



THE INCIDENCE OF CANDIDEMIA AMONG PATIENTS RECEIVING TOTAL PARENTERAL NUTRITION (TPN): A SINGLE-CENTER STUDY

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ABSTRACT

Objective: Hospitalized patients receiving Total Parenteral Nutrition (TPN) are at risk of developing several nosocomial infections, and namely candidemia. This study aimed to estimate this incidence in single center in Saudi Arabia, and to explore potential risk factors.

Methods: A retrospective review including all patients admitted to King Abdulaziz University Hospital in Jeddah, Saudi Arabia, between 2014 and 2015, and who were on TPN.

Results: One hundred and sixteen patients were included in this study. Male patients constituted (62.1%), and with a mean age of (55.6 ± 18.4) years. The incidence of candidemia was (11.2%). TPN duration was significantly longer in patients who tested positive for candidemia (26.1 ± 21.2 days), when compared to those who tested negative (14.2 ± 11.7 days; P = 0.002). Regarding risk factors; a history of solid organ malignancy, or being on corticosteroids prior to TPN were both significantly associated with being positive for candidemia (P=0.004 & P=0.019, respectively).

Conclusion: Hospitalized patients receiving TPN are at risk of candidemia, especially those on prolonged TPN or those on corticosteroids. Patients on TPN should be managed by a specialized and dedicated nutritional support team.

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INTRODUCTION

Candidemia is one of the most common nosocomial infections worldwide¹⁻⁵ and is considered a major cause of morbidity and mortality⁵⁻⁷. In Saudi Arabia, a recent increase in the incidence of candidemia among hospitalized patients was significantly associated with malignancy, admissions to the intensive care unit, the use of broad-spectrum antibiotics or corticosteroid therapy, and receipt of total parenteral nutrition (TPN).⁸⁻¹⁰

TPN refers to the nutrition provided exclusively via an intravenous route, when other means of feeding are not suitable for the patient's condition, or when other means are not providing optimal nutritional requirements¹¹. Despite the many benefits of TPN, it has also been reported to carry a considerable risk of mechanical, metabolic, and infectious complications^[11,12]; in addition, while TPN is recognized as an important risk factor of nosocomial candidemia, it is still widely used among hospitalized patients¹³⁻¹⁶. Thus, prior to considering TPN, it is crucial to thoroughly assess the patient's

needs and the suitability of TPN according to guidelines for the use of parenteral nutrition^{11,12}.

Limited literature supports the use of prophylactic antifungal medications in critically ill patients, namely those receiving TPN; in particular, there is no clear definition for high-risk patients in need of antifungal prophylaxis, and there is the possibility of organism-resistance to these agents¹⁷. Therefore, to improve patient care and minimize the risks of hospital-acquired candidemia, it is imperative to understand the infectious risks of TPN¹⁸. The purpose of this retrospective study was to 1) estimate the rate of candidemia among critically adult patients receiving TPN admitted to the intensive care unit (ICU) at the university hospital and 2) identify potential TPN-associated risk factors for candidemia.

MATERIALS AND METHODS

This was a retrospective review involving all hospitalized patients at the hospital in Saudi Arabia who were receiving TPN during their hospital stay during the years 2014 and 2015.

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Pediatric patients, adult patients who received TPN for less than 72 hours, those who received anti-fungal therapy prior to TPN initiation, and patients with pre-existing candidemia within 6 weeks prior to TPN initiation were excluded. The study was approved by the ethical and technical committee at King Abdulaziz University, and all other administrative authorizations were obtained before the start of data collection.

At King Abdulaziz University Hospital, parenteral nutrition (PN) prescriptions are requested using an electronic order form, completed by members of the attending medical team, who are of variable experience and competency in nutritional assessment and appropriate use of TPN. The hospital's pharmacy compounds the prescribed solution under strict aseptic technique, in accordance with international standards. Typically, PN is administered as a 2-in-1 dextrose-amino acid solution, with or without an intravenous soybean-based fat emulsion infused separately. Since peripheral PN is usually avoided, patients typically receive the prescribed solutions through a centrally or peripherally inserted central catheter (PICC) line.

