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# Mortality Patterns in Critically Ill Patients on Mechanical Ventilation with Candida Colonization of the Respiratory Tract with or without Gram-Negative Bacteria Ventilator-Associated Pneumonia in a Tertiary Hospital in Saudi Arabia

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## ABSTRACT

**Purpose:** Candida is often regarded as being non-pathogenic. Recent studies suggest that a high mortality exists among patients who have Candida and Gram-Negative Bacteria (GNB) Ventilator-Associated Pneumonia (VAP). This study determined mortality levels among patients with bronchial Candida colonization with or without GNB VAP. Mortality patterns between Candida albicans and non-albicans were also determined.

**Materials and Methods:** Critically ill patients on mechanical ventilation (MV) ≥ 48 hours enrolled from January to December 2019 were classified into four main groups based on tracheal aspirate culture (C. albicans only, C. albicans + GNB, C. non-albicans only and C. non-albicans + GNB.

**Results:** Mortality among the 173 patients was high and ranged from 50.0 % with C. albicans + GNB to 77.4 % with C. non-albicans + GNB. No significant difference in mortality occurred between compared groups except C. albicans + GNB versus C. non-albicans + GNB where a statistically significant odds ratio was found (2.73; 95 % confidence interval, 1.03-7.5; $p$ =0.025).

**Conclusions:** There is high mortality with Candida species colonization especially with concomitant GNB VAP. The highest mortality is with C. non-albicans. Further studies are needed to confirm this finding.


**Keywords**: Candida colonization; Mechanical ventilator; Ventilator-associated pneumonia; Gram-negative bacteria; Intensive care unit

## INTRODUCTION

There has been an increase in nosocomial fungal infections in the past two decades. This is considered problematic especially among Intensive Care Unit (ICU) patients [1]. Candida is an opportunistic pathogen that is typically observed among critically ill patients with compromising underlying conditions. This includes patients who endured multiple invasive procedures or patients who experienced prolonged hospitalization periods for various reasons including multiorgan failure [2]. Other factors such as diabetes mellitus, immunosuppressive therapy (including chemotherapy), and the overuse of extended spectrum antibiotics increased the risk for infections [3].

Candida species are frequently recovered from respiratory tract secretions in mechanically ventilated ICU patients. From a cohort study of 1,107 ICU patients with a median length of hospital stay of 17 days, 834 (75.3 %) were in the Candida species colonization group [4]. In another Canadian study done on ICU patients, 50 % of the patients grew positive Candida on respiratory or rectal cultures. The different Candida species from the respiratory or rectal cultures included *C. albicans* (72 %), *C. glabrata* (16 %), *C. tropicalis* (5 %), and *C. parapsilosis* (3 %) [5].

Of all Candida species, Candida albicans is the most pathogenic and most frequently identified in various candidiasis lesions in humans [6]. Over the last two decades, C. albicans was the most (80 %) recovered Candida species from patients with oral and systemic candidiasis. However, over the same period, the number of infections caused by non-albicans species has increased significantly [7].

Bronchial Candida species colonization is a common condition among critically ill patients [8,9]. Although Candida species are considered to be non-invasive and not usually implicated in pneumonia, in recent studies, there have been conflicting results [8-10]. A significant association between the presence of Candida species in the respiratory tract of patients and hospital mortality has been reported [11]. Candida colonization of the respiratory tract has also been implicated with bacteria Ventilator-Associated Pneumonia (VAP) [11]. Delislee, et al. [11] hypothesized that the presence of Candida species in respiratory tract secretions may explain the excess morbidity and mortality seen in critically ill patients with or without positive bacterial culture. Their conclusion suggests that the presence of Candida species in critically ill patients may be a pointer to the severity of disease. However, there is inadequate evidence on the hospital mortality among critically ill patients on Mechanical Ventilator (MV) with Candida in Saudi Arabia. Thus, the primary objective of this study was to determine the hospital mortality among critically ill patients on MV with respiratory tract culture of Candida species, with or without the presence of Gram-Negative Bacteria (GNB) and to determine whether mortality would differ between Candida albicans and non-albicans.

