Epidemiology, Clinical Characteristics, Sites of Infection and Treatment Outcomes of Mucocutaneous Candidiasis Caused by Non-*Albicans* Species of *Candida* at a Dermatologic Clinic

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Background: *Increasing numbers of mucocutaneous infection due to non-albicans species of Candida (N-CA) had been reported. Laboratory based studies showed multidrug resistance in N-CA population.*
Objective: *Demonstrate epidemiology, clinical characteristics, sites of infection, and treatment outcomes of mucocutaneous candidiasis caused by N-CA at a dermatologic clinic, including statistical evaluation data between N-CA and C. albicans infections.*
Material and Method: *This was a cross sectional study of outpatients with mucocutaneous infection due to Candida at Dermatologic clinic between January 2012 and June 2014. Vaginal candidiasis was excluded. Demographic, clinical, laboratory data, and treatment outcomes were collected.*
Results: *Among 760 patients presented with mucocutaneous candidiasis, 307 (40.4%) were infected with N-CA. The mean age (SD) of N-CA patients was 63.6 (10.4) years and 74.6% were female. The majority of N-CA cases were isolated from patients' nails (n = 293, 95.4%) while eight (2.6%) were detected from their skin, and six (2%) from oral mucosa. Comparison between N-CA and C. albicans, skin, and mucosa infection were significantly demonstrated in C. albicans groups ($p<0.001$). Among nail infected patients, C. albicans infections had significant higher severity than the N-CA infection ($p = 0.017$). Median time to cure in N-CA population was 169 days, which had no significant difference from C. albicans groups (211 days, $p = 0.499$).*
Conclusion: *Forty percent of mucocutaneous candidiasis was caused by N-CA. Nails were the most common sites of N-CA infections but N-CA was sometime found in skin and mucosa. Treatment outcomes of N-CA population were not significantly different from those of C. albicans groups.*

Keywords: *Epidemiology, Clinical characteristics, Treatment outcomes, Mucocutaneous candidiasis, Non-albicans species of Candida*

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Candidiasis has been increasing in recent years due to many immunosuppressive conditions such as AIDS. The common sites of *Candida* infection are oral mucosa, cutaneous, nail, and bloodstream. More than 30 species of *Candida* have been reported to cause infection. *Candida albicans* is the most common species identified in most setting. However, many studies reported the emergence of non-*albicans Candida* (N-CA) species and their potential to develop antifungal resistance[1].

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Epidemiology, risk factors, clinical presentations, outcomes of N-CA infection were mostly reported from patients with invasive candidiasis[2]. Several population-based and sentinel surveillance studies showed that 45 to 58% of candidemia cases were caused by *C. albicans*, 12 to 46.4% by *C. glabrata*, and 7 to 24.7% by *C. parapsilosis*[1,3]. The distributions of *Candida* species causing candidemia differ among geographical areas. *C. glabrata* and *C. krusei* are considered to be azole-resistant species. Since the fungal drug susceptibility is not usually available, the choice of empirical antifungal therapy would mostly base on the knowledge of the infecting species. Therefore, the change in distribution is considered important[1,3].

N-CA species had been detected more frequently in mucocutaneous isolation in recent years, particularly from patients with human immunodeficiency virus (HIV) infection. Laboratory based studies showed multidrug resistance in N-CA population[4]. The study about N-CA resulting in skin and mucosa infection was limited. The distributions of *Candida* species varied geographically. This study aimed to demonstrate epidemiology, risk factors, clinical characteristics, treatment, and outcomes of mucocutaneous candidiasis caused by N-CA. Additionally, this study had been included statistical evaluation comparing data between N-CA and *C. albicans* infections.

Material and Method

This was a cross-sectional study of out-patients with cutaneous infection due to *Candida* at Dermatologic clinic between January 2012 and June 2014. Demographic data, risk factors, clinical presentations, laboratory data, treatment, and outcomes were collected. Approval was provided by the Siriraj Institutional Review Boards. Mucocandidiasis was diagnosed by clinical features, direct microscopy, and culture. Mucocutaneous candidiasis was classified into mucosa (oral candidiasis and balanitis), cutaneous (intertrigo and folliculitis), and nail (paronychia and onychomycosis). Vaginal candidiasis was excluded due to most patients attended gynecological department.

Severity of paronychia was assessed to five stages as following: stage I, some redness and swelling of the proximal and/or lateral nail folds causing disruption of the cuticle, stage II, pronounced redness and swelling of the proximal and/or lateral nail folds with disruption of the cuticle seal, stage III, redness, swelling of the proximal nail fold, no cuticle, some discomfort, some nail plate changes, stage IV, redness and swelling of the proximal nail fold, no cuticle, tender/painful, extensive nail plate changes, and stage V, same as stage IV plus acute exacerbation (acute paronychia) of chronic paronychia[4].

