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Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study

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Abstract *Purpose:* Recovery of *Candida* from the respiratory tract is common. Large series on the incidence of histologically proven *Candida* pneumonia in intensive care unit (ICU) patients are lacking. *Methods:* A two-year prospective study of all autopsies performed on patients who died in the ICU was conducted. For autopsy-proven cases of *Candida* pneumonia, we required microscopic demonstration of yeast invasion in lung autopsy specimens that showed inflammation. We looked for differences in incidence in patients with and without respiratory samples positive for *Candida* species pre-mortem. *Results:* Of 1,587 patients admitted to the ICU, 301 (19%) died of whom 232 (77%) were autopsied. Of those, 135 patients (58%) had histopathological evidence of pneumonia. A total of 77 cases (57%) with pneumonia at autopsy had positive tracheal aspirate and/or BAL cultures for *Candida* spp. performed during the preceding two weeks. No cases of *Candida* pneumonia were identified amongst those 77 cases. In the other 58 patients with autopsy-proven pneumonia and no *Candida* isolation pre-mortem, no *Candida* pneumonia was observed either. *Conclusions:* Despite frequent isolation of *Candida* spp. from the airways, over a two-year period no single case of *Candida* pneumonia was found among the patients with evidence of pneumonia on autopsy. This study indicates that *Candida* pneumonia is an extremely rare occurrence in ICU patients and provides further evidence against the common use of antifungal therapy triggered by a microbiology report of *Candida* isolation from the respiratory tract.

Keywords *Candida* · Pneumonia · Intensive care unit · Autopsy

Introduction

Candida spp. are part of the normal flora on the skin and on the mucosal membranes of the oral cavity and gastrointestinal tract. *Candida* spp. can be recovered from sputum in 20% of health care personnel and 55% of hospitalized patients receiving antibiotics [1].

Virtually every organ can be infected with *Candida* spp. Extensive data for the treatment of acute hematogenous candidiasis are available [2]. *Candida* pneumonia, however, is one of the most challenging of all *Candida* infections to diagnose. *Candida* pneumonia is a very rare disorder and occurs primarily as a result of seeding of the lungs secondary to hematogenous dissemination, or it may follow the aspiration of colonized oropharyngeal or gastric contents [3]. A diagnosis of invasive pulmonary candidiasis faces the problem of differentiating between infection, being very rare and colonization, being very common. In intensive care unit (ICU) patients, airway colonization by *Candida* spp. probably reflects frequent

use of broad-spectrum antibiotics and immunoparalysis, with alterations to both neutrophil and alveolar macrophage function [4].

The value of tracheal surveillance cultures is controversial, although absence of *Candida* spp. in surveillance cultures has a high negative predictive value for disseminated candidiasis in patients who have leukemia or lymphoma, or in bone marrow transplant patients [5]. Rules for a practical and accurate diagnostic approach are elusive. The positive predictive value of a culture of sputum or even broncho-alveolar lavage (BAL) fluid is very low [5].

At present, the only sure method to establish that *Candida* is the primary lung pathogen is to demonstrate the presence of yeast cells or pseudohyphae in a lung biopsy [6]. However, in clinical practice, lung biopsies cannot be used for management of patients with suspected *Candida* infection. Based on limited data, current guidelines for both ventilator-associated pneumonia and *Candida* infections suggest that isolation of *Candida* spp. in BAL fluid from immunocompetent patients does not require treatment [7]. However, these recommendations are contrasted by a survey showing that 24% of intensive care physicians would prescribe antifungal therapy for an immunocompetent, mechanically ventilated patient with *Candida* spp. isolated from a tracheal aspirate [8]. Reduction of *Candida* colonization in order to prevent bacterial pneumonia might be another potential use of antifungal therapy. Indeed, both clinical and experimental evidence suggest that *Candida* colonization might promote bacterial infection [9].

Therefore, the significance of *Candida* isolation from respiratory samples of mechanically ventilated patients merits investigation in greater depth. This prospective autopsy study aims to define the incidence of *Candida* pneumonia and to define the value of *Candida* spp. isolation in airway samples from both immunocompetent and immunosuppressed patients who died in our Medical Intensive Care Unit and had evidence of pneumonia at autopsy.

Materials and methods

Patients and methods

This prospective study was conducted from 1 October 2004 to 1 October 2006, in a 17-bed medical ICU in a large, 1,900-bed, university hospital. The protocol was approved by our local ethical committee. Critically ill patients admitted to our medical ICU include adult patients from the emergency room and from hospital wards, referrals from other hospitals, patients with hematological malignancies, HIV infection, solid organ transplantation, and advanced cirrhosis, patients with other medical conditions, but no post-surgical patients.

