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Risk Factors for Candidemia in Critically Ill Patients

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Introduction:

Candida is the fourth most common pathogen identified in blood.[1] Candida, a yeast like fungus, is present in the oral cavity of 40 to 60% of the general population. [2,3]. Candida is most likely to cause disease in human beings[4]. Candida is common in the oral and gastro-intestinal flora. Its presence is increased in patients who are immune compromised, who use broad spectrum antibiotics, smokers and patients with dentures and xerostomia. Candidiasis of the oropharynx and esophagus is associated with HIV infection and is a clinical predictor of disease progression in HIV infected patients[5,6]. Systemic fungal infections are pathologies that particularly affect immunocompromised and severely ill patients.[7] Epidemiological studies have shown an increasing evidence of bloodstream infections by Candida species, given their colonization ability and therapeutic challenges arising from the development of resistance to some antifungal agents.[8,9]. The risk of invasive candidiasis is determined by the long-term administration of broad-spectrum antibiotics, surgery, organ transplant and use of invasive procedures.(indwelling catheters, mechanical ventilation purposes, parenteral nutrition, urinary catheters)[10,11] There is high mortality and morbidity associated with candidiasis according to various studies.[12, 13].

Materials and methods:

The aim of the study was to identify the risk factors associated with candidemia in critically ill patients and to identify the risk factors for mortality in candidemia patients. The study was conducted over a two year period in a tertiary care hospital on a prospective basis. All inpatients above the age of 18 years who had candidemia were included in the study. Candidemia was defined as a positive blood culture for candida in at least one sample sent during the course of stay in hospital. Clinical symptoms at the time of presentation, admitting diagnosis, history of co-morbid illness, chronic use of steroids, immunosuppressive medication were noted. The number and days of indwelling catheters, use of broad spectrum antibiotics, the presence of local candidiasis and other organisms that grew along with Candida spp. were noted. A complete blood picture, HbA1c and renal function were done. Patient was followed up till the final outcome. The total duration of stay in the hospital and the total number of ICU days were also noted. Blood cultures were done in the Microbiology department in our Central laboratory. All cultures were done using sabouraud's agar (Bactec). Species identification and differentiation were done using their differences in morphology. Results were expressed as mean for continuous variables and number (%). For categorical data univariate analysis was performed using Pearson Chi-square test. A 'p' value of <0.05 was considered as statistically significant. Chi-square test was used to analyze the association between the predisposing risk factors in candidemia patients. Odds ratio was used to analyze the association between risk factors and mortality in candidemia patients. Statistical analysis were performed using SPSS window version 17.0 software

Results:

In our study population comprising of 35 patients, 30 (85.7%) were males and 5 (14.3) were females, age ranging from 18 to 77 years with a mean age of 50.86 years. Of these 35 patients, 71.4% of patients had history of co-morbid medical illness. 17 patients (48.6%) were diabetic, 23 patients (65.4%) presented with uncontrolled sugars, 2 patients (5.7%) were on immunosuppressive medication, 5 patients (14.3%) were on oral steroids for multiple conditions and 5 patients (14.3%) presented with neutropenia. 31 (88.6%) of the 35 patients were managed in various intensive care units (ICU). 32(91.4%) patients were started on proton pump inhibitors (PPI) for stress ulcer prophylaxis and 2 patients (5.7%) were given total parenteral nutrition. The in-hospital mortality rates in these patients were 45.7% (16 patients). The use of more than three broad spectrum antibiotics was considered as a risk factor for candidemia. 30(85.7%) were given broad spectrum antibiotics (BSA). 93.8% of the patients who were on broad spectrum antibiotics had a poor outcome. The use of a central venous catheter along with an endotracheal tube or a urinary catheter was taken as a risk factor for candidemia and mortality associated in these patients. 31 patients (88.6%) had multiple indwelling catheters during their hospital stay. All patients who had a poor outcome in our study were on multiple indwelling catheters. As surgery produces damage to the integrity of the integument, it was taken as a risk factor for candida infection. 19 patients (54.3%), underwent a surgical procedure during this present admission. 50% of the total mortality in patients with candidemia had a recent surgery. Only 5(14.3%) patients had evidence of associated local candida infection (Eg:- UTI, Oral candidiasis). 17 (48.6%) patients had other organisms grown in cultures along with candida. Higher mortality occurred in this subset of patients (35% of the total mortality). More than 10 days in-hospital stay was taken as a risk factor for mortality in patients with candidemia. 29 (82.85%) patients stayed in the hospital for more than 10 days. Greater than 10 days in-hospital stay contributed to 81.25% of the total mortality in these patients. Candida tropicalis was the com-

