Risk Factors for Mortality in Fungal Infections

Mantar Enfeksiyonlarında Fataliteye Etki Eden Faktörler

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ABSTRACT Objective: This study aimed to investigate the frequency of fungal infections in our intensive care unit (ICU) and the risk factors directly associated with mortality. **Material and Methods:** The data of 625 patients admitted to the Medical ICU between 2003 and 2006 were reviewed retrospectively. **Results:** The percentage of patients with at least once fungal isolation was 11% (n= 73). Fungal species were isolated from blood samples (n= 35), urine (n= 28), deep tracheal aspirate (DTA, n= 40) and catheters (n= 14). The association between the localization of fungal infection and mortality was examined and a significant correlation between fungemia and mortality was found (p= 0.002); however, the correlation between mortality and fungal isolation from urine, DTA and catheters was not significant (p> 0.05). Multivariate logistic regression analysis to detect the factors for mortality in patients with isolated fungal species revealed that mortality was 5.2 times more frequent among fungemic patients in comparison to other groups (confidence interval: 1.11-25 p=0.036). **Conclusion:** In ICU patients, fungemia itself had a direct correlation with mortality. The goal of treatment should be the early detection of fungemia and reducing mortality with the initiation of the therapy as early as possible.

Key Words: Fungemia; risk factors; hospital mortality

ÖZET Amaç: Son yıllarda yoğun bakım ünitelerinde mantar enfeksiyonları giderek artmaktadır. Bu çalışmanın amacı, yoğun bakım ünitemizde karşılaşılan mantar enfeksiyonlarının sıklığını saptamak ve ilişkili risk faktörlerini belirlemektir. **Gereç ve Yöntemler:** Marmara Üniversitesi Tıp Fakültesi, Dahiliye Yoğun Bakım Ünitesinde, 2003-2006 yılları arasında 625 hasta retrospektif olarak incelendi. **Bulgular:** Çalışmanın sonunda 73 hastada mantar üremesine rastlandı. Hastaların 35'inde kanda üreme, 28'inde idrarda üreme, 40'ında derin trakeal aspirasyon (DTA) örneğinde üreme ve 14'ünde kataterde mantar üremesi tespit edildi. Mantar enfeksiyonunun saptandığı yer ve mortalite ilişkisine bakıldığında, fungemi istatistiksel olarak mortalite ile doğrudan ilişkili bulundu (p= 0.002). DTA, idrar ve kateterde mantar türlerinin saptanmasının mortalite ile istatistiksel ilişkisi gösterilemedi (p> 0.05). Mantar türlerinin izole edildiği hastalarda mortaliteye etki eden faktörlerin çok değişkenli lojistik regresyon analizi ile incelenmesinde, fungemi saptanan hastalarda, diğerlerine göre mortalite oranının 5 kat daha fazla olduğu belirlendi (p= 0.036). Geniş spektrumlu antibiyotik kullanımı, kan dışındaki yerlerden mantar üremeleri, yaş, APACHE II değeri, hemodiyaliz ve yoğun bakımda yatış süresinin mortaliteye etkisi gösterilemedi. **Sonuç:** Özellikle fungemi, yoğun bakım hastalarında mortaliteye doğrudan etkilidir. Fungeminin erken tanısı erken tedaviyi sağlayarak mortalite artışını önleyebilir.

Anahtar Kelimeler: Fungemi; risk faktörleri; hastane mortalitesi

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Within the last two decades the incidence of nosocomial fungal infections among intensive care unit (ICU) patients has a tendency to increase.[1-3] *Candida* species are the most frequently

isolated fungal pathogens in ICUs.[1,4] This increase was demonstrated in US, Europe and in many other countries all around the world.[5] The most frequently isolated subgroup is *Candida albicans*; however, the incidence of *Torulopsis glabrata* and *Candida tropicalis* is suggested to be associated with increasing frequency of complications and mortality.

Several studies demonstrated the risk factors for fungal infections. These were neutropenia, length of stay in ICU, intravascular catheters, malignancy, surgical operation, antibiotics, chemotherapy and steroid use.[6,7] Cheng, et al. retrospectively studied the risk factors in patients with candidemia associated with mortality. Multivariate analysis demonstrated that, only Acute Physiology and Chronic Health Evaluation (APACHE) II score was correlated with mortality among patients with candidemia.[8] However, the attributable mortality for candidemias was not detailed in previous studies.[9] In this study, we aimed to demonstrate the factors associated with mortality among patients with fungal infection in our intensive care unit.

