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Antifungal use in immunocompetent, critically ill patients with pneumonia does not improve clinical outcomes

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ABSTRACT

Purpose: To determine if treating bronchoalveolar lavage (BAL) culture-positive patients with antifungal therapy impacted mortality compared to not treating due to presumed colonization.
Methods: We conducted a retrospective study of immunocompetent, critically ill adult patients from 2010 to 2014. Patients with a BAL culture-positive for *Candida* or unspeciated yeast and a clinical suspicion of pneumonia were included. The treatment group received an antifungal agent for at least 5 days, and the control group received either no antifungal therapy or an antifungal agent for less than 48 h. Recruitment occurred in a 2:1 ratio of untreated versus treated patients.
Results: Seventy-five patients were included. In-hospital mortality was similar between treated and untreated groups (24% vs. 26%, $P = 0.85$). Length of stay and duration of mechanical ventilation also did not differ between the two groups.
Conclusion: We did not observe a difference in mortality or clinical outcomes in patients treated with antifungal agents. Presumptive antifungal therapy for BAL-positive *Candida* or yeast in immunocompetent patients did not result in improved clinical outcomes.

Introduction

Candida species account for 9% of hospital-acquired bloodstream infections and candidemia is associated with a crude mortality of up to 47%.[1] However, *Candida albicans*, the most common species of yeast, is an oropharyngeal colonizer in up to 20% of healthy individuals and 55% of hospitalized patients.[2] The diagnosis of candidal pneumonia in non-neutropenic patients is extremely rare. Indeed, candidal pneumonia requires histopathologic confirmation with findings of yeast cells or pseudohyphae on lung biopsy, which is a practice not routinely performed.[3] *Candida* isolated from bronchoscopic specimens is usually thought to be non-pathogenic.[2] Several studies have confirmed that isolation of *Candida* from a bronchoalveolar lavage (BAL), although common in hospitalized patients, is rarely an active source of pneumonia.[3–5] As such, current guidelines for candidiasis do not recommend the initiation of antifungal treatment based on a positive BAL alone due to the frequent rate of colonization, the poor predictive value of this finding, and the rarity of candidal pneumonia.[6]

Despite these guideline recommendations, providers frequently prescribe antifungal agents for critically ill, febrile patients with no clear evidence of invasive fungal infection. Indeed, our recent unpublished institutional survey of 64 providers from trauma surgical critical care, pulmonary critical care, and infectious diseases demonstrated significant variability in self-reported prescribing practices of antifungal therapy in critically ill patients. Up to 24% of respondents reported the empiric use of antifungal therapy for clinical suspicion of pneumonia, and 42% would initiate antifungal treatment of BAL cultures positive for *C. albicans*. Overall, trauma surgical critical care providers were most likely to consider *Candida* to be a cause of pneumonia and to prescribe antifungals. By contrast, infectious diseases physicians were the least likely to

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prescribe antifungal therapy for pneumonia. The practice of prescribing antifungals in this clinical setting is not limited to our institution. Our survey results are consistent with a study assessing antifungal prescribing practices in critically ill, non-neutropenic patients in France, where 24% of intensivists reported prescribing antifungal therapy for patients with chronic obstructive pulmonary disease requiring mechanical ventilation with a tracheal aspirate positive for *Candida* species.[7]

The overuse of antifungal therapy can lead to unintended consequences including adverse effects and increased resistance.[8] Previous azole exposure is a risk factor for subsequent *Candida* infections with decreased susceptibility profiles, such as *Candida glabrata* and *Candida krusei*.[9] The Infectious Diseases Society of America (IDSA) guidelines recommend the empiric use of an echinocandin in patients with recent treatment with an azole for this very reason.[6]

The purpose of the study was to determine if treating patients with antifungal therapy for a BAL culture positive for *Candida* or unspeciated yeast had an impact on mortality compared to not treating due to presumed colonization. The primary outcome was a comparison of in-hospital mortality between the treatment and non-treatment groups. Secondary outcomes included hospital length of stay (LOS), intensive care unit (ICU) LOS, duration of mechanical ventilation, and time to mortality from BAL culture.

Methods

Design

This was a single-center, retrospective chart review of critically ill adult patients admitted to one of three ICUs (medical ICU, surgical trauma ICU and neurosurgical ICU) at an academic medical center from January 1, 2010 to July 31, 2014. This study received Institutional Review Board approval.

