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BRIEF REPORT

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Candida sp. isolated from bronchoalveolar lavage: clinical significance in critically ill trauma patients

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Abstract *Objective:* Based on limited data, *Candida* sp. isolates from bronchoalveolar lavage (BAL) cultures in immunocompetent patients are thought to be contaminants rather than pathogens. The objective of this study was to determine the clinical significance of *Candida* sp. isolated from BAL cultures in critically ill trauma patients. *Design and setting:* Retrospective study in a level 1 trauma intensive care unit. *Patients and participants:* All patients with *Candida* sp. isolated from BAL cultures over a 3-year period; 85 *Candida* positive BAL cultures from 62 patients were studied. *Measurements and results:* The primary outcomes were the incidence of *Candida* sp. in BAL, antifungal use, course of the possible infection, and mortality. Of 1077 BAL cultures 85 (8%) grew *Candida* sp., representing 64 episodes of possible *Candida* sp. ventilator-associated pneumonia. No colony counts exceeded the diagnostic threshold for bacterial VAP ($\geq 10^5$ cfu/ml). Only 2 of 64 episodes (3%) were treated with systemic antifungals. Three other episodes (5%) were treated because of concomitant therapy for *Candida* sp. at other sites. The majority of episodes were not treated with antifungals and were considered contaminants (59/64, 92%). No patients developed subsequent candidemia, and most follow-up BALs (74%) were negative for *Candida* sp. Overall mortality (17%) was similar to previous patients with similar severity of injury at the study center (18%). *Conclusions:* The results of this study suggest that isolation of *Candida* sp. from BAL in quantities below the diagnostic threshold for VAP in this population does not require antifungal therapy.

Keywords *Candida* sp. · Ventilator-associated pneumonia · Infection · Critical illness · Multiple trauma

Introduction

Ventilator-associated pneumonia (VAP) is an important cause of morbidity and mortality in critically ill patients [1, 2, 3]. Optimal diagnosis of VAP includes a combination of traditional clinical signs and symptoms plus distal pulmonary quantitative cultures [1, 2, 3]. The diagnostic threshold for bacterial VAP using bronchoalveolar lavage (BAL) is 10^4 or 10^5 cfu/ml [1, 2]. However, a fairly common clinical dilemma is interpreting the presence of *Candida* sp. in BAL cultures. If the growth of *Candida* sp. from BAL indicates true infection, prompt antifungal therapy would be indicated because of high mortality rates associated with fungal pneumonia as well as inappropriate empirical therapy of VAP [1, 3, 4]. Alternatively, unnecessary use of antifungal agents in patients with mere colonization is undesirable due to the development of resistance, adverse drug events, and high cost.

Based on limited data, current guidelines for both VAP and candidal infections suggest that isolation of *Candida* sp. from BAL in immunocompetent patients does not require treatment [1, 2, 4]. However, these recommen-

dations are contrasted by a recent survey showing that 24% of intensivists would prescribe antifungal therapy for an immunocompetent, mechanically ventilated patient with *Candida* sp. isolated from a tracheal aspirate [5]. As such, experts in the field consider this an unresolved question and have called for more data on the role of *Candida* sp. in nosocomial pneumonia [3, 6]. The purpose of this study was to determine the clinical significance of *Candida* sp. isolated from diagnostic BAL cultures in critically ill trauma patients [7].

Methods

This study was conducted at the Presley Regional Trauma Center housed within the Regional Medical Center in Memphis, Tenn., USA. It was approved by the University of Tennessee Institutional Review Board and conducted in accordance with the Revised Declaration of Helsinki. The need for written informed consent was waived by the institutional review board. This was a retrospective study of all patients in the trauma ICU with *Candida* sp. isolated from diagnostic BAL cultures between 1 September 1998 and 31 August 2001. Patients were identified from a clinical database. Additional data were obtained from the trauma registry (NTRACS version 3.0, American College of Surgeons Committee on Trauma).