A data collection sheet was developed to collect relevant patient information including the following: A) demographic data such as age, sex, weight, and body mass index (BMI); B) clinical profile including serum albumin level at admission, length of hospital stay, history of ICU admission, and incidence of 28-day mortality. We also collected data on significant medical conditions such as diabetes mellitus, dialysis, abdominal surgeries (all during the same admission), immunosuppression (defined as an absolute neutrophil count $< 2000/\text{mm}^3$ of blood), hematological malignancies, solid malignancies, liver disease, and the usage of steroids and antibiotics prior to TPN initiation; C) history of TPN including date and site of TPN initiation (i.e., in ICU or hospital ward), TPN duration in days, vascular access for TPN administration (a PICC line or a central line); and D) history of *Candida* infection, i.e., evidence of candidemia, source of blood isolation (central vs. peripheral), isolation of *Candida* in other cultures (e.g., urine, respiratory droplets), and the isolated subtypes of *Candida*.

To collect the above information, a list of all TPN prescriptions dispensed during the years 2014 and 2015 was retrieved from the pharmacy department, with patients' medical record numbers. Regarding candidemia information, a corresponding patient list was prepared, in collaboration with the clinical microbiology laboratory using the above medical record number, to compare data on *Candida* isolation. The identification of candidemia followed the standard protocol used at KAUH, as follows. Blood cultures were performed using an automated blood culture system (BacT/Alert, Organon, Teknika, USA). Five milliliters of blood was inoculated into a single pediatric bottle and loaded into the blood culture system, and it remained there until either designated positive or for a maximum of 5 days of incubation. Samples from all bottles designated positive were Gram stained, and those found positive for yeast cells were subcultured on Sabouraud dextrose agar. The yeasts were identified using VITEK MS (bioMerieux, Inc., France) on the same day of sufficient growth on Sabouraud dextrose agar; the identification was confirmed using the VITEK $\text{\textcircled{R}}$ 2 system, and the yeasts then underwent antifungal-susceptibility testing.

Descriptive statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA),

version 22. Categorical data were presented as counts and frequencies, while continuous data were presented as means and standard deviations. The chi-squared and independent t-tests were used to test for differences between groups. A p-value < 0.05 was set as statistically significant.

RESULTS

One hundred and sixteen patients were included in this study (male, $n = 72$ [62.1%]; female, $n = 44$ [37.9%]; mean age, 55.6 ± 18.4 years; mean body weight, 64.1 ± 18.1 kg; BMI, 24.9 ± 6.1 kg/m^2 ; mean serum albumin, 25.6 ± 7.9 g/dL). Additional characteristics of the study population are provided in Table 1. Of the 116 TPN cases, 13 patients (11.2%) were positive for candidemia. Those with candidemia experienced non-significantly longer hospital stays than those without candidemia (74.5 ± 85.2 vs. 51.3 ± 73.1 , respectively, $P = 0.159$). Of those with candidemia, 61.5% were admitted to the ICU, while only 43.7% of patients without candidemia had a history of ICU admission ($P = 0.223$). Moreover, more than half (53.8%) of the patients receiving TPN with candidemia started TPN in the ICU, whereas less than one-third (30.1%) of those without candidemia started TPN in the ICU. Neither ICU admission nor the start of TPN in the ICU was associated with increasing rates of candidemia. TPN duration was significantly longer in patients with candidemia (26.1 ± 21.2 days) than in those without candidemia (14.2 ± 11.7 days; $P = 0.002$). On the other hand, the candidemia incidence in relation to TPN site showed no difference between patients with and without candidemia ($P = 0.695$). The 28-day mortality rate for the total included sample was 17.2% ($N = 20$). Of these, three patients tested positive for candidemia, whereas the remaining 17 patients tested negative ($P = 0.554$) (Table 2).