The specimens scraped from mucosa, skin, and nails were placed directly on a microscopic slide, covered with 20% potassium hydroxide (KOH) and examined under a light microscope for fungal elements. The specimens were inoculated on Sabouraud dextrose agar with 0.005% chloramphenicol and incubated for 1 week at room temperature. By visual inspection, colonies suspected of *Candida* were isolated for further confirmation and species identification by chromogenic medium (Candiselect®4, BioRad) and RapID Yeast Plus system (Innovative Diagnostic Systems, Norcross, Ga.). *C. dubliniensis* was identified from *C. albicans* by inability of growth at 43°C. Antifungal susceptibility testing was not included in the present study. A criterion of cure was defined as normal appearance of skin or nail and negative result of mycological laboratory.

Statistical analysis

Descriptive analyses were used for baseline characteristics and subgroup analyses. The compared data between N-CA and *C. albicans* groups were analyzed using an unpaired t-test for continuous variables and a Chi-square test for categorical data. The survival distribution function and median survival time were estimated using Kaplan-Meier method. Log rank test was used to compare survival curves between two groups. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 18.0; Chicago, IL, USA).

Results

Of the 179,176 patients attending dermatologic clinic, 760 patients were diagnosed with mucocutaneous candidiasis. The prevalence was 0.42%. Among 760 patients, 307 (40.4%) were infected with N-CA. Mean prevalence of N-CA infection was 0.17% of the patients attending dermatologic clinic with increasing trend from 0.07% in 2012 to 0.27 in 2014. The identified species were *C. krusei* (58.3%), *C. dubliniensis* (40.3%), *C. tropicalis* (0.7%), and *C. glabrata* (0.7%).

In N-CA group, the mean age (SD) was 63.6 (10.4) years and 74.6% were female. The majority of N-CA cases were isolated from patients' nails (n = 293, 95.5%) while eight (2.6%) were detected from their skin, and six (2%) from oral mucosa. In the present study, there were 260 complete case record forms for analysis. The most common clinical presentation of nail infection was chronic paronychia (60.9%) and nail thickening (28.6%). Most of the affected were fingernails (84.8%). The majority of skin infection presented as macerated erythematous plagues (84.6%) and folliculitis (15.4%) at inguinal fold areas. As for oral infection, pseudomembrane lesion (82.8%) at buccal mucosa was the common characteristic. Moreover, overall median time to cure is 183 days.

Skin and mucosa infection were significantly demonstrated in *C. albicans* groups ($p<0.001$). Among nail-infected patients, *C. albicans* infections had significant higher severity than the N-CA infection ($p = 0.017$). Most of patients (73%) were treated with topical azole. There were 5.4% treated with topical azole with steroid cream and only 0.4% received

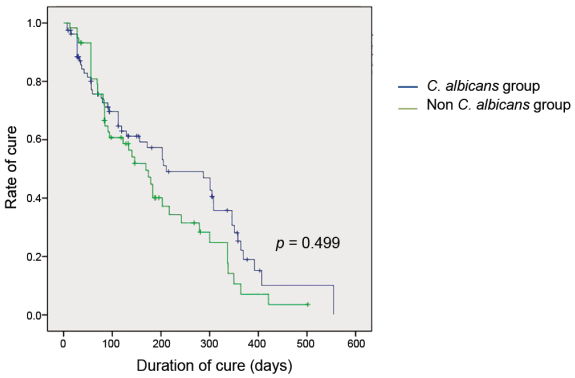

Fig. 1 Kaplan-Meier analysis illustrated that time to cure of both groups including *Candida albicans* and Non-*Candida albicans* groups.

systemic azole. Median time to cure in N-CA population was 169 days, not different from *C. albicans* groups (211 days, $p = 0.499$) (Fig. 1).

Regarding predisposing factors, hyperhidrosis was the most common host factor (88.5%) and frequent exposure to water (97.7%) was the most common environment factor. Hyperhidrosis was significantly found more common in patients with *C. albicans* infection than N-CA infection (Table 1). Among patients with oral candidiasis, dental wear was significantly associated with N-CA infection in comparison with *C. albicans* infection ($p = 0.02$).

Discussion

Superficial *Candida* infections along with invasive candidiasis have been observed more frequently in recent years, especially in immuno-compromised patients[1,3-6]. The most common causative species is *C. albicans*, whereas N-CA species ranks second. Many previous studies demonstrated that the prevalence of candidemia caused by the N-CA group is rising[1-3]. However, the study on mucocutaneous candidiasis is limited. One study from Iran reported N-CA prevalence of 27.7% second only to *C. albicans*[5]. The current study showed N-CA prevalence of as high as 40.4% reflecting an emergence of N-CA species as an important causative agent of superficial fungal infection.