## MATERIALS AND METHODS

### Study setting

Approval for this study was obtained from the ethics committee of King Abdul-Aziz University Hospital and the Ministry of Education. This study was conducted at the Molecular and Clinical Microbiology Laboratory at a teaching tertiary hospital, Jeddah, kingdom of Saudi Arabia from January 2019 till December 2019.

### Study design

**Patients:** Patients who met the inclusion criteria were 173 critically ill patients who had been on MV for 48 hours or more. We excluded patients with fungemia (defined as the presence of fungi or yeasts in the blood) and patients on antifungal treatment The patients were classified into four main groups based on the presence of Candida species with or without GNB VAP in the patients' tracheal aspirate as follows: *C. albicans* alone group or *C. albicans* and GNB group or *C. non-albicans* alone group or *C. non-albicans* and GNB group

### Trachea aspirate culture procedure

a. Identification and susceptibility of bacteria isolated from tracheal aspirate samples: The trachea aspirate samples obtained from each patient were cultured for bacteria and fungi.

Each tracheal aspirate specimen was processed and cultured on Blood agar, MacConkey agar and Chocolate agar and Sabouraud Agar (SDA: Saudi Prepared Media Laboratories, Riyadh, Kingdom of Saudi Arabia). The cultured plates were incubated for 18 to 24 hours (MacConkey agar at 35-37°c in ordinary incubator (Forma

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Scientific Incubator, Germany). Blood agar and Chocolate agar plates were incubated at 35-37°c in 5-10 % CO2 incubator (Sanyo CO2 Incubator, Japan). The colonies were identified by gram staining for further identification and Antibiotic Sensitivity Testing (AST) of bacteria by Vitek ® 2 system (bioMerieux, Inc., France). The isolated pure colonies were selected and a purity plate was done to ensure that a pure culture was used for testing. Then, 3 ml of 0.45 % sterile saline was aseptically added into clear plastic test tube. A sufficient number of morphologically similar colonies were then transferred by a sterile loop to the saline tube and its density was checked by using Vitek 2 DensiCheck (bioMerieux, Inc., France) equivalent to 0.5 to 0.63 McFarland. The suspension tube was placed in the cassette, followed by an empty tube. The identification card was placed in the suspension tube and the AST card was placed in the empty tube. When the sample cycle was finished, the cassettes and the tubes were discarded. Minimal Inhibitory Concentration (MIC) was calculated and represented as (sensitive, intermediate or resistant). MIC of amikacin and meropenem with Acinetobacter baumannii were not done by Vitek 2 system, but done by E- test strips (bioMerieux SA, RCS LYON, Marcy-l´ Etolle, France).

The GNB identified included Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter cloacae, Enterobacter aerogenes, Stenotrophomonas maltophila, and Haemophilus influenza. Of the GNB, 37(60.7 %) were Multi-Drug Resistant (MDR).

b. Identification of yeast isolated from tracheal aspirate samples by API®20 C AUX: (bioMerieux, Inc., France)

A portion of yeast colonies was picked up from a young culture (18-24 h) on SDA and a suspension with a turbidity equal to 2 McFarland was prepared. Then 100 µl of this suspension was transferred to the ampule of the API C medium and homogenized by a pipette; they were then added into the cupules of each strip that contained the API suspension medium. The strip was incubated at 29°C ± 2°C for 48-72 hours and after that, the identification was done automatically by the ATB™/Mini API® instrument (bioMerieux SA, Marcy-l´ Etolle, France) using database (V4.0).

### Data collection

Patients' baseline characteristics, including age and underlying conditions as well as the baseline laboratory parameters were obtained from the patients' clinical records. The length of ICU stay, number of days on mechanical ventilation before culture and the number of days on prior anti-microbial treatment were recorded for each patient. To determine disease severity at ICU admission, the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) scoring system was used.

### Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 18 software. Continuous variables were presented as mean, standard deviation, and range. Categorical variables were reported in percentages. Chi-square test was utilized to test for the association and/or difference between categorical variables. Mortality outcomes among the C. albicans and non-albicans groups were reported as percentages and compared using chi square test. Mortality differences between C. albicans and non-albicans groups were determined between the following groups: C. albicans only versus C. albicans + GNB, non-albicans only versus non-albicans + GNB, C. albicans only versus non-albicans only as well as C. albicans + GNB versus non-albicans + GNB. Odds ratio and 95 % confidence interval were reported. P-values less than 0.05 were considered statistically significant.