MATERIAL AND METHODS

The patients admitted to the medical ICU of Marmara University Faculty of Medicine Hospital between 2003 and 2006 were reviewed retrospectively. The patients with isolated fungus species from blood, urine, deep tracheal aspirate or catheters during their stay in the ICU were included. The patients monitored in ICU for at least 48 hours were included. Antibiotic use, age, hemodialysis, intravascular catheter, length of stay in ICU, mechanical ventilation and APACHE II score during admission were documented.

Fungemia was defined as the isolation of one fungus species at least once from the blood culture. Nosocomial fungemia was defined as fungal infection 72 hours after admission to the ICU. For microbiologic culture and examination, 5 cm distal segments of intravascular catheters were sent to the laboratory in sterile conditions. After 48 hours of incubation on blood agar, colony count was performed.

Statistical Analysis

Data were analyzed using Stata Statistical Software, version 9.0 (STATA corporation, Texas, USA). Proportion comparisons for categorical variables were done using chi-square tests, although Fisher's exact test was used when data were sparse. Significance was set at $p< 0.05$ using two-sided comparisons. Logistic regression analysis was performed to detect the parameters for mortality. The variables of length of stay, carbepenem use, fungemia, device utilization were included in the multivariable model.

RESULTS

A total of 625 patients admitted to the ICU were reviewed and 76 were included in the study. The demographic characteristics of 76 patients who had any fungal infection were listed in Table 1.

Fungal species were isolated from blood samples (n= 35), urine (n= 28), deep tracheal aspirate samples (n= 40) and catheters (n= 14).

The most common fungal pathogen was *C. albicans*. Overall 82% of blood cultures (29/35) and 82% of urine cultures (23/28) yielded *C. albicans*. *C. albicans* was the most common fungal isolate in deep tracheal aspiration samples and intravascular catheters (85% and 86% respectively). Isolated fungal species were summarized in Table 2.

A significant association between fungemia and mortality was detected (p= 0.002). Among the fatal cases, 76% received noninvasive mechanical ventilation (NIMV), whereas 91% received invasive mechanical ventilation (IMV).

TABLE 1: Demographic characteristics of the patients.

	n= 73 (%)
Females	38 (52)
Mean age (standart deviation)	64 (15)
Underlying diseases	
Cardiovascular diseases	39 (53)
Malignities	17 (23)
Renal diseases	7 (10)
Pulmonary diseases	9 (12)
Mean APACHE on admission (standard deviation)	23 (6)
Length of stay (standard deviation)	20 (15)

TABLE 2: Isolated fungus species.

	Blood		Urine		Deep Tracheal Aspirate		Catheters	
	n= 35	(%)	n= 28	(%)	n= 40	(%)	n= 14	(%)
Candida albicans	29	(83)	23	(82)	34	(85)	12	(86)
Candida kefyr	3	(9)	-		6	(15)	4	(29)
Candida tropicalis	3	(9)	3	(11)	4	(10)	2	(14)
Candida glabrata	5	(14)	1	(4)	3	(8)	1	(7)
Candida parapsilosis	1	(3)	3	(11)	2	(5)	-	
Trichosporon spp.	2	(6)	1	(4)	2	(5)	-	
Aspergillus spp.	2	(6)	-		3	(8)	1	(7)

There was no significant association between mortality and fungal isolation from urine, DTA or catheter (p> 0.05, Table 3).

In multivariate logistic regression analysis of patients with fungal infection, mortality was 5.2 times more frequent among patients with fungemia compared to those without (confidence interval= 1.11-25, p= 0.036, Table 4).

TABLE 3: Location of fungal infection and its association with fatality.

	Isolated Fungus Species	Fatality	
	n= 73	n= 34 (%)	p
Blood	35 (48)	23 (68)	0.002
Deep tracheal aspirate	40 (55)	16 (47)	0.170
Urine	28 (38)	14 (41)	0.706
Catheter	14 (19)	8 (24)	0.253

DISCUSSION

This study showed that among many risk factors, fungemia itself was directly associated with mortality. The most common fungal species in our ICU was *C. albicans*. Therefore, the early diagnosis of fungemia and initiation of therapy soon is an important measure to decrease the rate of mortality.

