Diagnostic Value of Candida Colonization Index in The Early Diagnosis of Invasive Candidal Infection

İnvaziv Kandida İnfeksiyonlarının Erken Tanısında Kandida Kolonizasyon İndeksinin Tanı Değeri

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ABSTRACT

Objective: To investigate the diagnostic value of *Candida* colonization index (CCI) in the early diagnosis of invasive candidal infection in medical mix (medical and surgical intensive care units (ICU).
Methods: Mouth, axillae, nasogastric catheter, rectum, and urine culture samples taken from the patients admitted to the reanimation and neurological ICU for 19 months were retrospectively evaluated and CCI were calculated.
Results: CCI reached ≥0,5 in the cultures of 29 patients. 29 patients developed candidal infection; 27 (27/29) of them had CCI ≥0,5. 18 patients developed urinary infections, 10 patients developed candidemia, and 1 patient developed wound infection. CCI ≥0,5 was found as the only independent predictor for invasive candidal infection (p<0,001, OR: 701,553, %95 CI; 28,310-17385,22). The positive predictive value, sensitivity, and specifity of CCI for the candidal infection were found to be 93.1% and 96.2%, respectively.
Conclusions: We concluded that monitoring for CCI in patients with unknown fever, severe sepsis or septic shock in the medical ICU offers an early diagnosis and intervention to prevent invasive candidal infection. Independently from the other risk factors, CCI may be considered as an effective test for early diagnosis of invasive candidal infection in medical and surgical ICU patients.

Key Words: Candidal infections, *Candida* colonization index, intensive care unit

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ÖZET

Amaç: Kandida kolonizasyon indeksinin (KKİ), karışık (dahili ve cerrahi yoğun bakım ünitelerinde) (YBÜ) invaziv kandida enfeksiyonun erken tanısında tanı değerini araştırmak.
Yöntem: Reanimasyon ve nörolojik yoğun bakım ünitesine 19 ay boyunca başvuran hastalardan alınan ağız, aksilla, nazogastrik kateter, rektum ve idrar kültürü örnekleri retrospektif olarak değerlendirildi ve KKİ hesaplandı.
Bulgular: Yirmidokuz hastanın kültürlerinde KKİ ≥0,5 seviyelerine erişti. 29 hastada kandida enfeksiyonu gelişti; 27(27/29) si KKİ ≥0,5 tespit edildi. 18 hastada üriner sistem enfeksiyonu, 10 hastada kandidemi, 1 hastada yara yeri enfeksiyonu gelişti. KKİ ≥0,5, invaziv kandida enfeksiyonu için tek bağımsız risk faktörü olarak bulundu. (p<0,001, OR: 701,553, %95 CI; 28,310-17385,22) KKİ'nin kandida enfeksiyonları için pozitif prediktif değerinin duyarlılığı ve seçiciliği sırası ile, %93,1 ve %96,2 olarak bulundu
Sonuç: Dahili YBÜ'de bilinmeyen ateş, şiddetli sepsis ve septik şok tanılı hastalarda KKİ'nin takibinin yapılmasının, invaziv kandidal enfeksiyonun önlenmesi için erken tanı ve önlemeye olduğu sonucuna vardık. Diğer risk faktörlerinden bağımsız olarak KKİ dahili ve cerrahi YBÜ'de erken tanı için etkili bir test olarak düşünülebilinir.

Anahtar Sözcükler: Kandida enfeksiyonları, kandida kolonizasyon indeksi, yoğun bakım ünitesi

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INTRODUCTION

There has been an overall increase in fungal health care–associated infections (HAIs), including patients in intensive care units (ICU), in the last few decades (1). This increase in invasive fungal infections is multifactorial which is likely a consequence of the advances in medical and surgical therapies. In spite of the the new development of diagnosis and treatment of candidiasis, fungal infection still causes high mortality rates (2).