## RESULTS

### Patients' demographic and clinical characteristics

Overall, 173 patients met the inclusion criteria and were enrolled from January 2019 till December 2019. The baseline demographic and clinical characteristics are shown in Table 1. The overall age ranged from 17 to 96 years and the majority, 105 (60.7 %) were males. Most common underlying diseases included diabetes mellitus, 82 (47.4 %) followed by heart diseases, 66 (38.2 %), length of ICU stay and APACHE score was similar among all groups as shown in table 1.

Mortality outcomes among *C. albicans* and non-albicans groups

In table 2, mortality was least with 50.0 % among the C. albicans + GNB group while the highest mortality occurred with 77.4 % among the C. non-albicans + GNB group. More than half (55.9 %) and (58.5 %) mortality occurred among the *C. albicans* and the *C. non-albicans* only groups respectively. There were no significant differences

**Table 1:** Patients baseline demographic and clinical characteristics by *C. albicans* or non - albicans groups.

| | C. albicans alone group | C. albicans and GNB group | Non - albicans alone group | Non - albicans and GNB group |
|---|---|---|---|---|
| | n= 59 (%) | n= 30 (%) | n= 53 (%) | n= 31 (%) |
| Age | (17 - 90) | (17 - 96) | (15 - 89) | (23 - 84) |
| Range Mean ± SD | 56.13 ± 19.29 | 60.37 ± 17.05 | 57.39 ± 18.8 | 60.96 ± 15.52 |
| Sex | | | | |
| Male | 27 (45.8 %) | 22 (73.3 %) | 35 (66 %) | 21 (67.6 %) |
| Female | 32 (54.2 %) | 8 (26.7 %) | 18 (34 %) | 10 (32.3 %) |
| Underlying diseases COPD | 3 (5.2 %) | 1 (3.3 %) | 1 (1.9 %) | 3 (9.7 %) |
| Chronic renal impairment | 13 (22 %) | 8 (26.7 %) | 14 (26.4 %) | 9 (29 %) |
| Heart diseases | 22 (37.3 %) | 12 (40 %) | 21 (39.6 %) | 11 (35.5 %) |
| Liver diseases | 2 (3.4 %) | 1 (3.3 %) | 1 (1.9 %) | 2 (6.5 %) |
| Surgical operations | 13 (22 %) | 1 (3.3 %) | 7 (13.2 %) | 1 (3.2 %) |
| Diabetes Millitis | 21 (35.6 | 15 (50 %) | 26 (49.1 %) | 20 (64.5 %) |
| Immunosuppression | 10 (16.9 %) | 1 (3.3 %) | 3 (5.7 %) | 4 (12.9 %) |
| Stroke | 5 (8.5 %) | 1 (3.3 %) | 4 (7.5 %) | 0 (0 %) |
| No of days of ICU stay | 4.57 ± 5.46 | 10.16 ± 21.5 | 3.56 ± 5.05 | 6.9 ± 8.59 |
| Mechanical ventilation before culture | 50 (84.1 %) | 20 (66.6 %) | 32 (60.4 %) | 17 (54.8 %) |
| Mean ± SD (days) | 4.2 ± 5.53 | 9.9 ± 21.6 | 3.13 ± 5.26 | 6.38 ± 8.88 |
| Prior anti - microbial treatment | 55 (93.2 %) | 25 (83.3 %) | 34 (64.2 %) | 21 (67.7 %) |
| Mean ± SD (days) | 8.13 ± 11.88 | 10.76 ± 19.80 | 4.24 ± 6.23 | 7.58 ± 10.16 |
| Apache score | 9–32 | 12–33 | 13–31 | 17–34 |
| Range Mean ± SD | 20.74 ± 6.16 | 20.86 ± 4.19 | 20.47 ± 4.61 | 23.24 ± 4.6 |

COPD: Chronic Obstructive Pulmonary Diseases; GNB: Gram Negative Bacteria; ICU: Intensive Care Unit; SD: Standard Deviation.

