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

İnvaziv Kandida Infeksiyonlarının 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 specificity 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), karşık (dahili ve cerrahi yoğun bakım ünitesinde) (YBÜ) invaziv kandida enfeksiyonun en önemli tanısında tanılayabileceği araştırımyoruz.

Yöntem: Reanimasyon ve nöroloji yoğun bakım ünitesinde 19 ay boyunca başvuran hastaların ağız, aksilla, nazogastrik kateter, rektum ve idrar kültürü örnekleri retrospektif olarak değerlendirildi ve KKI hesaplandı.

Bulgular: 29 hastanın kültürlerinde KKI ≥0,5 seviyesine ulaşmasına rastlandı. 29 hastada kandida enfeksiyonu gelişti; 27 (27/29) kişi KKI ≥0,5 tespit edildi. 18 hastada üriner sistem enfeksiyonu, 10 hastada kandidemi, 1 hasta yara yeri enfeksiyonu gelişti. KKI ≥0,5, invaziv kandida enfeksiyonu için tek bağımsız risk faktörü olarak bulundu. (p<0,001, OR: 701,553, %95 CI; 28,310-17385,22) KKI'nın kandida enfeksiyonları için pozitif prediktif değerinin duyarlılığı ve seççiliği sırası ile, %93,1 ve %96,2 olarak bulundu.

Sonuç: Dahili YBÜ'de bilinmeyen ateş, şiddetli sepse veya sepsis şoku tani için KKI'nın takipinin yapılması, invaziv kandidal enfeksiyonun önlenmesi için en önemli tanı ve önleme olduğu sonucuna varıldı. Diğer risk faktörlerinden bağımsız olarak KKI dahili ve cerrahi YBÜ'de erken tanı için etkili bir test olarak değerlendirilmesi önerilir.

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 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. (7%-90) and Aspergillus spp. (6%-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 a 50%-80% risk 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, previous 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°C or <36°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 snap 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).

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). Candidia 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 |
|-------|------------------|
| NO    | YES              |
| CCI<0,5 | 0 2 53         |
| (n:53) |                  |
| CCI≥0,5 |16 2            |
| (n:29) |                  |

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 1.04 to 6.373). 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 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<0,005 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).

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.
We determined that CCI was an independent risk factor for the development of invasive candidiasis in medical ICU patients (24). 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). Similar to this study, in our study APACHE II scores were >25 among the patients who developed multiple site Candida colonization.

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 further studies (25). Smilar to this study, in our study APACHE II scores were >25 among the patients who developed multiple site Candida colonization.

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

| Candida Infection | YES n(%) | NO n(%) | p       |
|-------------------|----------|---------|---------|
| Ward              |          |         |         |
| ARICU             | 20 (69)  | 15 (28.3)| 0.001   |
| NICU              | 9 (37.6) | 38 (71.7)|         |
| Age               |          |         |         |
| ≥65 year          | 19 (65.5)| 16 (30.8)| 0.023   |
| <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 | |         | 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         | 2(6.8)   | 2(6.8)  |         |
| 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   |
| Invasive procedures |        |         |         |
| Peripheral arterial catheter | 10(31)| 6(13.5)| 0.011   |
| Central venous catheter | 19(65.5)| 21(39.6)| 0.025   |
| Intubation         | 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., conduces biofilm 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-Angvald et al (20), showed that high colonization index in the presence of large gastrointestinal 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 (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 antibiotic usage was found to be associated with Candida colonization 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 data 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 candidiasis in medical ICU patients with unknown fever, severe sepsis or septic shock and APACHE II scores are high.
Prospective trials with a large patient population in medical ICU based on CCI and other risk factors such as APACHEE score, prior antibiotic usage, length of hospital stay etc. would be useful.

Conflict of interest
No conflict of interest was declared by the authors.

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