Our routine is to perform an autopsy, when legally possible, on all patients who die in our ICU. If the family objects, no autopsy is performed.

For patients who died in the ICU, the following data were collected: duration of mechanical ventilation, length of ICU stay, underlying disease, recovery of another respiratory pathogen, *Candida* spp. isolated from tracheal aspirate or BAL specimens, identification of *Candida* spp. in a culture of another specimen (blood, urine, abdominal or pleural fluid) $\leq$14 days before death, and antifungal treatment. Tracheal surveillance cultures are taken on a weekly basis. An additional sample was obtained when signs of respiratory infection were suspected and new or worsening infiltrates were seen on chest X-ray. The main indication for a BAL in our unit is unexplained pulmonary infiltrates in immunocompromised patients.

Primary diagnoses on admission and the clinical cause of death were classified according to the International Classification of Diseases, ninth revision [10, 11].

A Pearson chi-squared test was used to assess differences between patients with pneumonia and positive respiratory samples for *Candida* spp. versus patients with pneumonia but without positive airway sample for *Candida* spp.

Microbiological procedures

Respiratory samples were mainly obtained by BAL (2×20 ml normal saline in the most severely affected segment of the lung) or tracheal aspirate and were immediately transferred to the microbiological laboratory for culture and identification. For recovery of fungal pathogens, the specimens were cultured on to Sabouraud dextrose slants and blood agar plates (5% horse blood) with a chloramphenicol disk. The Sabouraud dextrose slants were incubated for 2 days at 37°C and up to 3 weeks at 30°C. Cultures were considered positive in cases of growth of yeasts. The cultures were evaluated semiquantitatively (three grades: +, ++, +++).

Postmortem examination

We used a predefined procedure, as described previously [12], for pathologic examination of the lungs. Postmortem study was performed within 24 h of death. After removal from the thorax, the lungs were inflated with 10% formalin to a pressure of 35 cm of water and were fixed in block with 10% formalin. After 48 h, the lungs were cut into slices 1 cm thick. We took samples for microscopic analysis from each pulmonary lobe and additional samples from areas with macroscopic injuries. Two pathologists independently analyzed each sample.

Histologic criteria for diagnosis of acute pneumonia included the presence of intense neutrophilic infiltration

in the interstitium and intra-alveolar spaces. *Candida* organisms were identified histologically on the basis of typical morphological features in these abnormal lung sections. All biopsied respiratory samples were stained with hematoxylin and eosin and Gomori's methenamine silver. Typical features are clusters of both pseudohyphae and budding yeasts with various amounts of acute inflammation. The yeasts are round, ranging from 4 to 6 μm. The pseudohyphae consist of elongated blastospores that are arranged in chains. In order to characterize the pathogenesis of *Candida* pneumonia (i.e., whether hematogenous or aspiration), the distribution of the organisms and their relationship to blood vessels and airways and the presence of aspiration were studied.

Definitions

For definition of *Candida* pneumonia, we required an autopsy specimen that yielded microscopic demonstration of yeast invasion on a background of inflammatory alveolar and interstitial lesions (with or without central necrosis).

For definition of bacterial ventilator-associated pneumonia (VAP), the patients had to have clinical signs and symptoms [(fever or hypothermia (>38 or <36°C)], leukocytosis or leukopenia (>12,000 or <4,000/mm^3), macroscopically purulent sputum, new or changing infiltrate on chest radiograph, and isolation of bacteria via tracheal aspirate or BAL in the last two weeks premortem.

