Risk factors for candida blood stream infection in medical ICU and role of colonization – A retrospective study

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Abstract
Candida blood stream infection (candidaemia) is one of the most serious hospital acquired infections with high morbidity and mortality rates in the Intensive Care Unit (ICU). A number of risk factors have been identified in a variety of studies. ICU patients are frequently colonised with Candida species. The role of Candida colonisation as a causal factor for candidaemia remains controversial. Our objective for the study was to evaluate the risk factors for candidaemia and to evaluate the role of colonisation to predict candidaemia. We evaluated a total of 1483 patients aged over 18 years who stayed in ICU for more than 7 days. We collected various data about risk factors for candidaemia. A total of 56 patients (3.77%) developed candidaemia. We collected demographic and risk factor data including Candida colonisation of the urinary and respiratory tract. Binary logistic regression with forward likelihood ratio method model was used to analyse these risk factors. In our study, total parenteral nutrition (odds ratio (OR)- 3.274, 95% confidence interval (CI) 1.263-8.486), presence of central venous line (OR- 1.895, CI 1.032-3.478), previous or current antibiotic use (OR 3.268, CI 1.532-6.972), respiratory tract colonisation (OR 2.150, CI 1.078-4.289) and urinary tract colonisation (OR 3.508, CI 1.926-6.388) were significant risk factors for Candida blood stream infection (BSI). Based on the model, we calculated the candidaemia risk score and based on the receiver operative curve analysis, a score more than 2 would be associated with a higher risk of candidaemia. Candida species isolated in the respiratory tract or urine were similar to that found in Candida BSI (Kappa coefficient for agreement of 0.83 and 0.47 respectively). So, it can be concluded that Candida colonisation of the respiratory tract and/or urine is a significant risk factor for Candida BSI along with the other risk factors.

Keywords: Candidemia, Risk factors, Central Venous line, Colonization.

Abbreviations: ICU- intensive care unit, OR- odds ratio, CI- confidence interval, BSI- blood stream infection, HIV- Human immunodeficiency virus, IDSA- Infectious Disease Society of America, COPD- Chronic obstructive pulmonary disease, DM- Diabetes Mellitus, ESRD- End stage renal disease, TPN- Total parenteral nutrition.

Introduction:
Candida species is a leading cause of nosocomial infections and the most common fungal infection in intensive care units. Candida infection ranges from invasive candidal disease to bloodstream infections (candidaemia). The incidence of Candida infection has been rising over the past two decades, particularly with the use of immunosuppressive drugs for cancer and HIV1,2,3, and most of these infections occur in ICU settings.4 Candida infection is associated with high mortality and morbidity. Studies have shown that mortality attributable to candidaemia ranges from 5 to 71% depending on the study.5,6,7 Candidaemia is also associated with longer length of hospital stay and higher cost of care.

Early recognition of Candida BSI has been associated with improved outcome. Candida sepsis should be suspected in a patient who fails to improve and has multiple risk factors for invasive and bloodstream Candida infection. A variety of risk factors identified for candidaemia include previous use of antibiotics, sepsis, immunosuppression, total parenteral nutrition, central venous line, surgery, malignancy and neutropenia. Patients admitted to ICU are frequently colonised with Candida species. The role of colonisation in Candida blood stream infection and invasive candidal disease has always been debated. Few studies support the use of presumptive antifungal treatment in ICU based on colonisation and number of sites colonised by Candida. The NEMIS study has raised doubt about this approach of presumptive treatment. The Infectious Disease Society of America (IDSA) 2009 guidelines identify Candida colonisation as one of the risk factors for invasive candidiasis, but warn about the low positive predictive value of the level of Candida colonisation.8 We conducted a retrospective cohort study in our medical ICU to identify risk factors for Candida blood stream infections including the role of Candida colonisation.