Patients with clinical signs and symptoms of VAP [fever or hypothermia ($> 38°C$ or $< 36°C$), leukocytosis or leukopenia ($> 12{,}000/mm^3$ or $< 4{,}000/mm^3$), macroscopically purulent sputum, new or changing infiltrate on chest radiography] underwent a bronchoscopic bronchoalveolar lavage (BAL) using a procedure previously described [8]. Quantitative cultures of BAL samples were performed by the hospital's laboratory using standard procedures from the National Committee for Clinical Laboratory Standards. The laboratory determined the species of *Candida* only if grown in high amounts in the BAL ($\geq 10^5$ cfu/ml). Lung biopsies for histopathological analyses were not performed. Patients with bacterial BAL culture results of 10^5 cfu/ml or higher were diagnosed with bacterial VAP [8]. Some clinicians prefer 10^4 cfu/ml as the diagnostic threshold for VAP; however, using 10^5 cfu/ml has been validated in trauma patients [9, 10]. Follow-up BALs were performed as part of a general sepsis work-up each time patients met the clinical criteria outlined above. *Candida* sp. bloodstream infections were defined as growth of *Candida* sp. from any blood culture. *Candida* sp. urinary tract infection (UTI) was defined as growth of 10^5 cfu/ml or more from a urine culture. While there seems to be a degree of relative immune disruption after trauma [11], this study population was considered "immunocompetent" prior to admission in that no patients were neutropenic, receiving immunosuppressive mediations, or had other previous immunodepression (e.g., AIDS).

For the purposes of the study *Candida* sp. isolated from a BAL was considered a possible episode of *Candida* sp. VAP. *Candida* sp. isolated from subsequent BALs within 14 days of the original BAL were considered "follow-up" rather than a new episode. *Candida* sp. isolated from a BAL more than 14 days after the original BAL was considered a new episode.

In contrast to bacterial VAP, the medical team did not have a standard definition for *Candida* sp. VAP. Indeed, no such BAL thresholds exist for *Candida* sp. [1, 2, 3]. The decision to treat *Candida* sp. was at the discretion of the attending physician. Thus for the purposes of this study episodes treated with systemic antifungals were considered to be *Candida* sp. VAP. Patients with *Candida* sp. isolated from BAL did not have further cultures routinely performed (e.g., blood, urine) to look for further *Candida* sp. colonization. Primary outcomes studied were the incidence of *Candida* sp. in BAL, use of antifungal therapy, resolution of the possible *Candida* sp. VAP on subsequent BALs (when available), incidence of subsequent systemic fungal infections, and mortality compared to a previous group from the study center. Statistical comparisons of dichotomous data were performed using the χ^2 test (SigmaStat, SPSS). Differences at a p value less than 0.05 was considered statistically significant.

Results

A total of 1,077 BAL cultures were performed in 555 patients over the 3-year study period. *Candida* sp. was isolated from 85 BAL cultures in 62 patients. The species of *Candida* were not reported by the laboratory. Demographic and outcome data are summarized in Table 1. Seven of the 85 isolates grew 10,000–99,999 cfu/ml, ten grew 1001–9,999 cfu/ml, and 68 grew 1000 cfu/ml or fewer. Two patients had a second episode of *Candida* sp. from BAL (> 14 days after the first isolation) for a total of 64 episodes in 62 patients. The remaining 21 BAL cultures of *Candida* sp. were isolated from 46 follow-up BALs that occurred within 14 days of the original BAL. Nine of these 21 patients had another follow-up BAL, none of which grew *Candida* sp. Most episodes were concurrent with bacterial VAP and/or antibiotic therapy (Table 1). No patients developed candidemia or systemic candidal infections after isolation of *Candida* sp. from the BAL.