For patients with candidemia, the organism was isolated from different TPN sites as follows: PICC line (53.8%), central line (38.5%), and both lines (7.7%). Of those testing positive, *Candida* was isolated in cultures other than blood for eight patients (Figure 1A); of these eight patients, six (46.1%) were negative in other tissues, one (7.7%) was positive in urine, and one (7.7%) was positive in other tissues. The distribution of *Candida* subtypes isolated is shown in Figure 1B.

Regarding the possible risk factors for candidemia, having a medical history of solid organ malignancy and being on corticosteroids prior to TPN were significantly associated with candidemia ($P = 0.004$ and $P = 0.019$, respectively). On the contrary, diabetes, dialysis, immunosuppression, history of hematological malignancy or liver disease, and antibiotic usage prior to TPN were not associated with candidemia.

Table 1 Patient characteristics and medical history

| Characteristics | Total | (+ ve) | (- ve) | P-value |
|--------------------------------|-----------------|---------------------------------|----------------------------------|---------|
| | | Candidemia N = 13 (11.2%) | Candidemia N = 103 (88.8%) | |
| | | Mean \pm SD | Mean \pm SD | |
| Age (y) | 55.6 \pm 18.4 | 54.5 \pm 16.0 | 55.7 \pm 18.6 | 0.559 |
| Weight (kg) | 64.1 \pm 18.1 | 66.5 \pm 17.3 | 65.2 \pm 18.2 | 0.896 |
| BMI (kg/m^2) | 24.9 \pm 6.1 | 23.8 \pm 6.3 | 25.0 \pm 6.1 | 0.697 |
| Serum albumin (g/dL) | 25.6 \pm 7.9 | 20.1 \pm 6.9 | 26.3 \pm 7.8 | 0.045 |
| Characteristics | Total | N (%) | N (%) | P-value |
| | | Sex | | |
| Male | 72 (62.1%) | 7 (53.8%) | 65 (63.1%) | 0.517 |
| Female | 44 (37.9%) | 6 (46.2%) | 38 (36.9%) | |
| | | Diabetes | | |
| Yes | 35 (30.2%) | 3 (23.1%) | 32 (31.1%) | 0.554 |
| No | 81 (69.8%) | 10 (76.9%) | 71 (68.9%) | |

| | | | | |
|--|-------------|------------|-------------|-------|
| <i>On dialysis</i> | | | | |
| Yes | 4 (3.4%) | 1 (7.7%) | 3 (2.9%) | 0.373 |
| No | 112 (96.6%) | 12 (92.3%) | 100 (97.1%) | |
| <i>Immunosuppressed/neutropenia</i> | | | | |
| Yes | 13 (11.2%) | 1 (7.7%) | 12 (11.7%) | 0.670 |
| No | 103 (88.8%) | 12 (92.3%) | 91 (88.3%) | |
| <i>PMH-abdominal surgery</i> | | | | |
| Yes | 78 (67.2%) | 6 (46.2%) | 72 (69.9%) | 0.086 |
| No | 38 (32.8%) | 7 (53.8%) | 31 (30.1%) | |
| <i>PMH-hematological malignancy</i> | | | | |
| Yes | 0 (0%) | 0 (0%) | 0 (0%) | ----- |
| No | 116 (100%) | 13 (100%) | 103 (100%) | |
| <i>PMH-solid organ malignancy</i> | | | | |
| Yes | 62 (53.4%) | 2 (15.4%) | 60 (58.3%) | 0.004 |
| No | 54 (46.6%) | 11 (84.6%) | 43 (41.7%) | |
| <i>PMH-liver disease</i> | | | | |
| Yes | 8 (6.9%) | 1 (7.7%) | 7 (6.8%) | 0.904 |
| No | 108 (93.1%) | 12 (92.3%) | 96 (93.2%) | |
| <i>Corticosteroid use prior to TPN</i> | | | | |
| Yes | 31 (26.7%) | 7 (53.8%) | 24 (23.3%) | 0.019 |
| No | 85 (73.3%) | 6 (46.2%) | 79 (76.7%) | |
| <i>Antibiotics use prior to TPN</i> | | | | |
| Yes | 102 (87.9%) | 12 (92.3%) | 90 (87.4%) | 0.607 |
| No | 14 (12.1%) | 1 (7.7%) | 13 (12.6%) | |