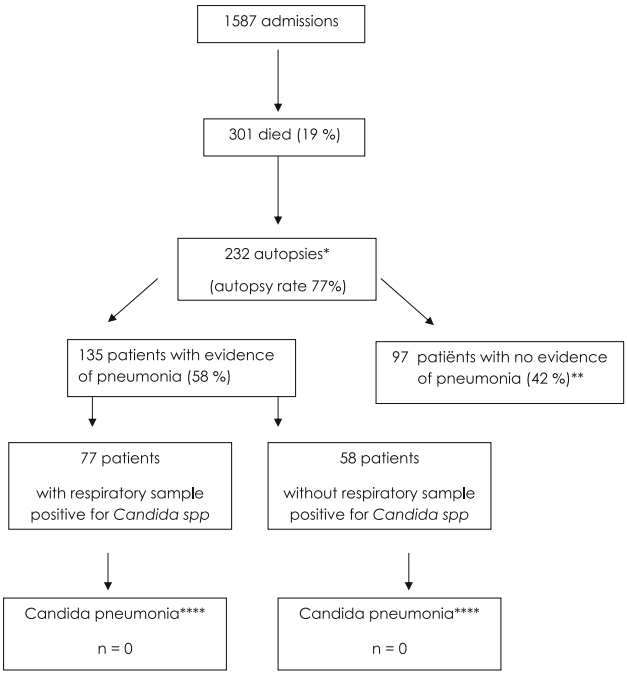

Fig. 1 Patients in the study (October 2004–October 2006). Overall, 124 patients (53%) had a positive tracheal aspirate and/or BAL culture for *Candida* spp. within the two weeks prior to death (*). Forty-seven patients had a positive respiratory sample for *Candida* spp. despite the absence of pneumonia on autopsy (**). Positive respiratory sample means a positive tracheal aspirate and/or BAL culture for *Candida* spp. within the two weeks prior to death (***). *Candida* pneumonia means microscopic demonstration of yeast invasion in autopsy lung tissue samples taken from a compatible macroscopic lesion with microscopical evidence of pneumonitis (****)

Results

During the study, 1,587 patients were admitted to our ICU, of whom 301 (19%) died during their ICU stay and 232 (77%) were autopsied. Mean APACHE II score of all 1,587 patients was 20.4. Of those, 135 patients (58%) had histopathological evidence of pneumonia (Fig. 1). The mean time elapsed from the day the last respiratory sample was taken to the autopsy was two days. On average, four samples per patient were taken in the two weeks preceding death. Forty-seven patients (48%) without pneumonia upon autopsy had a positive airway sample for *Candida* spp. in the two weeks preceding death. The clinical characteristics of autopsied patients with and without positive airway samples for *Candida* spp. prior to death are summarized in Table 1. The rate of death directly related to underlying pneumonia and refractory hypoxia was 22% (30/135). Other primary causes of death that were confirmed at autopsy were multiple organ failure and shock (79/135, 59%), myocardial infarction (9/135, 7%), pulmonary embolism (4/135, 3%), and miscellaneous causes (13/135, 9%).

Of the 77 patients with pneumonia upon autopsy and positive cultures for *Candida* spp. pre-mortem (57%), 41 specimens were retrieved through tracheal aspirates and 36 through BAL. Both procedures were performed during the two weeks before death. The mean time elapsed from the day that the sample was taken to the autopsy was three days. *Candida* spp. grew abundantly (+++), moderately (++), and with a few colonies only (+) in 42, 23, and 12 patients, respectively. None of those 77 patients had *Candida* pneumonia. Primary diagnoses are shown in Table 2. Seventy-one cases (92%) were intubated with a mean duration of mechanical ventilation prior to isolation of *Candida* spp. from an airway sample of 6.3 days. Mean APACHE II score was 22.2 ± 6.3 compared with 20.0 ± 7.4 in the overall population. Mean ICU length of stay was thirteen days compared with eight days in the overall population. Eight patients (10%) were receiving steroids and nine patients (12%) were neutropenic (<500/mm^3). *Candida* spp. were isolated from tracheal aspirate ($n = 56$), from BAL ($n = 12$) and from both ($n = 9$). One hundred ninety-nine respiratory samples (55%) were positive for *Candida* spp. during ICU stay out of a total of

Table 1 Clinical characteristics of deceased patients with evidence of pneumonia at autopsy

	With positive airway sample ($n = 77$)[a]	Without positive airway sample ($n = 58$)[a]	*P* value
Age, year (mean)	69	65	0.86
Sex (M/F)	52/25	32/26	0.12
APACHE II (mean)	22.2	23.3	0.82
Mechanical ventilation (yes/no)	71/6	56/2	0.29
ICU length of stay days (mean)	13	12	0.78
Bacterial pathogen (yes/no)[b]	43/34	27/31	0.074
Concurrent bacterial VAP (yes/no)[c]	40/37	23/35	0.98
Steroids (yes/no)	8/69	11/47	0.16
Neutropenia (yes/no)	9/68	14/44	0.057
Antifungal treatment(yes/no)	7/70	4/54	0.65
Candidemia (yes/no)[a]	7/70	4/54	0.65
Candida spp. in urinary sample (yes/no)[a]	19/58	4/54	0.007
Cause of admission			
Acute respiratory failure, *n*	37	30	
Sepsis or septic shock, *n*	28	16	
Cardiogenic shock, *n*	7	1	
Hypovolemic shock, *n*	4	5	
Encephalopathy, *n*	3	6	
Candida pneumonia, *n*[d]	0	0	1.0

[a] Positive airway sample means a positive tracheal aspirate and/or BAL culture for *Candida* spp. within the two weeks prior to death. The same period of time applies to the presence or absence of candidemia or *Candida* spp. in the urine