Of the seven isolates that grew 10^4 cfu/ml or more, three had follow-up BALs with substantially lower colony counts ($< 10^3$ cfu/ml), and four had no follow-up BALs. None of these seven patients were treated with antifungals. Two died from unrelated causes. Mortality was statistically similar between patients with fewer than 10^4 cfu/ml and those with 10^4 cfu/ml or more of *Candida* sp. (15% vs. 29%, $p = 0.338$). Overall mortality in the current study (17%) was similar that in a previous

Table 1 Demographics and outcomes of patients with *Candida* sp. isolated from bronchoalveolar lavage (*IQR* interquartile range) ($n = 59$)[a]

Age, mean (years)	47 ± 19
Sex: M/F	32/27
Mechanism of injury (blunt/penetrating)	52/7
Injury Severity Score, mean	28 ± 10
Concurrent bacterial VAP	26/64 (41%)
Concurrent systemic antibiotics	40/62 (65%)
Duration of mechanical ventilation, median (days; IQR)	23 (13–41)
Length of intensive care unit stay, median (days; IQR)	32 (19–45)
Length of hospitalization, median (days; IQR)	40 (26–56)
Mortality	10 (17%)

[a] Data unavailable for 3/62 patients except where noted

cohort of patients who underwent diagnostic BALs at the study center (18%) [8]. This historical control group had similar basic demographic characteristics to those of the current population, including mean Injury Severity Score (30), length of hospitalization (37 days), and incidence of bacterial VAP (39%) [8].

Nine patients were treated with systemic antifungal therapy. Two patients received intravenous fluconazole for 4–5 days specifically for suspected *Candida* sp. VAP. Both patients had low colony counts of *Candida* sp. (100 and 430 cfu/ml), and both had follow-up BALs that showed no *Candida* sp. Three other patients were previously receiving antifungal therapy because of *Candida* sp. infections at other sites at the time of their *Candida* positive BALs (10, 40, 200 cfu/ml, respectively). Two patients with *C. albicans* fungemia were successfully treated with intravenous fluconazole and amphotericin B lipid complex, respectively, and a third patient with a *Candida* sp. UTI was treated with intravenous fluconazole. Four patients received treatment for candidal UTIs that developed 1–6 days after the *Candida* positive BALs (40, 40, 70, 180 cfu/ml, respectively).

Discussion

Candida sp. was isolated from 8% of diagnostic BALs in critically ill trauma patients over a 3-year period. These isolates likely indicated colonization rather than true VAP. Based on the physician's decision to treat, 92% of episodes (59/64) were thought to be colonization, 3% (2/64) were thought to be VAP, and 5% (3/64) were inconclusive because of treatment for previous fungal infections. When performed, 46% of first follow-up BALs and 100% of second follow-up BALs were negative for *Candida* sp.

There are two primary reasons we feel that these *Candida* sp. BAL isolates indicated colonization rather than true VAP: (a) there was no development of subsequent systemic candidal infections despite the lack of antifungal therapy, and (b) there was no excessive mortality in these patients despite the lack of antifungal therapy. Correlations between a *Candida* positive BAL and the existence of previous fungal infections (two bacteremia, one UTI), or subsequent fungal infections (four UTI) in this study are unknown. However, the critical finding is that no patients developed candidemia or serious fungal infections after isolation of *Candida* sp. in the BAL. This is important because current guidelines recognize the risk of systemic dissemination of *Candida* sp. infections [4]. Similarly, we have recently shown that 25% of patients with a *Candida* sp. UTI later develop systemic candidemia [12]. Thus the fact that no patients in the current study developed subsequent systemic fungal infections strongly suggests that that *Candida* sp. in the BAL does not indicate a true infection.