Inclusion criteria consisted of age $\geq$18 years old, mechanical ventilation at the time of BAL and at least one BAL positive for *Candida* or unspeciated yeast during ICU admission. Patients who met criteria for clinical suspicion of nosocomial pneumonia on the day of BAL were included. These criteria consisted of the presence of infiltrate on chest radiograph or chest computerized tomography (CT) based on radiology reports, new onset purulent sputum, changes in secretions or secretions noted on BAL, and either a temperature of $\geq$38 °C or $\leq$36 °C and/or a white blood cell (WBC) of $\geq$12,000 or $\leq$ 4000 cells/mm^3.

Patients were excluded if they were severely immunocompromised, defined as patients with a history of hematopoietic-stem cell transplantation, chemotherapy in the last 30 days, solid organ transplantation, human immunodeficiency virus (HIV) with a CD4 T-lymphocyte count of <200 cells/mm^3, or daily corticosteroid therapy with a dose equivalent to $\geq$20 mg of prednisone for $\geq$14 days. Patients who received antifungals for reasons other than pneumonia were excluded using the following criteria: medical record documentation of antifungal use for other indications, presence of positive blood, fluid, or urine cultures with *Candida* species 7 days prior to or during antifungal therapy, receiving an antifungal agent other than fluconazole or an echinocandin, and receiving antifungal treatment duration of >48 hours but <5 days. Patients were also excluded if they were diagnosed with community-acquired pneumonia (CAP), pregnant, had a BAL growing a carbapenem-resistant or pan-resistant organism, previously included in the study, or if there was an absence of data to assess clinical suspicion of pneumonia. Patients with bacteria isolated in a BAL culture could be included if the organism was adequately treated with an antibiotic the organism was susceptible to for at least seven days.

Variables and outcome measures

Data included age, gender, race, weight, and comorbidities. Characteristics related to pneumonia consisted of presumed pneumonia, radiographic evidence of pneumonia by either chest radiograph or CT scan, and ratio of partial pressure of arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2). Disease severity scores were assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II on day of ICU admission and Clinical Pulmonary Infection Score (CPIS) on day of BAL. Microbiologic data included bacterial species isolated from the respiratory tract and bronchoscopy findings, including purulent sputum. Cultures within 28 days were also reviewed for presence of fluconazole-resistant, or non-albicans *Candida* species and *Pseudomonas* species. WBC count and maximum temperature were collected on the day of BAL and persistence of these factors were assessed on day 8 from BAL. Maximum heart rate, respiratory rate or partial pressure of arterial carbon dioxide ($PaCO_2$), systolic blood pressure, and lactate were collected on the day of BAL. Pertinent antimicrobial therapy included duration of concurrent antibiotics, duration of antifungal therapy, time from bronchoscopy to initiation of antifungal therapy, antifungal agent prescribed (fluconazole or echinocandin), fluconazole dose and route, and echinocandin doses. Clinical endpoints consisted of in-hospital mortality, time to mortality from BAL culture, hospital length of stay (LOS), ICU LOS, duration of mechanical ventilation, and cause of death per death records documented within patient charts. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Carolinas HealthCare System.[10] REDCap is a secure, web-based application which provides an interface for validated data entry, audit trails for tracking data manipulation and export procedures, and automated export procedures for data downloads.

Statistical analysis

Data were analyzed using descriptive statistics consisting of means, medians, and percentages. The primary analysis was a chi-square test comparing in-hospital mortality for the two treatment groups and the corresponding 95% confidence intervals on the difference in the proportions. Secondary outcomes were analyzed with the non-parametric Wilcoxon rank-sum test. SAS Enterprise Guide®, version 5.1. A two-tailed *P*-value of less than 0.05 was considered statistically significant.

Results

Due to low enrollment in the treatment group, the IRB-approved protocol was modified to include patients in a 2 to 1 ratio in reverse chronological order until a total of 75 patients were included. There were a total of 25 patients in the treated group and 50 patients in the non-treated group (Fig. 1). A total of 224 patients were excluded from the study, of which 22.8% were found to have evidence of *Candida* or unspeciated yeast in other cultures. The majority of patients were Caucasian males, with a median age of 59 years old (Table 1). Most patients had clinical suspicion of ventilator-associated pneumonia (VAP) with a median APACHE II score of 25 in the treated group and 27 in the non-treated group. Of note, APACHE II scores were not able to be calculated for four patients in the treated group and three patients in the non-treated group due to lack of data. Differences between groups occurred in relation to ICU-specialty, with significantly more treated patients residing in the surgical trauma ICU compared to the other ICUs ($P = 0.0013$). A subgroup analysis of all patients in the medical ICU and surgical trauma ICU showed average APACHE II scores of 34 and 29 respectively ($P = 0.2684$). Additionally, mortality between medical