

Candida spp. isolation from critically ill patients' respiratory tract. Does antifungal treatment affect survival?

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Abstract

Introduction Isolation of *Candida* spp. from bronchial samples of patients on mechanical ventilation is common. Even though it may not always reflect infection, it may induce immunological changes that can facilitate bacterial pneumonia. In this case, antifungal treatment is of uncertain value. This study examined the impact of antifungal treatment on the outcome of intensive care unit (ICU)-acquired respiratory tract infection (RTI) of critically ill, immunocompetent patients, with *Candida* isolation from their respiratory tract.

Methods This is a retrospective cohort study of adult patients hospitalized in the ICU of the University Hospital of Heraklion, Greece, from 2014 through 2016 with ICU-acquired RTI and *Candida* spp. isolated from their bronchial secretions. Data regarding medical history, demographics (gender, age), reason for ICU admission, previous antimicrobial use or hospitalization, SOFA and APACHE II score, clinical outcomes (primary clinical outcome: overall mortality during hospitalization; secondary clinical outcome: mortality during the ICU stay and duration of ICU and hospital stay) at the end of their ICU stay and at the end of their hospital stay were recorded and consequently evaluated. A logistic regression analysis model evaluated the effect of the recorded parameters in association with ICU mortality and overall mortality during hospitalization.

Results A total of 90 individuals were enrolled. Of them, 47 (52.2%) were treated with antifungals during their hospitalization around the time of *Candida* isolation. Patients treated with antifungals had higher SOFA and APACHE II scores, longer duration of stay in the ICU, more days on ventilator and higher total mortality during hospitalization. Multivariate logistic regression analysis identified antifungal use to be independently associated with total mortality during hospitalization.

Conclusions Antifungal use in patients with ICU-acquired RTI was associated with higher overall mortality as compared to those not receiving such agents.

Keywords *Candida*, colonization, critical care, antifungal, VAP, ICU.

Introduction

Isolation of *Candida* spp. from the bronchial samples of patients on mechanical ventilation (MV) is common. It is estimated to occur in about 30% of patients on MV for more than 2

days, and in about 50% of those suspected to have a ventilator-associated pneumonia (VAP).¹ Isolation of *Candida* spp. from respiratory tract samples is associated with increased duration of MV, increased intensive care unit (ICU) and

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hospital stay, as well as worse outcomes.^{2,4} Furthermore, *Candida* colonization of the respiratory tract may facilitate subsequent pneumonia, as shown in a study using a rat model colonized in the respiratory tract by *C. albicans* and subsequently infected by *Acinetobacter baumannii*.⁵ In that study, rats with their respiratory tract colonized by *C. albicans* developed experimental pneumonia more often, had higher bacterial loads and had lower interleukin 17 (IL-17) and higher gamma interferon (IFN- γ) concentrations in the lungs compared to controls.⁵ Another study showed that rats' respiratory tract colonization by *C. albicans* elicited a Th1-Th17 immune response, favoring the development of bacterial pneumonia by inhibiting bacterial phagocytosis by alveolar macrophages, while antifungal treatment decreased the risk of bacterial pneumonia.⁶ In another rat model, *C. albicans* colonization of the respiratory tract has been shown to impede alveolar macrophage reactive oxygen species production and was correlated with increased rates of *Pseudomonas aeruginosa* pneumonia.⁷

Candida pneumonia is rarely diagnosed due to difficulties in distinguishing colonization from infection. However, *Candida* may cause pneumonia in severely immunocompromised individuals either due to aspiration of *Candida* spp. colonizing the oral cavity or as part of disseminated candidiasis.⁸

There are data suggesting that *Candida* colonization of the respiratory tract may possibly facilitate the development of pneumonia.⁹ Although data are contradictory, co-colonization of the respiratory tract by both bacteria and fungi may augment the risk of infection, facilitate the development of pneumonia and increase the disease's severity.¹⁰ *Candida* can produce biofilm, which is a network of hyphae, pseudohyphae and

