61.5%, sputum 20.5%, blood 7%, stool 4%, genital tract 3%, pus and body fluid 2% and catheter 2%)

Species	% (n = 200*)	MIC range	% Susceptible**	% Intermediate**	% Resistant**
C. albicans	47.0 (94)	0.094 to >256	62.24	2.05	35.71
C. tropicalis	33.0 (66)	0.120 to >256	84.62	1.53	13.85
C. glabrata	5.5 (11)	0.125 to 3	100.00	-	-
C. guilliermondii	5.0 (10)	0.120 to >256	60.00	20.00	20.00
C. parapsilosis	4.5 (9)	0.100 to 4	100.00	-	-
C. zeylanoides	2.0 (4)	0.380 to >256	50.00	-	50.00
C. pseudotropicalis	1.0 (2)	0.380 to 0.5	100.00	-	-
C. lusitaniae	0.5 (1)	0.38	100.00	-	-

* There were 3 specimens which could not be identified.
** The MIC for fluconazole was ≤8 considered as sensitive, 16-32 considered as intermediate and ≥64 considered as resistance

Table 2. Fluconazole susceptibility of *Candida* spp. isolates from blood specimens

Species	n	MIC range	% Susceptible*	% Intermediate*	% Resistant*
C. tropicalis	8	0.13 to >256	75.00	-	25.00
C. parapsilosis	2	0.38 to 4	100.00	-	-
C. pseudotropicalis	1	0.38	100.00	-	-
C. glabrata	1	0.13	100.00	-	-
C. guilliermondii	1	16	-	100.00	-
C. zeylanoides	1	0.38	100.00	-	-

* The MIC for fluconazole was ≤8 considered as sensitive, 16-32 considered as intermediate and ≥64 considered as resistance

our study time.

In recent decades, epidemiology of *Candida* spp. has been changed. The incidence of non-albicans *Candida* spp. was increased. The causative agents for candidemia were non-albicans *Candida* spp. greater than *C. albicans*[9,10]. Interesting findings for candidemia in HRH Princess Maha Chakri Sirindhon Medical Center was that all causative agents were non-albicans *Candida* spp., though most of these non-albicans *Candida* spp. were a response to fluconazole. This finding was different from other university hospitals where non-albicans *Candida* spp. were species, which were more resistant to fluconazole[9,10].

Fluconazole could still be used as an empirical therapy for candidemia in HRH Princess Maha Chakri Sirindhorn Medical Center. Although fluconazole was the preferred choice for empirical therapy for candidemia, the use in this setting might need thorough evaluation regarding response. If there were no improvement after administration of fluconazole in the first 24 hours and laboratory results such as germ tube testing suggesting of *C. albicans*, empirical treatment for candidemia should be adjusted. Empirical treatment with amphotericin B and stepping down to fluconazole when sensitivity suggested might be the recommendation for severe cases. In the setting of previous azole exposure, empirical treatment with amphotericin B should be considered.

Conclusion

Fluconazole could be used as the first-line antifungal for candidiasis at HRH Princess Maha Chakri Sirindhorn Medical Center because most of candidemia cases were non-albicans *Candida* spp. that would be sensitive to fluconazole. Empirical treatment with amphotericin B and stepping down to fluconazole when sensitivity is suggested might be the recommendation for severe cases in our setting since the outcome of treatment would not be effective as the expectation if the causative agent were *C. albicans*.

What is already known on this topic ?

The epidemiology of candida infections has changed, with more prevalence of non-albicans

candida spp. in tertiary care medical centers.

Individual setting has different *Candida* species distribution and antifungal susceptibility.

Epidemiological review is required to develop the appropriate antifungal usage guideline.

There were no previous data on *Candida* species distribution and antifungal susceptibility for HRH Princess Maha Chakri Sirindhorn Medical Center.

What this study adds ?

The percentage of non-albicans *Candida* spp. was slightly higher than *C. albicans* in HRH Princess Maha Chakri Sirindhorn Medical Center.

Most of *Candida* spp. detected in HRH Princess Maha Chakri Sirindhorn Medical Center was susceptible to fluconazole.

Fluconazole could be used as the first-line antifungal for candidiasis at HRH Princess Maha Chakri Sirindhorn Medical Center.

Acknowledgement

This work was funded by research grant from Faculty of Medicine, Srinakharinwirot University (341/2553)

Potential conflicts of interest

None.