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**Table 2:** Mortality outcomes among the patient groups.

| | Deceased n=103 n (%) | Survived n=70 n (%) | $\chi^2$ | P - value | 95 % CI | Mean ± SD of day till death | 28 days Mortality n (%) |
|---|---|---|---|---|---|---|---|
| C. albicans alone group n= 59 | 33 (55.9) | 26 (44.1) | 0.28 | 0.59 | 0.80 (0.40 - 1.59) | 15.24 ± 10.65 | 30 (90.9) |
| C. albicans and GNB Group n= 30 | 15 (50) | 15 (50) | 0.99 | 0.31 | 0.62(0.26 - 1.46) | 25.66 ± 23.67 | 10 (66.7) |
| C. non - albicans alone group n= 53 | 31 (58.5) | 22 (41.5) | 0.03 | 0.85 | 0.90(0.42 - 1.84) | 13.35 ± 13.73 | 26 (83.9) |
| C. non - albicans and GNB n= 31 | 24 (77.4) | 7 (22.6) | 4.98 | 0.025* | 2.73(1.03 - 7.5) | 13.54 ± 10.55 | 20 (83.3) |

$\chi^2$ Chi square statistical test; CI: Confidence Interval; GNB: Gram-Negative Bacteria; n: Sample Size

between those who died and those who survived with *C. albicans* only, Odds Ratio (OR), 0.80; 95 % Confidence Interval [CI], 0.4-1.59; $p = 0.59$, *C. albicans* + GNB OR, 0.62; 95 % CI, 0.26-1.46; $p = 0.31$) as well as non-albicans only OR, 0.90; 95 % CI, 0.42-1.84; $p = 0.85$. However, the chi square test showed a significant difference between those who died and those who survived with C. non-albicans + GNB OR, 2.73; 95 % CI, 1.03-7.5; $p = 0.025$

Mortality differences between *C. albicans* and non-albicans groups with $\chi^2$ and *p*-value

In table 3, the findings of the comparison between groups are shown. No significant differences occurred when *C. albicans* only versus *C. albicans* + GNB or non-albicans only versus non-albicans + GNB or *C. albicans* only versus non-albicans only were compared. However, the comparison of mortality between only two groups (C. albicans + GNB versus C. non-albicans + GNB) showed statistically significant difference ($p < 0.05$).

**Table 3:** Mortality differences between C. albicans and non - albicans groups with $\chi^2$ and $p$ – value.

| | Deceased n=103 (%) | Survived n=70 (%) | $\chi^2$ | P value |
|---|---|---|---|---|
| Albicans alone (n=59) | 33 (55.9 %) | 26 (44.1 %) | 0.28 | 0.99 |
| Albicans + GNB (n=30) | 15 (50 %) | 15 (50 %) | | |
| Non albicans alone (n=53) | 31 (58.5 %) | 22 (41.5 %) | 3.1 | 0.78 |
| Non albicans + GNB (n=31) | 24 (77.4 %) | 7 (22.6 %) | | |
| Albicans alone (n=59) | 33 (55.9 %) | 26 (44.1 %) | 0.07 | 0.78 |
| Non albicans alone (n=53) | 31 (58.5 %) | 22 (41.5 %) | | |
| Albicans + GNB (n=30) | 15 (50 %) | 15 (50 %) | 4.97 | 0.025* |
| Non albicans + GNB (n=31) | 24 (77.4 %) | 7 (22.6 %) | | |

*$p < 0.05$; $\chi^2$ Chi square statistical test; GNB: Gram-Negative Bacteria; n: Sample Size.

## DISCUSSION

Candida colonization remains a dilemma among mechanically ventilated patients. The primary objective of our study is to determine the mortality among ventilated patients with Candida colonization, with or without the presence of GNB and to determine mortality differences among different Candida species groups.

Based on the four groups of patients studied, we observed high mortality with Candida species colonization with *C. albicans* only group and the non-albicans only group (55.9 % and 58.5 % respectively). This same finding has been observed in other studies. Hamet, et al. [12] found that mortality was significantly higher in mechanically ventilated patients colonized with Candida (44 %) versus controls (31 %) [12]. Other studies showed similar higher mortality findings among patients with Candida colonization (43 % and 34 %) and controls (36 % and 21 %) by Azoulay, et al. [10] and Delisle, et al. [13] respectively. The consistency of findings persisted over the years as reported in 2011 by Delisle, et al. [11], among the same patient population with suspected VAP and no bacterial culture growth, but with Candida colonization, higher mortality even after controlling and adjusting for confounders persisted.