yeasts in a matrix of polysaccharides, proteins and other factors, resulting in the protection of fungi from host defenses and the development of antifungal resistance.¹¹ Within the biofilm, several interactions between fungi and bacteria through quorum sensing are possible, through a wide range of cell to cell communications and metabolic processes, leading to synergistic or antagonistic interactions.¹¹⁻¹⁴ For example, in an experimental model of rats injected with *C. albicans*, increased production of inflammatory mediators such as IL-6, TNF- α and IFN- γ led to inhibition of phagocytosis by alveolar macrophages leading to changes in airway microecology and increased likelihood of colonization by *P. aeruginosa*, while similar results also exist regarding increased colonization by *S. aureus* and Enterobacteriaceae.^{13,14} In another example, quorum sensing between *C. albicans* and *A. baumannii* leads to changes of morphology of *C. albicans* and changes in movement and production of virulence factors of *A. baumannii*, likely resulting in increased alveolar invasiveness of *A. baumannii* in mice colonized by *Candida*.^{5,12} However, critically ill patients with respiratory tract colonization by *Candida* receiving antifungal treatment, such as with aerosolized amphotericin B, have not had a lower risk for VAP, despite reduction of *Candida* colonization.¹⁵ Empirical antifungal treatment of patients with VAP and *Candida* respiratory colonization did not affect the diseases' outcome, while treatment with micafungin did not affect the risk of VAP in immunocompetent mechanically ventilated patients.^{16,17}

Moreover, colonization by *Candida* as well as antifungal treatment may alter the fungal microbiome of patients, and these alterations, along with further changes of the rest of the microbiome due to concomitant antimicrobial use may negatively affect patients' survival.¹⁸⁻²⁰ Thus, the effect of antifungal treatment of critically ill patients with *Candida* isolation from their respiratory secretions, remains uncertain.

The aim of this study was to examine the impact of antifungal treatment on outcome of critically ill immunocompetent patients, with ICU-acquired respiratory tract infection (RTI)

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and *Candida* spp. isolation from their respiratory tract.

Methods

Study population

This is a retrospective cohort study of adult patients hospitalized in the ICU of the University Hospital of Heraklion, Greece, from January 2014 through December 2016 with ICU-acquired RTI and *Candida* spp. isolation in their bronchial secretions. ICU-acquired RTI was defined as a new RTI in a patient hospitalized in the ICU for at least 48 hours. More specifically, eligibility criteria were the following: onset of symptoms after 48 hours of admission to the ICU and new or evolving infiltrate on chest X-ray or computerized tomography or lung ultrasonography along with auscultatory findings consistent with pneumonia/pulmonary consolidation (e.g., rales, dullness on percussion or bronchial lung sounds) or hypoxemia, new onset of cough or worsening of pre-existent hypoxemia or new onset need for mechanical ventilation along with fever of at least 38°C or elevated total peripheral white blood cell (WBC) count to more than 10,000/mm³ or leukopenia with a WBC count of less than 4,000/mm³. All previously immunocompetent adult patients hospitalized in the ICU for at least 48 hours that developed an ICU-acquired RTI and had *Candida* spp. isolated in their bronchial secretions [tracheal aspirate, sputum or bronchoalveolar lavage (BAL)] were included. Data regarding demographics (age, gender), medical history, reason for ICU admission, antimicrobial use during the previous month or hospitalization during the last three months, APACHE II and SOFA scores, antifungal treatment for any reason ± 10 days around *Candida* spp. isolation, clinical outcomes at the end of their ICU stay and at the end of their hospital stay were recorded and evaluated. The primary clinical outcome of this study was overall mortality during hospitalization, and the secondary outcome was mortality during the ICU stay and duration of ICU and hospital stay. Patients with previous immunosuppression (neutropenia, bone marrow or solid organ transplantation, corticosteroid treatment

consisting of >2 mg/kg of methylprednisolone or equivalent) were excluded.

The study was approved by the Ethics Committee of the University Hospital of Heraklion, Crete.

Microbiological methods

Samples of the lower respiratory tract (sputum, tracheobronchial aspirate and BAL) were collected for quantitative bacterial and fungal cultures. Only sputum and tracheal aspirates of high quality (i.e., with more than 25 leucocytes and fewer than 10 squamous epithelial cells per high-power field) were processed for culture. For the isolation of *Candida* spp., specimens were inoculated on Sabouraud dextrose agar supplemented with chloramphenicol (50 mg/mL) (Oxoid Limited, UK) and incubated at 36°C for 72 hours. Results were expressed as colony forming units (CFUs) per milliliter (mL) (CFU/mL). For BAL and sputum cultures the accepted threshold was $\geq 10^4$ CFU/mL and for endotracheal aspirate cultures it was $\geq 10^6$ CFU/mL. Identification to the species level was performed by sugar assimilation tests using the API 20 C AUX system and/or the Vitek 2 automated system (both BioMérieux, France). Susceptibility to antifungal agents was determined using the Vitek 2 system.