Hospital and Definitions:
This study was conducted at Interfaith Medical Center, Brooklyn, New York. It is a 280 bed community hospital with 13 medical ICU beds. A case of nosocomial Candida blood stream infection was defined as a growth of Candida Species in a blood culture drawn after 48 hours of admission. Cultures in our hospital are routinely done by the Bactec Method – aerobic and anaerobic cultures. Cultures are usually kept for 5 days at our facility and if yeast growth is identified, then species identification is done. In our ICU it is routine practice to do endotracheal culture and urine culture for all patients who are on mechanical ventilator supports and failing to improve. In
patients who are not mechanically ventilated, it is routine practice to send sputum culture and nasal swabs to identify MRSA colonisation.

Study Design:

This study was a retrospective cohort study. We retrospectively reviewed all patients’ charts admitted to our medical ICU from 2000 to 2010 which stayed in the ICU for more than 7 days, irrespective of their diagnosis. Data were collected for demographics – age and sex. Data were also collected for risk factors for candidaemia – co-morbidities (HIV, cancer, COPD, diabetes mellitus, end-stage renal failure (ESRF)), presence or absence of sepsis, current or previous use of antibiotics, presence of central venous lines, steroid use during ICU stay, requirement of vasopressor support and use of total parenteral nutrition (TPN). Culture results for Candida including species identification were obtained for blood, urine and endotracheal aspirates.

Statistical Methods:

Patients were divided in two groups based on presence or absence of Candida BSI. Demographic data and risk factors were analysed using the chi square test to look at the difference between the two groups. Endotracheal aspirates and sputum cultures were combined to create a group with Candida respiratory tract colonisation. Binary logistic regression with forward likelihood ratio method was used to create models. Different models were generated for risk factors. Interactions between antibiotic use, steroid use, vasopressor support and sepsis were analysed in different models. Interactions between urine cultures and endotracheal aspirates/sputum cultures were also analysed by a different model. The model with the lowest Akaike information criterion (AIC) was chosen as the final model. The candidaemia risk score was calculated based on this final model to predict the risk of Candida BSI. Receiver operating curve (ROC) analysis was used to select the best cut-off value for the candidaemia risk score. Candida species in urine and endotracheal aspirates were compared with Candida species in blood culture using the kappa test. Data were analysed using SPSS statistical analysis software version 18.

Study Results:

A total of 1483 patients were included in the study. 56 patients (3.77%) had a blood culture positive for Candida species. Table 1 demonstrates demographic characteristics of the study population. There were no significant differences in the both groups for age, sex, diabetes mellitus, COPD, HIV, cancer and ESRF. As demonstrated in the table, 82.1% of patients in candidaemia groups recently used or were taking antibiotics as compared to 39.6% of patients in groups with no candidaemia. The P value was significant for this difference. Similarly, 71.4% of patients in the group with candidaemia had sepsis as compared to 30.6% in the other group with a P value of 0.000. Use of vasopressor (severe septic shock) was different between two groups – 23.2% and 10.1%, P value of 0.004. Steroid use, central lines and total parenteral nutrition use was higher in the candidaemia group as compared to the group without candidaemia. Similarly the rate of positive Candida cultures in urine and endotracheal aspirates was higher in the candidaemia group as compared to the group without.