Considering nosocomial infections, fungemic infections are among the most important causes of morbidity and mortality.[1-4] *C. species* are the fourth most frequently isolated pathogen in ICUs.[4] The review of records of 625 patients admitted to the ICU between 2003 and 2006 revealed that in 73 patients (11%) a fungal species was isolated at least once. Studies demonstrated the gradual increase of fungal infections in ICU since 1980. Similar results were obtained in studies conducted in Turkey.[10] The most common fungal species is *C. albicans*, followed by other *C. species*. The frequency of isolation for *C. albicans* was 83-86% in our study.

Previous studies showed that invasive candidiasis had the highest mortality and isolation of *Candida* from other anatomical regions was a risk

TABLE 4: Multivariate analysis for the fatality among the patients with fungal infection.

	Odds ratio	Confidence interval	p
Carbapenem use	1.58	0.36-6.83	0.540
Fungemia	5.2	1.11-25	0.036
Device use			
Urinary catheter	2.19	0.54-8.93	0.270
Invasive mechanical ventilation	4.15	0.29-57.87	0.290
Non-invasive mechanical ventilation	0.24	0.01-3.8	0.31
Central venous catheter	1.79	0.17-18.46	0.624
Length of stay	0.98	0.94-1.03	0.693
APACHE score on admission	1.04	0.93-1.17	0.417

factor for invasive candidiasis.[11] Also isolation from two or more different locations and fungemia were associated with higher mortality in comparison to isolation from only one anatomical region. However, no single site of isolation is superior to others in predicting which patients are likely to develop systemic infection.[12] In our study, we studied the association between the location of isolation and mortality and only fungemia was associated with mortality. Mortality rates were 65% for fungemia, 40% for deep tracheal isolation, 50% for urine isolation and 57% for catheter isolation.

Gradual increase in the incidence of fungal infections in recent years and their association with high mortality raised a need to detect the risk factors related to fungal infection. Previous studies demonstrated that broad spectrum antibiotic use, corticosteroid use, chemotherapy, malignancy, neutropenia, serious surgical intervention and burns were the risk factors associated with fungal infections.[6,7] Also Swan-Ganz and CVP catheter use, total parenteral nutrition and mechanical ventilation were suggested to be associated with increased risk of fungal infections.[6,7] In some studies, even hospitalization or admission to ICU alone were reported as risk factors.[1,13-15] In our study, in patients with isolated fungal infections, logistic regression analysis of factors associated with mortality revealed that mortality rate was 5-fold higher in patients with fungemia in comparison to others.

Broad spectrum antibiotic use, isolation of the fungus from deep tracheal aspirate, urine and catheters, age, APACHE II score, hemodialysis, mechanical ventilation and length of stay in ICU in patients with fungal isolation were not significantly associated with increased mortality. In the study of Cheng et al including 78 patients with candidemia, factors associated with mortality were studied and APACHE II score was associated with mortality.[8]

Non-invasive mechanical ventilation was found to have protective effect on fungal infections. Among the fatal cases, 76% received NIMV, whereas 91% received IMV. Some patients received both invasive and non-invasive mechanical ventilation.

Non-invasive ventilation provides ventilation without using endotracheal intubation and in recent years its use has been increasing gradually in ICU units. Non-invasive ventilation might decrease the frequency of both nosocomial pneumonia and nosocomial infections in comparison to endotracheal intubation.[16,17] This may account for the protective effect of non-invasive ventilation demonstrated in our study.

In ICU with fungal infection, early diagnosis and treatment of fungemia, as a factor directly associated with mortality, is particularly important. In a study, candidemia patients with treatment initiated within the first 48 hours had a tendency to have higher survival rates in comparison to those with initiation of treatment after 48 hours but the difference between the two groups was not significant.[18] The early markers of invasive fungal infections were studied and the number of studies on this issue has been increasing gradually but there is no marker on routine clinical use currently.[19,20]

In conclusion, fungemia by itself was demonstrated to be directly associated with fatality among ICU patients. Early diagnosis and treatment of fungemia is critical to decrease the rate of fatality.

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