Statistics

Categorical data were analyzed with Fisher's exact test. Continuous variables were compared using Student's t-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. All tests were two-tailed and p-values <0.05 were considered significant. Data are presented as numbers (%) for categorical variables and median [interquartile range (IQR)] or mean [$\pm$ standard deviation (SD)] for continuous variables. A logistic regression analysis model was developed to evaluate the effect of gender, age, weight, body mass index (BMI), APACHE II and SOFA score on admission, prior hospitalization, prior surgery, antimicrobial use, tracheostomy, positive blood culture(s), antifungal agents used and duration of ICU stay with ICU mortality and overall

mortality during hospitalization. All were calculated with GraphPad Prism 6.0 (GraphPad Software, Inc., USA). A multivariate logistic regression analysis model was developed to evaluate the association of factors identified in the univariate analysis with a $p < 0.1$ with overall mortality in the hospital. Multivariate analysis was performed using SPSS version 23.0 (IBM Corp., USA).

Results

In total, 90 individuals, (67 males; 74.4% and 23 females; 25.6%) with a mean age of 67.1 ± 15.9 years were evaluated. The most common patients' comorbidities were hypertension in 42 (46.7%), chronic pulmonary disease in 25 (27.8%), diabetes in 31 (34.4%), congestive heart failure in 19 (21.1%), neurological disorders in 11 (12.2%), and myocardial infarction in 8 (8.9%). The most common reasons for ICU admission were respiratory failure in 36 patients (40%), trauma in 15 (16.7%), septic shock in 10 (11.1%) and intracranial bleeding in 9 (10%). Table 1 shows the characteristics of patients with a respiratory sample culture positive for *Candida* spp. Positive cultures derived from bronchial secretions in 53 patients (58.9%), BAL in 31 (34.4%) and sputum culture in 6 (6.7%). Table 2 shows the isolated fungal species and Table 3 shows the isolated bacterial species from the respiratory specimens.

Among all patients, 47 (52.2%) were treated with antifungals during their hospitalization around the time of *Candida* spp. isolation. Antifungals used were fluconazole in 15 (31.9%), micafungin in 15 (31.9%), anidulafungin in 13 (27.7%), caspofungin in 9 (19.1%), amphotericin B in 4 (8.5%) and voriconazole in 1 (2.1%). As shown in Table 1, where a comparison of characteristics of patients treated with antifungals with those not treated with such agents is presented, age, gender, previous antimicrobial use and hospitalization, tracheostomy, bacteremia, duration of stay in the hospital and ICU mortality were similar in the two groups. Patients treated with antifungals had higher acuity of illness than those not treated, as they had higher APACHE II and SOFA score, longer duration of stay in the ICU, more days on

ventilator and higher total mortality during the hospitalization. As shown in Table 4, a multivariate logistic regression analysis identified antifungal use to be independently associated with total mortality during hospitalization.

Discussion

The results of this study have shown that about half of the patients with an ICU-acquired RTI and *Candida* spp. isolation from their respiratory secretions were treated with antifungals. These patients had a higher acuity of illness than those not treated with such agents. They had higher SOFA and APACHE II scores on admission, longer duration of ventilation, longer stay in the ICU and higher total mortality during hospitalization. These data complicate the present analysis, as patients in a more critical condition could be treated with antifungals more often. Furthermore, treatment with antifungals and longer duration of ventilation were independently associated with increased total mortality during hospitalization.