Another indicator that these BAL results did not denote true VAP was that the mortality rate (17%) was much lower than the 67% mortality rate previously reported for biopsy-confirmed fungal pneumonia, albeit in the general population rather than specifically among trauma patients [13]. In addition, the mortality rate in the current study was the same as a similar population from the study center (18%) [8]. If the critically ill patients in this study truly had untreated *Candida* sp. VAP, a higher mortality rate would be expected [1]. Indeed, the crude mortality rate for bacterial VAP is 25–75% [1]. Thus we feel that neither antifungal therapy nor a systematic work up for candidal infections at other sites is warranted in these patients. In addition, a recent study showed that formal pan-culturing to determine a "colonization index" does not find a relationship between *Candida* sp. colonization and mortality [14]. We also do not use fluconazole prophylaxis because it does not consistently decrease mortality (even with previous colonization) and is not recommended except in unusual circumstances [4].

The results of the current study are remarkably similar to the findings of previous studies in this area. Rello et al. [15] retrospectively examined incidences of *Candida* sp. isolates in BAL cultures over a 5-year period. *Candida* sp. was considered to be a definite or probable contaminant in 89% of episodes (33/37), similar to the findings of the current study (92%). No patients were definitively diagnosed with *Candida* sp. pneumonia, although seven patients received systemic antifungal therapy (five amphotericin B, two fluconazole). Importantly, a high percentage of protected specimen brush (PSB) samples (86%) were above the diagnostic threshold for bacterial pneumonia (10^3 cfu/ml). The authors concluded that PSB samples do not distinguish between *Candida* sp. colonization and pneumonia, and that even high amounts of *Candida* sp. from PSB cultures do not require treatment [15].

Other studies have examined correlations between *Candida* sp. in BAL and histopathological samples; the

traditional standard of diagnosis for fungal pneumonia. El-Ebiary et al. [16] reported that *Candida* sp. colonization based on histology was common in the lungs of 25 immunocompetent, critically ill patients who died (40%). *Candida* sp. was isolated from 9% of BAL cultures in these patients; similar to the current study (8%). Two patients had *Candida* sp. pneumonia diagnosed by biopsy. Neither BAL nor PSB cultures were correlated well with quantitative biopsy cultures. The authors concluded that BAL and PSB were not effective at distinguishing between colonization and true infection [16]. Similarly, studies in immunocompromised patients show only limited usefulness for BAL in diagnosing *Candida* sp. pneumonia [17, 18].

A primary limitation of the current study is that there was no large control group of patients treated with antifungals. This would have been ideal. As such, this study really serves as a large case series of patients with *Candida* sp. from BAL who were not treated. The next best approach would be to compare overall mortality of this patient series with a historical control group from the same center and with broadly similar demographic characteristics. This comparison gave a modest, indirect indication that this group of patients with *Candida*-positive BALs did not have a curiously high mortality rate despite not receiving antifungal treatment. If these patients truly had *Candida* sp. VAP and were not treated, then the mortality rate would have been expected to be higher [13]. Despite the fact that mortality directly attributable to VAP is sometime difficult to detect [1], we feel that the results of this study indicate that low colony counts of *Candida* sp. from BAL do not require treatment.

Another weakness is that a comparison of BAL and histological results were not possible because no lung biopsies were performed. Other limitations include the retrospective design and a lack of patients that met the diagnostic threshold for bacterial VAP used in our center (10^5 cfu/ml). Thus the clinical significance of patients having 10^5 cfu/ml or more of *Candida* sp. from BAL remains unknown. Antifungal therapy may be prudent in patients with high colony counts of *Candida* sp. from a BAL with no other explanation for their signs and symptoms of infection. Lastly, it is unknown whether there could have been different outcomes from various *Candida* species (e.g., *C. albicans* vs. *C. glabrata*) because the laboratory reported BAL isolates as "*Candida* sp."

In conclusion, the vast majority of critically ill trauma patients with *Candida* sp. isolated from BAL were not treated with antifungals. This did not result in subsequent candidemia. These results suggest that BAL colony counts of *Candida* sp. below the diagnostic threshold for VAP in this population indicate colonization and do not require antifungal therapy. However, further research is needed to develop appropriate diagnostic methods to detect true *Candida* sp. VAP in critically ill patients.

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