[b] Bacterial pathogen isolated from a tracheal aspirate or BAL culture in the two weeks prior to death

[c] VAP, ventilator-associated pneumonia, defined as: clinical signs and symptoms (fever or hypothermia (>38 or <36°C), leukocytosis or leukopenia (>12,000 or <4,000/mm^3), macroscopically purulent sputum, new or changing infiltrate on chest radiograph, and isolation of bacteria via tracheal aspirate or BAL

[d] *Candida* pneumonia defined as: microscopic demonstration of yeast invasion in autopsy lung tissue samples taken from a compatible macroscopic lesion with microscopical evidence of pneumonitis

Table 2 Primary diagnosis of 77 patients with pneumonia at autopsy and positive respiratory sample for *Candida* prior to death

Conditions	Patients
Chronic obstructive pulmonary disease	16
Cirrhosis	13
ARDS[a]	10
Hematological malignancy	9
Solid organ malignancy	7
Cardiogenic shock	5
Systemic disease	5
Miscellaneous[b]	5
Solid organ transplant recipients	5
Pancreatitis	2

[a] ARDS, Adult respiratory distress syndrome meeting the definition of ARDS and not fitting one of the other primary conditions

[b] Miscellaneous were spondylodiscitis, pulmonary fibrosis, vascular surgery, orthopaedic surgery, yellow nail syndrome

359 airway samples taken from the 77 patients who had pneumonia upon autopsy and at least one positive airway sample fourteen days prior to death.

Candida albicans was the most frequently identified fungal species ($n = 42$, 55%). Other species [(*Candida glabrata* ($n = 10$), *Candida tropicalis* ($n = 3$), *Candida parapsilosis* ($n = 5$), and/or *Candida krusei* ($n = 2$)] were recovered in 20 patients (26%). The remaining 15 patients (19%) had a mixture of *Candida albicans* and non-*albicans* spp. Other fungal isolates were *Aspergillus fumigatus* ($n = 7$) and *Rhizopus* spp. ($n = 1$). Associated bacterial pathogens were documented in 43 cases (56%) (15 *Pseudomonas aeruginosa*, 6 *Staphylococcus aureus*, 3 *Escherichia coli*, 2 *Haemophilus influenzae*, 2 *Serratia marcescens*, 2 *Acinetobacter baumannii*, 2 *Klebsiella oxytoca*, 1 *Streptococcus pneumoniae*, and 10 with mixed flora). Forty patients (52%) fulfilled the definition of VAP in the two weeks before death. Antifungal therapy (for candidemia ($n = 7$), *Candida* peritonitis ($n = 3$) or probable aspergillosis ($n = 4$)) was instituted in 14 patients (18%): five received fluconazole, four received voriconazole, three received amphotericin B, and two received caspofungin. None of the patients was treated solely with antifungal agents for pneumonia. The most frequent indication for antifungal therapy was catheter-related candidemia. Antifungal agents were always used in conjunction with various antibacterial agents. The mean duration of treatment with antifungals was nine days. None of the deaths was thought to be related to side effects of antifungal agents or to the lack of antifungal treatment. Seven patients (9%) had candidemia in association with isolation of *Candida* spp. from the airways. Nineteen patients (25%) had candiduria, which was not treated.

There were 58 cases with pneumonia at autopsy but without positive airway samples for *Candida* spp. None of these 58 patients had *Candida* pneumonia upon autopsy.

Mean APACHE II score was 23.3 ± 4.2 and mean ICU length of stay was 12 days. Eleven patients (14%) were receiving steroids and 14 patients (24%) were neutropenic (<500/mm^3). Associated bacterial pathogens were documented in 27 cases (47%) (7 *P. aeruginosa*, 6 *S. aureus*, 2 *E. coli*, 2 *S. marcescens,* 2 *Enterobacter aerogenes*, 2 *Streptococcus pneumonia,* 1 *Mycobacterium tuberculosis*, and 5 with mixed flora). Twenty-three patients (40%) had VAP in the two weeks before death. Four patients (7%) had candidemia and another four patients (7%) had candiduria.

Patients with *Candida* isolated from the respiratory tract had significantly more candiduria (19/77 vs. 4/58, $P = 0.007$).

Discussion

In our study, in which all autopsies performed over a two-year period in an adult medical ICU were examined at a very high 77% autopsy rate, no single case of *Candida* pneumonia was identified, even in the patients who had a positive respiratory sample for *Candida* spp. prior to death. In contrast, isolation of *Candida* spp. from respiratory specimens was very frequent in patients who died with pneumonia, occurring in 57%.