We found a very high mortality with Candida non-albicans + GNB in our study. From the findings of a few studies on the virulence factors of non-albicans, the mortality differences observed in our study among Candida species may be explained by their virulence factors. Biofilms is one of the virulence factors of Candida species. Deorukhkar, et al. [14] noted a greater biofilm forming ability in *C. tropicalis* compared to *C. albicans* while Pongracz, et al. [15] reported that C. non-albicans produce more biofilm than C. albicans. Biofilm formation protects Candida species against host defenses and also carries a significant resistance to antifungal therapy [16]. Significant antifungal activities have been reported in a study [17].

There is a high mortality observed in our study from the combination of fungi and bacteria. Evidence from previous studies showed that *C. albicans* protects bacteria from clearance by the host defense system and also enhances bacterial virulence [18]. There is a strong interaction between Candida, gram-positive bacteria and GNB through quorum sensing which explains the protective role that the Candida plays to the bacteria [19]. This might explain our finding of a high mortality with the combination of fungi and bacteria. It has also been demonstrated in many studies that Candida species colonization increases inflammation and is associated with poor clinical outcome [20-22]. However, similar findings have also been observed with other GNB VAP such as Pseudomonas. Azoulay, et al. [10] studied

colonized and non-colonized Candida in mechanically ventilated patients over four years and suggested that bronchial Candida colonization is an independent factor for pneumonia and the risk is greatest for Pseudomonas VAP [10,23]. In our study we found that 37(60.7 %) of GNB were Multi-Drug Resistant (MDR), 20 of them were associated with C. albicans and 17 of them were associated with Non-Albicans Candida (NAC). Hamet, et al. [12] reported similar findings that Candida colonization was an independent risk factor for MDR bacteria isolation.

We found that mortality is higher with Candida colonization in general and particularly in non-albicans + GNB VAP. Hence, it is essential to ensure that appropriate treatment modalities are sought to enhance survival and quality of life of these critically ill patients. Therefore, it is crucial to consider further studies on the possible role of treatment and whether this would result in reduced risk of colonization. Conflicting findings about the role of treatment with antifungal agents have been reported. Nasir, et al. [24] showed that antifungal treatment decreased the risk of Pseudomonas VAP in tracheobronchial Candida Colonized Patients. In another more recent study (the famous CANTREAT study) [25], with antifungal treatment, mortality and length of hospital stay were not reduced. Ong, et al. [26] studied nebulized antifungal treatment as a part of decolonization. They found that nebulized amphotericin B reduces the duration of Candida colonization but failed to improve clinical outcomes [26].

Although selective digestive decontamination in mechanically ventilated patients significantly decreased the colonization rate of GNB and of Candida species as demonstrated in many studies, the role remains unclear and hence not recommended in modern practice [27,28].

## STRENGTH AND LIMITATIONS

### Strength

The strength of our study comes from its unique design and that the study was positioned at a time period before the patients were placed on antifungal treatment. In addition, those with candidemia were excluded to ensure that mortality due to Candida could be directly estimated among critically ill patients on MV in our hospital.

### Limitations

Due to small sample size, we could not include the data on gram-positive bacteria + Candida. However, it was not thought that this would enhance the study much more. Another weakness of this study is the absence of histopathologic examination of enrolled patients. However, from a previous study among patients and in post-mortem studies, the incidence of invasive candidiasis were extremely low [29]. Since this study was done on mechanically ventilated patients with Candida colonization with or without GNB VAP, the clinical outcome found in this study population cannot be generalized to other patients including those with other respiratory diseases such as cystic fibrosis who are not mechanically ventilated.

## CONCLUSION

There is a high mortality rate with Candida species colonization especially with concomitant GNB VAP. The highest mortality occurred with C. non-albicans. To our knowledge, this is the first study from Saudi Arabia that assessed USCS mortality in mechanically ventilated patients colonized with Candida species + GNB VAP. Further studies are still needed to determine whether treating or decolonizing the respiratory tract with antifungal therapy will decrease GNB VAP, length of hospital stay or mortality.

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