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monest organism grown in our hospital (62.9%). C.albicans and C.krusei contributed to 2 patients each. All patients who grew C.albicans had poor outcomes. All patients who grew C.krusei survived. C.tropicalis contributed to 62.5% of the total mortality. Species differentiation was not possible in 25.71% patients. Since the sample size was small and no controls were used, Chi-square tests did not show significant values. Hence, Odds ratio was used to correlate the association of risk factors with mortality in candidemia patients.

Discussion:

Our study that consisted of 35 patients with candidemia provides information on species distribution and outcome associated in patients with bloodstream candidiasis. It reports a progressive increase in the incidence of candidemia in hospitalized patients. Most cases of candidemia occurred in patients who required ICU care. This study adds evidence to the already recognized risk factors for candida infections. The risk factors associated with mortality in these patients were also studied. The high mortality among these patients is a strong reason for health teams to be aware of risk factors potentially leading to candida infections. Our study consisted of patients ranging from 18 years to 77 years of age. Children were not included in the study. The mean age in our study group was 50.86 years with a standard deviation of 17.19 years. 25 of the 35 patients (71.42%) were above the age of 40 years. Death was higher in patients above 40 years of age with candidemia (81.25% of total mortality). Luzzati R et al[14], in his study, Candidemia in an Italian tertiary care hospital, supported that increasing age, was a potential risk factor for mortality in candidemia patients. Mean age = 58 ± 19 years. The mean duration of stay in hospital in our study group was 31.23 ± 26.8 days. Greater than 10 days in-hospital stay was taken a risk factor for candidemia as well as for mortality. 29 of the 35 patients stayed in the hospital for more than 10 days. They were associated with higher mortality (81.25% of total mortality). Luzzati R et al[14], in his study, Candidemia in an Italian tertiary care hospital, concluded that the 30-day crude mortality rate was 45%. A longer duration of candidemia was significantly associated with poor outcome. Candidemia also lengthens the duration of hospital stay. Ming-Fang Cheng[15], in his study Risk factors for fatal Candidemia, said that candidemia is not only associated with a higher mortality (30% to 40%) but also extends the length of hospital stay and increases the costs of medical care. In our study 31 out of 35 patients were admitted in various intensive care units. ICU care was associated with an increased risk of candidemia and an increased risk for mortality in these patients. 93.5% of the total mortality was attributed to patients admitted in ICU (OR-2.82). Ming-Fang Cheng, in his study, Risk factors for fatal Candidemia, supported that ICU care was associated with an increased mortality risk in candidemia patients (93.5%). Gabrino J et al[16], in his study, Frequency, mortality and risk factors for candidemia, concluded that, among the risk factors analyzed, only ICU stay was statistically significant (OR- 3.2). Diabetes is considered one of the major risk factors for fungal infections. 17 of the 35 patients were known diabetics and all of them had poor glycemic control on presentation (HbA1c > 7.5). A total of 23 patients had uncontrolled sugars on presentation. 18 patients, had uncontrolled sugars as a single predisposing risk factor. It was associated with the highest risk for candidemia. 75% of the total mortality was attributed to patients with uncontrolled sugars. Every second patient with uncontrolled sugars and candidemia had a poor outcome. Mortality was significantly high in patients who presented with uncontrolled sugars (OR-2.18). Yu-Ren Cheng[17], in his study, Risk factors for Candidemia- related mortality in Taiwan, concluded that Cancer (38.5%) and Diabetes mellitus (36.3%) were the two most common underlying pre-disposing conditions associated with candidemia. 2 patients were on prior immunosuppressive therapy in the form of azathioprine and anti-cancer drugs. Both patients had a poor outcome. Immunosuppressive therapy was considered as a high risk for mortality in candidemia patients (OR- 2.71).This was supported by other studies Karabi A et al, in his study, Risk factors for Candidemia in Cancer patients, said, chemotherapy was associated with a significant risk for candidemia. 5 patients were on prior steroid use for various reasons such as chronic asthma and connective tissue disorders. 3 of the 5 patients (60%) had a poor outcome. Chronic steroid use attributed to a high risk for mortality (OR- 1.96). This was similar to other studies. Nucci M and Colombo a et al[18], in their study, Risk factors for breakthrough candidemia, supported that, use of corticosteroids was identified as a risk factor for candidemia(OR-3.17). Nucci M[19], in another study, Risk factors for death in patients with candidemia, said that, corticosteroid therapy was significantly associated with candidemia related death. 5 of the 35 patients had neutropenia at the time of presentation, of which 60% were associated with a poor outcome. Neutropenia was associated with a significant risk for mortality (OR- 1.96). Karabi A et al, in his study, Risk factors for candidemia in cancer patients, concluded that neutropenia was associated with an increased risk for candidemia (p = 0.05). The in-hospital use of PPI's for stress ulcer prophylaxis and APD is associated with breakthrough candidemia from the GI tract. 32 of the 35 patients were put on PPI's for stress ulcer prophylaxis (91.4%). Mortality was associated with 43.5% of patients on PPI's (85% of the total mortality). But PPI use did not show statistical significance for mortality in candidemia patients (OR- 0.39). In-hospital PPI use is associated with increased of acquiring candidemia. Only one patient was on TPN and he had a poor outcome. Mortality among patients on TPN was considered significant (OR- 1.2). 30 of the 35 patients were put on BSA's since the time of admission. It was considered to be one of the risk factors for acquiring candida infections (85.7%). This is supported by many studies. Conde-Rosa et al[20], in his study, Candidemia distribution, risk factors and mortality, supported that, use of broad spectrum antibiotics was one of the predominant risk factors for candidemia (95.6%). 93.5% of patients who had a poor outcome were put on BSA's. Attributed mortality was significantly high (OR- 4.0). It is not similar to a study by A Viudes et al, Epidemiology, treatment, clinical outcome and risk factors for candidemia, where BSA use was not associated with significant mortality. Similarity was found with a study done by Conde-Rosa et al. 31 of the 35 patients had multiple indwelling catheters since presentation. It had a statistical significance for acquiring candidemia (p=0.05). Surgeries recently performed were considered as a high risk for acquiring candidemia (54.3%). This was similar to a study done by Playford et al[21], Candidemia in non-neutropenic patients, who concluded, prior GI surgery attributed to high risk acquiring candida-non albicans infection (OR- 4.6). 50% of patients who underwent surgeries had a poor outcome. Recent surgery was not significantly attributed to mortality in candidemia patients (OR- 0.73). C.tropicalis was the most common organism isolated in our study (62.85%). This was similar to a study done in North India done by Xess et al[22], Epidemiology of candidemia in North India, who said, C.tropicalis was most commonly identified (35.3%). C.non-albicans are the most frequent organisms isolated in candidemia patients