Isolation of *Candida* spp. in the airways from critically ill patients poses significant problems in interpretation. *Candida* pneumonia has rarely been reported, but histological proof is almost always lacking. Yeasts are very frequently isolated from respiratory tract specimens in the absence of invasive disease. One prospective study examined the role of isolating *Candida* spp. from 25 non-neutropenic patients who had been mechanically ventilated for at least three days [13]. Just after death, multiple specimens were obtained by bronchoscopic techniques. Although ten patients had at least one biopsy specimen positive for *Candida* spp., only one case was confirmed histopathologically to have invasive pulmonary candidiasis.

Our data are in agreement with those of Fagon et al. [14] who found no definite proof of *Candida* pneumonia in 205 ICU patients with *Candida albicans* in the airways. In the retrospective cohort series published by Rello [15], no cases of *Candida* pneumonia could be found in 37 non-neutropenic critically ill adult patients, although 24 of 28 patients showed protected specimen brush cultures $\geq 10^3$ cfu/ml.

One reason to report *Candida* spp. in respiratory samples could be the value of the colonization index. In the largest multicenter study performed to date, there was no correlation between the number of sites colonized and the likelihood of developing invasive candidiasis. It seems to be appropriate to view *Candida* colonization at any clinically important site as a risk factor and not as a disease [16]. The rate of candidemia in our study was not different in patients with colonization compared with those who were not colonized in the airways.

Moreover, a study by Barenfanger et al. [17] describes the practice of limiting identification of rapidly growing yeasts (i.e. *Candida* spp.) in respiratory secretions and its impact on patients. If rapidly growing yeasts were detected in a culture, they were then reported as "yeasts" without further identification. This strategy did not have a negative impact on patient outcome. A potential benefit of not reporting *Candida* spp. in respiratory secretions is the decrease in selective pressure for fungi to develop resistance to antifungal agents.

Some studies demonstrate an association between *Candida* colonization of the respiratory tract and subsequent ventilator-associated pneumonia (VAP) secondary to bacteria. *C. albicans* impedes alveolar macrophage function and is correlated with an increase of *P. aeruginosa* pneumonia in rat [9]. This is in agreement with the finding that *Candida* and *Pseudomonas* are among the most common pathogens retrieved from endotracheal tubes and from respiratory specimens in patients with VAP [18]. Azoulay et al. [19] showed that mechanically ventilated patients colonized with *Candida* spp. in the airways were at increased risk of *Pseudomonas* VAP. Our study could not draw conclusions regarding this issue, because only 19% of all patients admitted during the study period were screened, i.e. patients who died and underwent an autopsy.

Although we could not identify a single case of *Candida* pneumonia, this does not mean this entity does not exist. Kontoyiannis et al. [6] found 36 cases of autopsy-proven *Candida* pneumonia over the course of five years in their study. Haron et al. [20] describe 31 cases of *Candida* pneumonia in patients admitted to a large cancer center during a 20-year period. Both series were limited to patients with cancer and neutropenia. In our series, which included only nine cases with neutropenia and 13 patients with cancer, isolation of *Candida* spp. from the airways was not associated with a post mortem diagnosis of *Candida* pneumonia. This could be related to the fact that some patients were treated with antifungals. However, in our ICU, no antifungal therapy is ever prescribed on the basis of isolation of *Candida* spp. from respiratory specimens. Further studies are needed to reveal which patients indeed need antifungal treatment for *Candida* pneumonia. In the meantime it is probably wise to prescribe antifungal treatment to neutropenic critically ill patients with two or more correlative positive samples for *Candida* spp. in the airways, the presence of pneumonia, and deterioration despite broad-spectrum antibiotics.

Our study has several limitations. First, the pre-mortem cultures were not performed quantitatively. Also, the post-mortem specimens were analyzed microscopically without culture. Second, biopsies for histological examination of the lungs were not always performed immediately post-

mortem. There was a 24 h time window. Also, all the airway specimens positive for *Candida* spp. were taken into account during the two weeks before death. No additional samples were collected immediately prior to or after death. Finally, because only deceased patients were included, we cannot exclude the possibility that patients who survived and were treated with antifungals for various reasons in fact had *Candida* pneumonia.

In conclusion, we present data from severely ill, mostly immunocompromised, adult patients from a tertiary care unit. A stringent autopsy protocol has been achieved given the very high 77% autopsy rate. In none of these patients could *Candida* pneumonia be found. No antifungal treatment should be given to ICU patients solely on the basis of the presence of pneumonia and a positive respiratory sample for *Candida*. Future studies are needed to confirm these findings, especially in the neutropenic population.

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