The importance of *Candida* spp. isolation from the respiratory tract of critically ill patients with ICU-acquired RTI is unclear. It has been shown that isolation of *Candida* spp. is associated with higher mortality, increased duration of ventilation and increased ICU and hospital stay.^{3,9,21} The role of bacterial-fungal interactions in the lung microbiome has been shown to be important. There are studies suggesting higher probability of acquiring VAP in ventilated patients, if *Candida* spp. has been isolated from their respiratory tracts.^{9,22} To that end, colonization by *C. albicans* may be associated with impairment of macrophage function and immune dysregulation leading to increased likelihood of development of bacterial pneumonia as shown in rat models.^{6,7} Moreover, quorum sensing between *Candida* spp. and bacteria within the lung microbiome can lead to increased alveolar invasiveness by bacteria, such as *A. baumannii* and increased likelihood of infection.⁵ Furthermore, existence of biofilms may lead to development of antimicrobial resistance of bacteria. For example, *S. aureus* can

Table 1. Characteristics of patients with *Candida* spp. isolation from the respiratory tract

	All patients (n=90)	Treated with antifungals (n=47)	Not treated with antifungals (n=43)	p	t and df or U value	Effect size (Cohen's d)
Age, mean±SD, years	67.1±15.9	68±15.1	66.2±16.8	0.587	t=0.5454 df=88	0.116
Male, n (%)	67 (74.4)	32 (68.1)	35 (81.4)	0.226	NA	NA
Prior hospitalization, n (%)	46 (51.1)	29 (61.7)	17 (39.5)	0.057	NA	NA
Prior antimicrobial use, n (%)	38 (42.2)	23 (48.9)	15 (34.9)	0.205	NA	NA
APACHE II score on admission, median (IQR)	22 (15-27)	23 (19-28.8)	20.5 (15-24)	0.031	U=640.5	0.664
SOFA score on admission, median (IQR)	10 (7-11)	11 (8.3-12)	9 (7-11)	0.042	U=654.5	0.636
Days on ventilator, median (IQR)	15.5 (7-27)	19 (9-30)	11 (6-19)	0.027	U=737.0	0.479
Tracheostomy, n (%)	55 (61.1)	32 (68.1)	23 (53.5)	0.196	NA	NA
Positive blood culture, n (%)	60 (66.7)	31 (66)	29 (67.4)	1	NA	NA
Duration of stay in ICU, days, median (IQR)	18.5 (10.8-30)	21 (13-33)	17 (9-25)	0.012	U=699.5	0.549
Duration of stay in hospital, days, median (IQR)	34 (21-49.5)	38 (23-49)	31.5 (19-50)	0.278	U=854.5	0.268
ICU mortality, n (%)	20 (22.2)	12 (25.5)	8 (18.6)	0.456	NA	NA
Total hospital mortality, n (%)	33 (36.7)	24 (51.1)	9 (20.9)	0.004	NA	NA

APACHE II – Acute physiology and chronic health evaluation II; ICU – intensive care unit; IQR – interquartile range; NA – not applicable; SD – standard deviation; SOFA – Sequential organ failure assessment.

Statistical tests performed for comparison of characteristics of critically ill patients with *Candida* spp. respiratory isolation, treated or not treated with antifungals, included Student's t-test for comparison of age, Mann-Whitney for comparison of APACHE II and SOFA score, duration of ventilation and duration of stay in ICU and the hospital, while Fischer's exact test was used for comparison of proportions of male, prior hospitalization, prior antimicrobial use, tracheostomy, positive blood cultures, ICU and total hospital mortality.

Table 2. Microbiology of isolated fungi from respiratory specimens

Species	n (%)
<i>C. albicans</i>	60 (66.7)
<i>C. tropicalis</i>	14 (15.6)
<i>C. parapsilosis</i>	6 (6.7)
<i>C. glabrata</i>	4 (4.4)
<i>C. lipolytica</i>	2 (2.2)
<i>C. krusei</i>	2 (2.2)
<i>C. lusitaniae</i>	1 (1.1)
<i>C. dubliniensis</i>	1 (1.1)

Table 3. Microbiology of isolated bacteria from respiratory specimens

Species	n (%)
<i>Acinetobacter baumannii</i>	40 (44.4)
<i>Pseudomonas aeruginosa</i>	30 (33.3)
<i>Klebsiella pneumoniae</i>	12 (13.3)
<i>Staphylococcus aureus</i>	6 (6.7)
<i>Proteus mirabilis</i>	5 (5.6)
<i>Enterococcus faecalis</i>	3 (3.3)
<i>Morganella morganii</i>	3 (3.3)
<i>Corynebacterium</i> spp.	2 (2.2)
<i>Enterobacter aerogenes</i>	2 (2.2)
<i>Enterobacter cloacae</i>	2 (2.2)
<i>Escherichia coli</i>	2 (2.2)
<i>Haemophilus influenzae</i>	1 (1.1)
<i>Moraxella catarrhalis</i>	1 (1.1)
<i>Staphylococcus saprophyticus</i>	1 (1.1)
<i>Stenotrophomonas maltophilia</i>	1 (1.1)
<i>Streptococcus pneumoniae</i>	1 (1.1)
<i>Proteus vulgaris</i>	1 (1.1)
<i>Staphylococcus haemolyticus</i>	1 (1.1)