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in the recent years. In our study, 62.5% of total mortality was attributed to patients who grew C.tropicalis. It was not statistically significant (OR- 0.97). Nguyen MH et al[23], in his study, the changing face of candidemia, emergence of non-C.albicans spp., concluded that C.non-albicans species were associated with a higher risk for mortality ($p < 0.005$). C.albicans was isolated in only 2 patients. Both patients had a poor outcome. Mortality in patients who grew C.albicans was 100%. C.krusei was isolated in 2 patients. There was no mortality associated in patients who grew C.krusei.

Conclusion:

The incidence of C.non albicans has increased in the past few years. C.tropicalis was the most common organism isolated in our study (62.85%). Uncontrolled sugars were found to be the strongest single pre-disposing risk factor for candidemia(65.7%). C.albicans was associated with a higher risk for mortality. The significant risk factors associated with candidemia were identified as ICU care (88.6%), uncontrolled sugars (65.7%), steroid use (14.3%), PPI use (91.4%), broad spectrum antibiotics (85.7%), use of indwelling catheters (88.6%), recent surgery (54.3%) and neutropenia (14.3%). The significant risk factors associated with mortality in candidemia patients were ICU care (OR- 2.82), uncontrolled sugars (OR- 2.18), immunosuppressive therapy (OR- 2.71), chronic steroid use (OR- 1.96), neutropenia (OR- 1.96), use of total parenteral nutrition (OR- 1.20), use of broad spectrum antibiotics (OR- 4.00), indwelling catheters (OR- 4.27) and the presence of pre-existing co-morbidities (OR- 5.35).

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