The geographical difference in *Candida* species distributions underlines the importance of fungal identification and antifungal susceptibility testing in order to provide appropriate treatment regimens. *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* were the leading causative organisms isolated from blood specimen of invasive candidiasis patients due to N-CA species in North America, accounted for 46.4%, 24.7%, and 13.9% respectively[1]. Another study from Japan; however, revealed *C. parapsilosis*, *C. glabrata*, and *C. tropicalis* as the top-three N-CA species, accounted for 22%, 15%, and 7% respectively[3]. Moreover, a study of risk factors and outcomes of *C. albicans* and N-CA species at a Thai tertiary care center published in 2009 reported that N-CA species bloodstream infection were caused by *C. glabrata* (33%), *C. krusei* (25%), *C. tropicalis* (25%), and *C. parapsilosis* (17%)[7]. Of mucocutaneous *Candida* infection, a study from Iran reported that the N-CA group was the second most common causative agents

Table 1. Demographic data and predisposing factors of *Candida* species infection

Factors	Total *Candida* infection (n = 260)	Non-*albicans Candida* (n = 88)	*Candida albican* (n = 172)	*p*-value
Sex: female	199 (76.5%)	67 (76.1%)	132 (76.7%)	0.913
Age (year), mean (SD)	59.1 (12.7)	60.8 (11.1)	58.1 (13.5)	0.900
Site of infection				
Nail	189 (72.7%)	84 (95.5%)	105 (55.6%)	<0.001
Cutaneous	42 (16.0%)	1 (1.1%)	41 (97.6%)	<0.001
Mucosa	29 (11.2%)	3 (3.4%)	26 (89.7%)	0.005
Risk factors				
Hyperhidrosis	230 (88.5%)	73 (83.0%)	157 (91.3%)	0.047
Diabetes mellitus	25 (9.6%)	7 (8.0%)	18 (10.5%)	0.516
Hematologic malignancy	5 (1.9%)	1 (1.1%)	4 (2.3%)	0.509
Pernicious anemia	3 (1.2%)	1 (1.1%)	2 (1.2%)	0.985
HIV infection	1 (0.4%)	0 (0%)	1 (0.6%)	0.474
Occlusive clothing	1 (0.4%)	0 (0%)	1 (0.6%)	0.474
Frequent exposure to water	254 (97.7%)	85 (96.6%)	169 (98.3%)	0.398
Chemotherapy	1 (0.4%)	1 (1.1%)	0 (0%)	0.161
Use of corticosteroid	14 (5.4%)	2 (2.3%)	12 (7.0%)	0.112
Long-term antibiotics	3 (1.2%)	0 (0%)	3 (1.7%)	0.213

following *C. albicans*. *C. parapsilosis*, *C. glabrata*, and *C. krusei* were the most prevalent species in the group, accounted for 11.6%, 4.6%, and 4.6% respectively[4]. In addition, the present study showed that the identified N-CA species were *C. krusei* (58.3%), *C. dubliniensis* (40.3%), *C. tropicalis* (0.7%), and *C. glabrata* (0.7%). These evidences highlighted the geographical diversity of *Candida* species distributions.

Of N-CA species, the present study demonstrated that the majority of N-CA cases were isolated from patients' nail (95.5%) whereas the skin and mucosa accounted for 1.1% and 3.4% respectively. To the best of our knowledge, there has not been any previous report on N-CA onychomycosis in comparison with mucocutaneous N-CA candidiasis. The present study suspected that some factors in nails might contribute to the N-CA growth and colonization. *C. albicans* has higher ability to develop pseudohyphae than N-CA so may result in more severity. Similarly, the present study supports that the severity of nail infection was significantly higher in *C. albicans* group. The relationship between *Candida* species and severity of infection required further study.

Several studies from different geographic regions reported rising trend of azoles antifungal resistance in systemic candidiasis[1-3,6-11]. Among superficial candidiasis, there were only in vitro study supporting the evidence of drug resistance in N-CA species. It showed that ketoconazole had the highest resistance rate. In addition, resistance to fluconazole was reported only in *C. krusei*[4]. The present study, however, did not include antifungal susceptibility testing in the protocol. Therefore, treatment outcomes were evaluated by clinical outcomes in which the duration of mycological cure was neither different from those aforementioned studies nor those of *C. albicans* group. Azoles antifungals still played a major role in superficial N-CA candidiasis treatment regimen but they should be prescribed with caution to avoid drug resistance.

Conclusion

Forty-percent of mucocutaneous candidiasis was caused by N-CA. Nails were the most common sites of N-CA infections but N-CA was less found in skin and mucosa. Treatment outcomes of N-CA population were not significantly different from those of *C. albicans* groups.

What is already known on this topic?

Many studies worldwide reported the emergence of N-CA species and their potential to develop antifungal resistance. The distributions of *Candida* species causing candidemia differ among geographical areas.