Table 4. Logistic regression analysis of overall mortality during hospitalization

	Univariate analysis	Multivariate analysis	OR (95% CI)
	p	p	
Female gender	0.030	0.296	1.881 (0.575-6.159)
Age (per year)	0.060	0.223	1.026 (0.984-1.069)
BMI (per kg/m ²)	0.010	0.114	1.071 (0.984-1.167)
APACHE II (per unit)	0.121	0.589	0.977 (0.900-1.062)
SOFA (per unit)	0.175	0.430	1.074 (0.899-1.283)
Antifungal use	0.003	0.010	4.104 (1.403-12.008)

APACHE II – Acute physiology and chronic health evaluation II; BMI – body mass index; SOFA – Sequential organ failure assessment.

form microcolonies on the fungal biofilm of *C. albicans*, when grown together, leading to polymicrobial biofilm with different phenotypes and single cell membranes, suggesting that *S. aureus* could be encapsulated in the matrix produced by *C. albicans*. The result is an increased resistance of *S. aureus* to vancomycin.^{23,24} However, whether antifungal treatment can reduce mortality, duration of ventilation, or ICU and hospital stay is disputable.^{15,16,21}

It is common practice to treat critically ill patients with *Candida* spp. isolation from their respiratory tracts with antifungals.²¹ In the present study patients treated with antifungals differed from the ones not receiving such agents, since those receiving antifungals had higher scores of clinical severity. Thus, the finding of increased total hospital mortality in the population treated with antifungals could be, in theory, a misinterpretation, since patients being in worse clinical condition could have received these agents more often. To that end, a

multivariate regression analysis was conducted identifying antifungal use as an independent factor associated with total hospital mortality.

The unexpected finding of association of antifungal use and higher mortality in critically ill patients with *Candida* spp. isolated from their respiratory samples is in contrast to the results of other studies identifying a protective role of antifungals in critically ill patients colonized with *Candida* spp.²⁵ For example, Zhang et al, in a retrospective study, found that treatment of respiratory *Candida* spp. colonization in critically ill mechanically ventilated patients was associated with a reduced multidrug-resistant (MDR) organism isolation ratio, duration of mechanical ventilation, incidence of VAP, length of ICU stay and total length of hospital stay. However, that study included only mechanically ventilated patients, who did not necessarily have an ICU-acquired RTI, as in the present study. In another study, by Lindau et al, antifungal treatment in critically ill patients with *Candida* colonization did not affect mortality, while SOFA score was an independent factor associated with mortality.²⁶

The present study has some limitations, such as the relatively small sample size, and the fact that it was performed in a single center, and this may limit generalization of its results. Furthermore, administration of antifungals was based on clinicians' discretion, which may have led patients in worse clinical condition to be treated with such agents more often. Moreover, the use of antifungals was reported for any reason ± 10 days around *Candida* spp. isolation, which may imply that these agents may have been used, in a very small number of cases, for other reasons. Finally, the observational retrospective design of the study may limit the ability for a causal analysis of the effect of antifungal therapy on clinical outcome.

Conclusions

In conclusion, herein, it was found that critically ill patients with ICU-acquired RTI having *Candida* spp. in their respiratory specimens, treated with antifungals, did not have any clinical benefit. Moreover, they may even have had higher total hospital mortality, even

though sicker patients received antifungals more often. Clinicians caring for such patients should be hesitant to treat them with antifungals, especially when an absolute indication is not present.

Authors' contributions statement: AV, NS, CA, AP, EP, AA and SM collected the data, PI, AV and NS analyzed the data, PI performed the statistical analysis, PI GS and DPK wrote the manuscript, and all authors edited the manuscript. DPK and GS supervised the study. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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