PMH, Past Medical History; TPN, total parenteral nutrition

Table 2 Association of total parenteral nutrition with admission to the intensive care unit

| Characteristics | Total | (+ ve) | (- ve) | P-value |
|-----------------------------|-------------|---|--|---------|
| | | Candidemia N = 13 (11.2%) Mean ± SD | Candidemia N = 103 (88.8%) Mean ± SD | |
| Length of hospital stay (d) | 53.9 ± 75.2 | 74.5 ± 85.2 | 51.3 ± 73.1 | 0.159 |
| TPN duration (d) | 15.6 ± 13.6 | 26.1 ± 21.2 | 14.2 ± 11.7 | 0.002 |
| Characteristics | Total | N (%) | N (%) | P-value |
| <i>ICU Admission</i> | | | | |
| Yes | 53 (45.7%) | 8 (61.5%) | 45 (43.7%) | 0.223 |
| No | 63 (54.3%) | 5 (38.5%) | 58 (56.3%) | |
| <i>TPN started in ICU</i> | | | | |
| Yes | 38 (32.8%) | 7 (53.8%) | 31 (30.1%) | 0.086 |
| No | 78 (76.2%) | 6 (46.2%) | 72 (69.9%) | |
| <i>TPN site</i> | | | | |
| PICC | 39 (33.6%) | 5 (38.5%) | 34 (33.1%) | 0.695 |
| Central | 77 (66.4%) | 8 (61.5%) | 69 (66.9%) | |
| <i>28-day mortality</i> | | | | |
| Yes | 20 (17.2%) | 3 (23.1%) | 17 (16.5%) | 0.554 |
| No | 96 (82.8%) | 10 (76.9%) | 86 (83.5%) | |

SD, standard deviation; TPN, total parenteral nutrition; ICU, intensive care unit; PICC, peripherally inserted central catheter

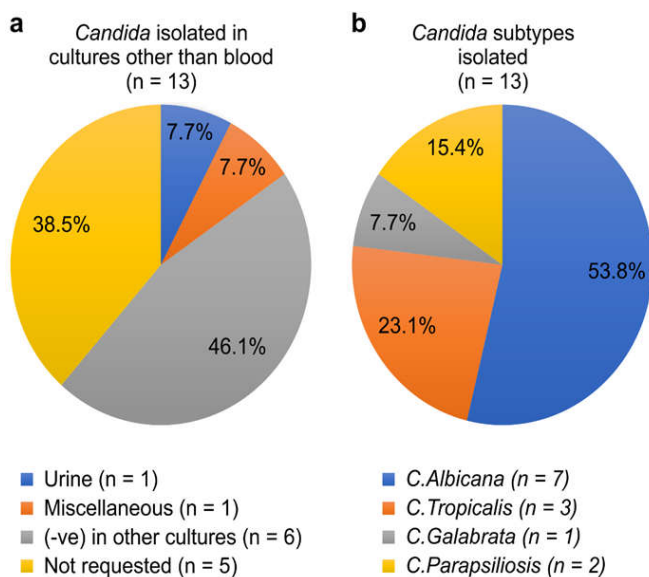


Figure 1 Candida subtypes isolated

DISCUSSION

PN can be appropriately utilized for hospitalized patients who are malnourished or at risk of malnutrition, namely when oral or enteral nutrition is not feasible or may not be tolerated. However, this method of nutritional support is commonly associated with bloodstream infections (BSIs), primarily those related to use of a central venous catheter. In fact, PN therapy has been shown to be an independent risk factor for central venous catheter-related infections¹⁹. A retrospective study from a single center in Australia reported a BSI incidence of 10.0/1000 PN days²⁰. Candidemia is of a special concern because of its high morbidity and mortality risks, especially if diagnosis and administration of appropriate anti-fungal therapy is delayed. For the above Australian cohort, *Candida* was the most frequently identified organism, and excessive delays in administration of antifungal therapy were revealed²⁰.