However, epidemiology, risk factors, clinical presentations, and outcomes of N-CA infection were mostly reported from patients with invasive candidiasis. Rarely, study regarding N-CA in mucocutaneous was reported.

What this study adds?

Forty percent of mucocutaneous candidiasis was caused by N-CA. Nails was the most common site of N-CA infections, but N-CA was less found in skin and mucosa.

Even through, previous laboratory based studies showed multidrug resistance in N-CA population, this study demonstrated that treatment outcomes of N-CA population were not significantly different from those of *C. albicans* groups.

Acknowledgement

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Potential conflicts of interest

None.

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ระบาดวิทยา ลักษณะทางคลินิก ตำแหน่งของการติดเชื้อ และผลการรักษาของการติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์บริเวณผิวหนังและเยื่อบุ ศึกษาที่คลินิกโรคผิวหนัง

จรัสศรี พียาพรรณ, สุมนัส บุณยะรัตเวช, ศุภร ฟุ้งลัดดา, ชุดา รุจิธารณวงศ์, พิชญา มณีประสพโชค, ธีทัต สุวรรณ, ไฉน เหมือนประสาท, ลลิตา มัฏฐาพันธ์

ภูมิหลัง: *ภาวะติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ที่ผิวหนังและเยื่อบุมีอัตราเพิ่มสูงขึ้น รวมทั้งมีการศึกษาทางห้องปฏิบัติการรายงานเกี่ยวกับภาวะการดื้อยาของเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ด้วย*

วัตถุประสงค์: *เพื่อศึกษาระบาดวิทยา ลักษณะทางคลินิก ตำแหน่งของการติดเชื้อ และผลการรักษาของภาวะติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ที่ผิวหนังและเยื่อบุ ณ คลินิกโรคผิวหนัง รวมถึงประเมินค่าทางสถิติระหว่างการติดเชื้อแคนดิดาแอลบิแคนส์และกลุ่มที่ไม่ใช่แอลบิแคนส์*

วัสดุและวิธีการ: *เป็นการศึกษาผู้ป่วยที่ได้รับการวินิจฉัยภาวะติดเชื้อแคนดิดาที่ผิวหนังและเยื่อบุที่หน่วยตรวจโรคผิวหนัง โรงพยาบาลศิริราช ช่วงระหว่างเดือนมกราคม พ.ศ. 2555 ถึง มิถุนายน พ.ศ. 2557 โดยไม่รวมการติดเชื้อที่เยื่อบุช่องคลอด การศึกษานี้ศึกษาโดยใช้ข้อมูลเกี่ยวกับกลุ่มประชากร ลักษณะทางคลินิก ข้อมูลทางห้องปฏิบัติการ และผลการรักษา*

ผลการศึกษา: *ผู้ป่วย 760 ราย ที่ได้รับการวินิจฉัยภาวะติดเชื้อแคนดิดาที่ผิวหนังและเยื่อบุ พบว่า 370 ราย (40.4%) เกิดจากเชื้อก่อโรคแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ ผู้ป่วยติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์มีอายุเฉลี่ย (SD) คือ 63.6 (10.4) ปี และ 74.6% เป็นเพศหญิงส่วนใหญ่เป็นที่เล็บ 293 ราย (95.4%) ที่ผิวหนัง 8 ราย (2.6%) และที่เยื่อบุช่องปาก 6 ราย (2%) โดยพบว่าการติดเชื้อที่ผิวหนังและเยื่อบุนอกจากเล็บนั้นเกิดจากเชื้อแคนดิดาแอลบิแคนส์ มากกว่าเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์อย่างมีนัยสำคัญทางสถิติ ($p<0.001$) ส่วนการติดเชื้อที่เล็บพบว่าความรุนแรงของภาวะติดเชื้อแคนดิดามากกว่าที่เกิดจากเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์อย่างมีนัยสำคัญทางสถิติเช่นกัน ($p = 0.017$) แต่ระยะเวลาในการรักษาจนหายของภาวะติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์เฉลี่ยประมาณ 169 วัน ซึ่งไม่แตกต่างกับภาวะติดเชื้อแคนดิดาแอลบิแคนส์ (ระยะเวลาเฉลี่ย 211 วัน, $p = 0.499$)*

สรุป: *40% ของภาวะติดเชื้อราที่ผิวหนังและเยื่อบุเกิดจากเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ โดยเล็บเป็นส่วนที่ติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ได้มากที่สุด แต่กลับพบได้น้อยกว่าที่ผิวหนังและเยื่อบุ ซึ่งผลการรักษาและระยะเวลาการรักษาของภาวะติดเชื้อแคนดิดากลุ่มที่ไม่ใช่แอลบิแคนส์ไม่แตกต่างกับภาวะติดเชื้อแคนดิดาแอลบิแคนส์*