Table 1: Demographic characteristic of study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Candidaemia (total 56)</th>
<th>No candidaemia (total 1427)</th>
<th>Chi Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>34 (60.7%)</td>
<td>676(47.40%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male sex</td>
<td>27 (48.2%)</td>
<td>694(48.6%)</td>
<td>0.530</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (39.3%)</td>
<td>506(35.5%)</td>
<td>0.325</td>
</tr>
<tr>
<td>COPD</td>
<td>1(1.8%)</td>
<td>75(5.3%)</td>
<td>0.206</td>
</tr>
<tr>
<td>HIV</td>
<td>9 (16.1%)</td>
<td>253(17.7%)</td>
<td>0.458</td>
</tr>
<tr>
<td>Cancer</td>
<td>4(7.1%)</td>
<td>99(6.9%)</td>
<td></td>
</tr>
<tr>
<td>ESRF</td>
<td>11(19.6%)</td>
<td>251(17.6%)</td>
<td>0.401</td>
</tr>
<tr>
<td>Previous or current antibiotic use</td>
<td>46 (82.1%)</td>
<td>565(39.6%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Sepsis</td>
<td>40(71.4%)</td>
<td>436(30.6%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Vasopressor support (Septic shock)</td>
<td>13(23.2%)</td>
<td>144(10.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Steroid use</td>
<td>27(48.2%)</td>
<td>431(30.2%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Central line</td>
<td>30(53.6%)</td>
<td>267(18.7%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>7(12.5%)</td>
<td>29(2.0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Candida in endotracheal aspirate/sputum culture</td>
<td>13(23.2%)</td>
<td>112(7.8%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Candida in urine culture</td>
<td>34(60.7%)</td>
<td>262(18.4%)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 2 shows that 57.1% of Candida BSI were caused by C. Albicans, 30.4% by C. Glabrata and 12.5% by C. Parapsilosis. This incidence rate of species is similar to that found in other studies. Table 3 shows the two models with the lowest AIC value. The only difference between these two models was antibiotic use- previous or current use of antibiotics compared to current use of antibiotic in sepsis. Table 4 shows that when multifocal site positivity (urine and endotracheal culture) were used in the model, the AIC value increased significantly. This means that when multifocal sites were used in place of individual sites for the model, good amounts of information were lost and this model did not have good predictive value as compared to the model where individual sites are used for prediction of candidaemia. The model with lowest AIC was chosen as the final model. Binary logistic regression analysis with forward conditional analysis showed that only TPN, central venous line, previous or current antibiotic use,
endotracheal aspirate culture positivity for Candida species and urine culture positive for Candida species were included in a statistical significant model. The final model had a P value of 0.000. Odds ratio with 95% confidence intervals and respective P values for all these risk factors are shown in Table 5. Age greater than 65 years, sex, sepsis or septic shock, co-morbidities and steroid use were not significant risk factors for candidaemia.

From this model, the candidaemia risk score calculated would be: Candidaemia risk score = 1.184 for previous or current antibiotic use + 0.639 for presence of central venous line + 1.186 for total parenteral nutrition + 0.760 for positive endotracheal culture for Candida + 1.255 for positive urine culture for Candida.

Table 6 shows the relationship between the Candida strain identified in endotracheal/sputum culture to that in blood culture. Similarly, Table 7 shows the relationship between the Candida strain identified in urine culture and that in blood culture. Strains identified in endotracheal aspirate culture had a very high value for the Kappa test and urine culture had a moderate value for agreement by the Kappa test. Thus, it can be inferred that Candida strain identified in blood culture was very similar to that identified in urine or endotracheal culture.

Table 2: Candida strains responsible for Candida blood stream infection

<table>
<thead>
<tr>
<th>Species in the blood culture</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida Albicans</td>
<td>32(57.1%)</td>
</tr>
<tr>
<td>Candida Glabrata</td>
<td>17 (30.4%)</td>
</tr>
<tr>
<td>Candida Parapsilosis</td>
<td>7 (12.5%)</td>
</tr>
</tbody>
</table>

Table 3: Models with lowest two AIC

<table>
<thead>
<tr>
<th>Variables</th>
<th>-2 log likelihood</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous or current antibiotic use CVP line Total parenteral nutrition Endotracheal culture Urine culture</td>
<td>394.822</td>
<td>406.822</td>
</tr>
<tr>
<td>CVP line Total parenteral nutrition Endotracheal culture Urine culture Current antibiotic use in sepsis</td>
<td>395.730</td>
<td>407.73</td>
</tr>
</tbody>
</table>

Table 4: Model with 2 sites positive for Candida

<table>
<thead>
<tr>
<th>Variables</th>
<th>-2 log likelihood</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis CVP line Total parenteral nutrition Endotracheal and urine culture</td>
<td>407.920</td>
<td>417.92</td>
</tr>
</tbody>
</table>