References

1. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999. Clin Infect Dis 2002; 35: 627-30.
2. Berrouane YF,Herwaldt LA, Pfaller MA. Trends in antifungal use and epidemiology of nosocomial yeast infections in a university hospital. J Clin Microbiol 1999; 37: 531-7.
3. Forrest GN, Weekes E, Johnson JK. Increasing incidence of *Candida parapsilosis* candidemia with caspofungin usage. J Infect 2008; 56: 126-9.
4. Diekema D, Arbefeville S, Boyken L, Kroeger J, Pfaller M. The changing epidemiology of healthcare-associated candidemia over three decades. Diagn Microbiol Infect Dis 2012; 73: 45-8.
5. Agrawal S, Jones B, Barnes R, Kibbler C, Millen M, Ashcroft M, et al. A practical critique of antifungal treatment guidelines for haemato-oncologists. Crit Rev Microbiol 2012; 38: 203-16.
6. Kanamaru A, Tatsumi Y. Microbiological data for patients with febrile neutropenia. Clin Infect Dis 2004; 39 Suppl 1: S7-10.
7. Pfaller MA, Diekema DJ, Gibbs DL, Newell VA, Meis JF, Gould IM, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance study, 1997 to 2005: an 8.5-year analysis of susceptibilities of Candida species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J Clin Microbiol 2007; 45: 1735-45.
8. Gonzalez GM, Elizondo M, Ayala J. Trends in species distribution and susceptibility of bloodstream isolates of Candida collected in Monterrey, Mexico, to seven antifungal agents: results of a 3-year (2004 to 2007) surveillance study. J Clin Microbiol 2008; 46: 2902-5.
9. Jutiamornlerd N, Chusri S, Siripaitoon P. Epidemiology of candidemia in Songklanagarind Hospital. J Med Assoc Thai 2011; 94: 927-32.
10. Chaiwarith R, Ounbang P, Khamwan C, Nuntachit N, Sirisanthana T, Supparatpinyo K. Epidemiology of adult candidemia at Chiang Mai University Hospital. Southeast Asian J Trop Med Public Health 2011; 42: 1505-14.
11. Apisarnthanarak A, Yatrasert A, Mundy LM. Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. Infect Control Hosp Epidemiol 2010; 31: 722-7.
12. Hazen KC, Howell SA. *Candida, Cryptococcus*, and other yeasts of medical importance. In: Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, editors. Manual of clinical microbiology. 9th ed. Washington, DC: ASM Press; 2007: 1762-88.

ระบาดวิทยาของการติดเชื้อรา Candida ในโรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี มหาวิทยาลัยศรีนครินทรวิโรฒ

วรพจน์ ตันติศิริวัฒน์, สมชาย สันติวัฒนกุล

วัตถุประสงค์: เพื่อศึกษาระบาดวิทยาของการติดเชื้อรา Candida ในโรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารีและทดสอบการไวต่อยา Fluconazole ของเชื้อราดังกล่าว

วัสดุและวิธีการ: เชื้อ Candida albicans และสายพันธุ์อื่น ๆ 200 สิ่งส่งตรวจทางคลินิก ถูกรวบรวมจากห้องปฏิบัติการจุลชีววิทยาระหว่าง เดือนมกราคม พ.ศ. 2553 ถึง เดือนเมษายน พ.ศ. 2555 เชื้อถูกวิเคราะห์ตามวิธีมาตรฐานและทำผลการตอบสนองต่อยา Fluconazole โดยใช้ fluconazole E test

ผลการศึกษา: มี Candida ทั้งหมด 8 สายพันธุ์ที่พบในการวิจัยนี้ ประกอบด้วย C. albicans (n = 94), C. tropicalis (n = 66), C. glabrata (n = 11), C. guilliermondii (n = 10), C. parapsilosis (n = 9), C. zeylanoides (n = 4), C. keyfr (C. pseudotropicalis) (n = 2), C. lusitaniae (n = 1), Candida species (n = 3) พบว่ามีสัดส่วนของ Candida non-albicans มากกว่า C. albicans เล็กน้อย (53% vs. 47%) C. tropicalis เป็นสายพันธุ์ที่มากที่สุดของ Candida non-albicans การดื้อต่อยา fluconazole พบได้ใน C. albicans (35.71%), C. tropicalis (13.85%), C. guilliermondii (20.0%) และ C. zeylanoides (50.0%) สายพันธุ์ที่พบบ่อยและมีเปอร์เซ็นต์ของการดื้อต่อยา fluconazole สูงสุดได้แก่ C. albicans

สรุป: Fluconazole สามารถนำมาใช้เป็นยาต้านเชื้อรา Candida หลักตัวแรกในโรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี การให้การรักษาโดยครอบคลุมด้วย amphotericin B และลดยาเป็น fluconazole ต่อไป เมื่อผลการไวต่อยายืนยันว่าใช้ได้น่าจะเป็นคำแนะนำสำหรับการรักษาการติดเชื้อรา Candida ที่รุนแรง