Candida infections occur five to ten times more often (2-6.7 in 1000 admitted patients) in ICUs than on medical or surgical wards. According to National Nosocomial Infections Surveillance (NNIS) data, *Candida* spp. (%70-90) and *Aspergillus* spp. (%10-20) are the most common causes of invasive fungal infections in critically ill patients (3,4). Unfortunately, the diagnosis of invasive candidiasis carries on a challenge because rapid microbiological markers are not available. Although serological tests are promising, the lack of sufficient studies among the patients in ICU, and extensive cost limit widely usage of these serological markers. Physicians often make the diagnosis of invasive *Candida* infection on the basis of symptoms and signs of an infection and the presence of risk factors (5,6). Many ICU patients represents risk factors for invasive candidiasis, and a large proportion of them become colonized with *Candida* spp. during the ICU stay (7-10). The patients were reported 50-80% to have *Candida* colonization during their stay in ICU (11). As assessed by the colonization index proposed by Pittet et al in 1994, increasing growth of *Candida* spp. from multiple body sites is predictive for subsequent invasive candidiasis (7). Prior colonization could allow recognition of these patients. On the other hand *Candida* colonization increase the risk of invasive candidiasis (12).

Candida scoring has been shown to be effective in surgical intensive care units but there is a few data on medical intensive care units. The aim of the study is to investigate the diagnostic value of *Candida* colonization index (CCI) in the early diagnosis of invasive candidal infection in the medical and mix (medical and surgical) ICU setting.

MATERIALS and METHODS

The study was designed in a 12-bed Anesthesiology and Reanimation ICU (ARICU), and in a 7-bed Neurological ICU (NICU) for the 19 months. All patients admitted to ICU were included in the study. The following data of the patients were collected and analyzed: age, gender, cause of ICU admission, previous hospital stay, previosus antibiotic use, duration of ICU stay, hemodialysis or hemofiltration, APACHE (Acute Physiologic and Chronic Health Evaluation) II score, the number and duration of invasive procedures such as mechanical ventilation, endotracheal tube, arterial line, peripheral and central venous catheters, urine catheter, and parenteral nutrition.

Culture samples were obtained from the urine, mouth, axillae, nasogastric aspiration, and rectum on admission to ICU, and then repeated three times in a week until death or discharge from ICU. Blood samples were obtained on admission and then repeated each time when two or more systemic inflammatory response syndrome (SIRS) criteria were present. Specimens were inoculated onto Sabouraud Dextrose and Corn-meal agar. Yeast identification was made based on combination of microscopic examination and biochemical characteristics in the API-32C® system (bioMerieux, France).

Blood cultures are obtained from both peripheral blood and, if exist, central venous catheter (CVC). In case of growth in CVC cultures, the catheter was removed. One or more positive blood culture yielding *Candida* spp., was accepted as an episode of candidemia. Severe non-bloodstream invasive candidal infections were defined as isolation of *Candida* spp. from sterile body sites, and the presence of at least one of the following conditions: body temperature ≥38^{0}C or <36^{0}C; unexplained prolonged arterial hypotension (systolic blood pressure <90 mmHg for at least 2 h, unresponded to volume challenge; absence of response to adequate antibiotic treatment for suspected bacterial infection (13). The diagnosis of candiduria required the recovery of at least 100 cfu/ml of the same *Candida* spp. in two distinct urine samples obtained within 1 week (14). *Candida* colonization was defined as the isolation of fungi in various body sites or fluid samples (urine, mouth, axillae, nasogastric aspiration, rectal swap samples) (15). A *Candida* colonization index (CCI) was determined as the ratio of the number of distinct body sites colonized with identical strains over the total number of distinct body sites tested (15).

The statistical analysis of the data was performed using the SPSS version 15.0 software package. Categorical variables were analyzed using chi-square or Fisher's exact tests where appropriate. Student's t-test was used for comparison of continuous variables. To test the independence of the risk factors for invasive candidiasis, a multivariate analysis was performed by logistic regression. Statistical significance was set at a p value of < 0.05.

RESULTS

A total of 82 patients (male/female 44/38) were included in this study; 35 patients were admitted to the ARICU, 47 to the NICU. The mean age of study population was 63,15±20,05. The mean of APACHE II score was 27,96±3,48, mean duration of hospitalization was 30,46±31,42 days in the overall study population.

Of 82 patients who stayed in ARICU and NICU, 56 developed at least one site of *Candida* colonization; 29 developed at least two sites of *Candida* colonization (CCI ≥0,5). *Candia* colonization rate were 51,4% and 23,4% in ARICU and NICU respectively. Among the 29 patients (CCI ≥0,5), 27 (93,1 %) who developed a candidal infection; 10 (34.5 %) developed candidemia. Only 2 of 53 (3.8%) patients with CCI<0,5 developed a candidal infection (p<0.001) (Table 1).