Discussion

Candida is the most common nosocomial fungal infection in the ICU. Candidaemia accounts for approximately 5-8% of nosocomial BSI in the hospitals in the US.9,10,11 It accounts for approximately 50-75% of the cases of invasive fungal infection in the ICU12,13 and its rate varies from 0.2-1.73 per 1000 patient days.9,14,15 In a study done by Theoklis et al., candidaemia was associated with a mean 10.1 day increase in length of stay and a mean $39,331 increase in hospital charges.16 A study of 1,765 patients in Europe found that Candida colonisation was associated with increased hospital length of stay and increase in cost of care by 8000 EUR.17 ICU patients are at increased risk of infection because of their underlying illness requiring ICU care, immunosuppressant use, invasive or surgical procedures and nosocomial transfer of infections. A number of risk factors have been identified in different studies. In a matched case-control trial, previous use of antibiotic therapy, Candida isolated at other sites, haemodialysis and presence of a Hickman catheter were associated with increased risk of candidaemia.18 Similarly age of more than 65
days after colonisation according to two studies.3,12,16,20 Even with treatment, there is high mortality as demonstrated in a study by Oude Lashof et al where out of 180 patients treated for candidaemia, 33% died during treatment and 55% completed treatment without complications.21 Risk factors for increased mortality in patients receiving antifungal treatment are delayed Candida antifungal treatment or inadequate dosing.22 Multivariate analysis of 157 patients with Candida BSI, APACHE II score, prior antibiotic treatment and delay in antifungal treatment were independent risk factors for mortality with odds ratio of 1.24, 4.05 and 2.09, respectively.23 Delayed treatment is also associated with increased fluconazole resistance as compared to early treatment and preventive treatment.24 Inadequate antifungal medication dose and retention of central venous catheters were also associated with increased mortality in a study of 245 Candida BSI, with adjusted odds ratios of 9.22 and 6.21, respectively.25,26

Candida albicans accounts for 38.8-79.4% of the cases of candidaemia in the US.32 Candida colonisation increases with the duration of ICU stay, use of urinary catheters and use of antibiotics.33,35,36 In another study, only 25.5% of colonised patients developed candidaemia within a mean time of 5-8 days after colonisation according to two studies.35,36 In another study, only 25.5% of colonised patients developed candidaemia.37 Similarity between strain identified in blood culture and that identified at various colonising sites was observed in one study.38 Candida colonisation by exogenously acquired species has also been implicated as a cause of candidaemia.39 In one study, 18-40% of cases of candidaemia were associated with clustering defined as “isolation of 2 or more strain with genotype that had more than 90% genetic relatedness in the same hospital within 90 days.”40 Similar correlations for clusters are also noted for C. tropicalis candiduria41 and for C. Parapsilosis.42 In a prospective study of 29 surgical ICU patients colonised with Candida, the APACHE II score, length of previous antibiotic therapy and intensity of Candida colonisation were associated with a significant risk of candidaemia. The Candida colonisation index calculated by

Candida BSI has a very high mortality rate. The attributable mortality varies from 5-71% in different studies.3,12,16,20 Other studies do not support Candida colonisation as a risk factor for candidaemia. In a case-control study of trauma patients, only total parenteral nutrition was associated with an increased risk of candidaemia.43 Early detection of Candida BSI in a colonised patient can be facilitated by using a score based on the risk factors.45 Similarly, b-D glucan assays can be used in patient
colonised with Candida, to determine Candida BSI and need for antifungal treatment. Combined use of such risk factor identification systems and b-D glucan assays will help to detect candidaemia in earlier stages and will decrease mortality. Our study suggests that total parenteral nutrition, previous or current antibiotic use, central lines, candiduria and respiratory tract colonisation are risk factors for Candida BSI. With the help of our candidaemia risk score system, a score of more than 2 is associated with a higher risk of Candida BSI. This risk factor scoring system along with b-D glucan assays can be used to detect Candida BSI in earlier stages.

Conclusion:

Our study suggests that urine or respiratory tract colonisation is associated with an increased risk of Candida BSI, along with total parenteral nutrition, central venous lines and previous or current antibiotic use. We identified a scoring system which can be used along with a b-D glucan assay to detect candidaemia earlier.

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None

Competing Interests

None

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