Another observational retrospective study assessed the incidence of and risk factors for candidemia in 286 recipients of PN in a tertiary medical center. In that study, 4.9% of these patients suffered from new-onset candidemia, an incidence rate of 1.6 episodes per 1000 hospital-days¹⁷. It was suggested that a guideline-directed PN may have tended to select more severely ill patients, who were already at high risk of candidemia. The setting of this prior study was similar to that of the current study, where the decision regarding PN provision is based on guidelines, is made by any member of the interdisciplinary attending team, and is not necessarily under the supervision of a dedicated nutritional support team. The latter may explain the relatively higher rate of candidemia (11.2%) detected among the current cohort of patients.

In general, predisposing factors for BSIs while receiving PN can be classified into the following categories: patient-related (e.g., current clinical status or co-morbidities), catheter-related, or PN composition-related. For the first group of factors, an increased disease severity was associated with increased candidemia risk. In a study by Stratman *et al.*, 83% of PN recipients with candidemia were categorized as “of a major or an extreme illness severity”¹⁷. Although our study did not record disease severity scores, a significant increase in the incidence of candidemia was noted among patients with lower serum albumin and those on corticosteroid therapy, both of which may reflect a more acute and severe disease status. Regardless, admission to the ICU, another possible predictive sign of condition severity, was not associated with a higher risk of candidemia. On the contrary, malnutrition is considered a risk factor for central venous catheter-related infections, as noted with the lower serum albumin for candidemia-positive patients; nevertheless, serum albumin is not a reliable indicator of patient nutritional status in acute settings²¹.

Duration of PN infusion is an important risk and possibly an independent risk factor for catheter-related BSIs, including candidemia^{14,17,22-24}. This may be partially due to the increased colonization risk associated with prolonged catheterization, especially when multi-lumen catheters are inserted in urgent situations, without being replaced in a timely manner²³. On the contrary, rates of colonization are usually lower when single-lumen catheters are solely used for PN²⁵. Another prospective study among non-critical patients showed that being on PN for more than 14 days was the only independent risk factor for developing BSIs²⁶. Moreover, a case control study focusing on nosocomial candidemia in elderly patients found a strong association between receiving PN for more than 7 days with a

higher candidemia risk²². Consistent with this previous study, candidemia in the present study was associated with longer PN duration. Thus, reducing the duration of PN should be considered as soon as resuming oral and/or enteral feeding is feasible.

Hyperglycemia is associated with several adverse outcomes in patients receiving PN, including severe sepsis²⁷. In a study by Townell *et al.*²⁰, *Candida* was the most common pathogen isolated from patients receiving PN, and insulin infusion (a marker of sustained hyperglycemia) was identified as a risk factor for developing PN-associated BSIs²⁰. For our patients, diabetes was not associated with higher risks of candidemia; however, although blood glucose levels were not recorded, patients who were on corticosteroids (a risk factor for hyperglycemia) prior to receiving PN experienced a higher incidence of candidemia. Interestingly, the most common cause of hyperglycemia is excess dextrose infusion and overfeeding, which is more likely to occur when PN is not supervised and is managed by a dedicated nutritional support team. Current guidelines recommend a target blood glucose range of 140 or 150–180 mg/dL for the general ICU population²⁸. The latter can be achieved by limiting dextrose infusion rates in patients at risk, proper monitoring, and the appropriate use of insulin.

We acknowledge the limitations of this study, which are mainly due to its retrospective design at a single center. The number of patients included did not allow for detecting differences in important risk factors such as diabetes, neutropenia, and type of venous access, nor did it allow examination of important outcomes such as length of ICU admission and hospital stay. Future prospective studies are needed to better identify risk factors for candidemia in TPN recipients and to understand the role of prophylactic therapy in high-risk patients.

CONCLUSIONS

The risk of candidemia in hospitalized patients receiving TPN is significant, especially for critically ill patients, those receiving corticosteroids, or those on prolonged TPN. Appropriate use of PN for the shortest necessary duration must be supervised by a professional nutrition team, with strict adherence to guidelines.

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