Table 1. Distribution of candida infections by CCI

CCI	*Candida* Infection		
	YES		NO
	Candidemi	Candiduria	
CCI≥0,5 (n:29)	10	16	2
CCI<0,5 (n:53)	0	2	53

There was no difference between patients with CCI≥0,5 and CCI<0,5 regarding to gender, prior hospitalization, prior bacterial infections, invasive procedures such as mechanic ventilation, urinary catheterization, peripheral venous catheter (p>0,05).

The mean time of onset of candidal infection was 22,41±3,39 days after ICU admission. The mean time until colonization was 9,90±10,16 days for the 29 patients who became colonized after admission to the ICU.

Previously established risk factors for invasive candidiasis were present in most of patients. 56,1% of them were hospitalized within prior 6 month, 90,3% had prior bacterial infection, 71,9% were exposed to broad spectrum antibiotics, 98,8% had peripheral venous catheter, 48,8% had central venous catheter, 82,9% were intubated, 81,7% required a mechanical ventilation, and 97,6% had urinary catheterization. The risk for the development of *Candida* infections was increased by the lengthened duration of hospitalization. The risk of *Candida* infection were 2.5 times higher in patients who stayed ≥16 days than those of patients who stayed <16 days in ICU (p <0.001, OR 2.54, 95% CI 0.45 to 0.373). The most common species isolated from the samples was *Candida albicans (*62,1 %).

Increased age (≥ 65), lengthened duration of hospitalization prior to ICU admission, stay in reanimation ICU, use of broad spectrum cephalosporins, presence of renal failure, loss of consciousness, invasive procedures such as central venous catheter, peripheral arterial catheter and intubation were determined as predictors of *Candida* colonization.

In a multivariate analysis, the presence of peripheral arterial catheter was found to be an independent risk factor for candida colonization (p<0,05 OR:23,8 95% CI: 1,130-501,087). Sulbactam-ampicillin usage was an inversely independent risk factor for the development of *Candida* colonization (p<0,05 OR:0,29 95% CI: 0,001-0,800).

Evaluation of the risk factors revealed that age (≥65 year), stay in ARICU, lengthened duration of hospitalization, prior urinary infection, use of broad spectrum antibiotics, recent antibiotic use (0-15 days), renal failure, peripheral arterial catheter, central venous catheter, and intubation were found to be associated with *Candida* infection (Table 2).

Table 2. The predictive factors for the development of *Candida* infection

	Candida Infection		
	YES n(%)	NO n(%)	p
Ward			0,001
ARICU	20 (69)	15 (28,3)	
NICU	9 (37,6)	38 (71,7)	
Age			0,023
≥65 year	19 (65,5)	16 (30,8)	
<65 year	10 (34,5)	37 (69,2)	
Duration of hospital before infection			0,001
0-15 day	15 (51,7)	53 (100)	
16-30 day	6(21,7)	0	
>30 day	8(27,6)	0	
Prior infection			
Urinary tract infection	12 (41,4)	11(20,8)	0,047
Use of broad spectrum antibiotics	26(44,1)	33 (55,9)	0,008
Prior antibiotic use			0,028
0-15 day	25 (89,7)	31(56,6)	
16-30 day	0	2(3,8)	
Currently using	1(3,4)	1(1,9)	
Rics factors			
Renal failure	4(3,8)	1(1,9)	0,031
Loss of consciousness	26(89,7)	3(69,8)	0,042
İnvasive procedures			
Peripheral arterial catheter	10(31)	6(13,52)	0,011
Central venous catheter	19(65,5)	21(39,6)	0,025
İntubation	27(93,1)	40(75,5)	0,048
Mechanical ventilation	27(93,1)	41(77,4)	0,07

In a multivariate logistic regression analysis, only prior *Candida* colonization was found to be an independent risk factor for the development of *Candida* infection (p<0,001, OR: 701,553, %95 CI; 28,310-17385,22)

DISCUSSION

Invasive candidiasis (IC) in patients admitted to the medical ICU is a serious problem and, of particular concern, associated with high mortality and morbidity (16). The adequate antifungal treatment is a major factor associated with a good prognosis in fungal infection (1). Intravascular catheters, endotracheal tubes, naso- and oro-gastric tubes, and foley catheters etc., conduce biofim formation by *Candida* spp. (15). Substantially these may explain progressive colonization of many patients after prolonged stay in the ICU (12,15). Among the different risk factors *Candida* colonization is an important one. In our study we observed only immunocompetent patients in ARICU and in NICU and complications and many of them were already colonized by *Candida* spp. During the observation period ten patients developed *Candida* bloodstream infection, who presented with CI ≥ 0.5.

Multiple site colonization and its degree has a crucial role in the development of invasive *Candida* infection (17-19). Pittet et al (7) proposed a clinically relevant colonization index in an attempt to assess fungal colonization density with time in high risk surgical ICU patients. Positive predictive value of CCI was determined as 66-100%. This was confirmed by several subsequent studies. It has been shown that the incidence of *Candida* colonization and candidiasis infection is increased due to translocation in the gastrointestinal tract during surgery and multiple trauma or damage to the skin and mucous membranes (12). In a study performed in the surgical ICU, Öhman-Agvald et al (20), showed that high colonization index in the presence of large gastroabdominal surgery may be predicting factor for invasive candidiasis (20). Similarly, Solomkin et al., reported that 31 of 63 surgical ICU patients were colonized with *Candida* spp. in at least two body sites before detected fungemia (21). Charles et al (22) showed that prior colonization with *Candida* spp. reaches to a higher density in patients admitted to medical ICU than those in the surgical ICU. The *Candida* Score (CS) combined in a predictive clinical the results of a prospective cohort study, where surgery, multifocal colonization, total parenteral nutrition and severe sepsis predicted invasive candidiasis, with 81% of sensitivity and 74% of specificity and a had negative predictive value (NPV) of 98% (23). We did not find these parameters as meaningful because of the low number of traumatized patients who underwent surgery in our study. In addition, no significant difference was found between hospitalization diagnoses and IC (p>0,05). CCI could be of predictive value for the diagnosis of systemic candidiasis in high-risk surgical patients, but a few studies have performed *Candida* score, and colonization index for identifying patients at risk of development of IC in medical ICU setting. Lahmer et al showed that fungal colonization is independently associated to mortality in cirrhotic ICU-patients (24). In a retrospective study of 29 critically ill patients, Chronic Health Evaluation II (APACHE II) score and duration of antibiotic exposure before colonization were higher among the 11 patients who ultimately developed invasive candidiasis (25). Smilar to this study, in our study APACHE II scores were >25 among the patients who developed multiple site *Candida* colonisation.

Massou et al (26) determined that the most common risk factors were broad-spectrum antibiotics and foreign material. The CI was greater than or equal to 0.5 at 53% of the patients, and less than 0.5 in 47% of the cases. Among the patients, 15% developed an invasive candidiasis. In multivariate analysis, the corticosteroid therapy was associated with a high colonisation (IC ≥ 0.5) and neutropenia with a high risk of systemic candidiasis. In contrast our study the positive predictive value of CI was 26%, the negative predictive value was 98%, the sensitivity and specificity was 93% and 48% respectively. Although they thought that it wasn't helpful with patients having an invasive candidiasis in medical intensive care unit, the positive predictive value, sensitivity and specifity of CCI were 93.1 %, 93.1%, and 96,2% for the candidal infection, and 52,6%, 100%, 74,6% for candidemia, respectively, in our study. Charles PE et al (27) found that broad-spectrum antibiotic therapy promote fungal growth in patients with prior colonization. They suggest that reducing antibiotic use could be useful in preventing fungal infections. In our study prior antibotic usage was found to be associated with *Candida* colonisation and infection.

Unfortunately, to date prospective surveillance studies of fungal colonization in the medical ICU are still limited. We determined that CCI was the only independent predictor for candidal infection by the logistic regression analysis (p<0,001, OR: 701,553, %95 CI; 28,310-17385,22). Several other risk factors found to be associated with candidemia in other studies were not independently associated with candidaemia in our study. The timely recognition of IC is essential to driving clinical decision processes and specific therapeutic strategies. Independently from the other risk factors, CCI may be considered as an effective test for early diagnosis of invasive candida infections in medical and surgical ICU patients. Therefore it may be a useful tool to prevent mortality.

It is obvious that *Candida* score could be of predictive value for the diagnosis of systemic candidiasis in high-risk surgical and trauma patients but the datas are limited in medical ICU. Although further studies are needed to compare, standardize and eventually confirm these data, our experience suggests that monitoring for CCI is a good predictor for candidasis in medical ICU patients with unknown fever, severe sepsis or septic shock and APACHEE scores are high.

Prospective trials with a large patient population in medical ICU based on CCI and other risc factors such as APACHEE score, prior antibiotic usage, lenght of hospital stay etc. would be useful.

Conflict of interest

No conflict of interest was declared by the authors.

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