Candida Pneumonia: What We Know and What We Don't

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The diagnosis of *Candida* pneumonia is a difficult one to make, and some experts often question whether the entity truly exists. This article assimilates the information currently available regarding *Candida* pulmonary infection to elucidate the presentation of the disease and the hosts in which it occurs. It also describes how to interpret the presence of *Candida* in respiratory secretions from both immunocompetent and immunocompromised patients. Finally, it describes how the diagnosis of *Candida* pneumonia can be made, which patients with suspected disease should be treated, and which antifungal agents should be used.

Introduction

Many experts often question whether *Candida* pneumonia truly exists. The topic of *Candida* pneumonia has been declared an “evidence-based-free zone” by many in the infectious disease community. In this article, we attempt to assimilate the current available information regarding *Candida* pulmonary infection to give a sense of where the evidence lies, where it is lacking, and what conclusions and recommendations we can make regarding suspicion of the disease, diagnosis of the disease, and management of the disease in both immunocompetent and immunosuppressed patients.

The History of *Candida* Pulmonary Infection

The diagnosis of *Candida* pneumonia has always been difficult, and clinicians have struggled for years with the ability to definitively recognize cases of such. Some argue that this is because the entity is extremely rare; others

argue that this is because effective diagnostic tools are lacking. Whatever the reason, it is difficult to generate a clinical case series to study this question, and as a result, most clinical case studies describing *Candida* pneumonia are based on autopsy studies.

The Spectrum of *Candida* Pulmonary Infection: Lessons From Autopsy Studies

A variety of autopsy studies aiming to better define *Candida* pneumonia have been reported in the literature over the past three decades. The most notable of these are described below and are summarized in Table 1.

In 1977, Masur et al. [1] published a series of 30 patients with histologic evidence of *Candida* pulmonary infection (ie, parenchymal invasion) that was identified after review of 995 consecutive autopsies from 1973 to 1974 at Memorial Sloan-Kettering Cancer Center and New York Hospital. This evidence suggested an incidence of *Candida* pneumonia in this population of 3% [1]. Twenty-eight of the 30 patients had underlying neoplastic disease; 24 of these 28 patients had neutropenia (absolute neutrophil count [ANC] < 500) for greater than 10 days. Interestingly, significant correlation between postmortem lung culture and histologic evidence of invasive candidiasis was lacking. In the 30 cases of invasive *Candida* pulmonary infection described by Masur et al. [1], only 18 lung cultures were positive for *Candida*. Similarly, of the 995 autopsies studied by Masur et al. [1], 61 resulted in postmortem pulmonary cultures positive for *Candida*; in only three of these 61 cases was histology positive for invasive disease.

Upon studying the distribution of organisms to the lungs in their autopsy series, Masur et al. [1] set out to characterize the route by which *Candida* spread to the lung. It was suggested that there are two sources of *Candida* pneumonia: 1) hematogenous dissemination, characterized by an absence of bronchial spread and presence of *Candida* pseudohyphae found growing from within pulmonary vessels into surrounding lung tissue; and 2) endobronchial dissemination, characterized by intrabronchial and alveolar changes associated with aspiration in many cases. Cases of *Candida* pneumonia caused by hematogenous dissemination were often characterized by finely nodular, diffuse

Table 1. The spectrum of *Candida* pulmonary infection: data from autopsy studies

Study / year	Patient population	Definition of <i>Candida</i> pneumonia	Underlying risk factor(s)	Clinical characteristics
Masur et al. [1] / 1977	Memorial Sloan-Kettering Cancer Center / New York Hospital, 1973–1974 (n = 30)	Evidence of pulmonary parenchymal invasion identified at the time of autopsy	28 of 30 patients with underlying neoplastic disease 24 of 28 patients with neutropenia (ANC < 500) for > 10 days	18 of 30 cases with cultures positive for <i>Candida</i> species 10 of 30 with hematogenous dissemination of infection 16 of 30 with endobronchial dissemination presumed secondary to aspiration 4 of 30 with uncertain route of infection
Mohsenifar et al. [2] / 1979	UCLA Department of Medicine, 1974–1978 (n = 20)	Histologic evidence of invasive candidiasis in pulmonary tissue at time of autopsy	16 of 20 patients with underlying disease requiring cytotoxic or immunosuppressive therapy 4 of 20 with complex medical disease requiring long-term broad-spectrum antibiotics	20 of 20 patients with cough, purulent sputum, and hypoxemia 16 of 20 with diffuse involvement of lungs on radiograph; 4 of 20 with lobar infiltrates
Haron et al. [3] / 1993	University of Texas, M.D. Anderson Cancer Center, 1966–1986 (n = 31)	Histologic evidence of invasive pulmonary <i>Candida</i> infection was not primary (ie, it was secondary to hematogenous dissemination); 320 patients with evidence of hematogenous dissemination were excluded	31 of 31 with underlying malignancy (48% with hematologic malignancy, 52% with solid tumors) 42% of patients with ANC > 1000 throughout entire hospitalization	97% with tachypnea, 87% with fever, 90% with hypoxemia, 61% with altered mental status, 26% with clinical evidence of aspiration 50% with diffuse involvement of lungs on radiograph; 50% with lobar infiltrates 17 of 19 patients with antemortem sputum cultures that were positive 13 of 15 with postmortem culture of lung tissue positive
ANC—absolute neutrophil count.				

infiltrates and occasionally necrotizing pneumonias and acute pulmonary mycetoma. Cases of *Candida* pneumonia caused by endobronchial dissemination were often characterized by evidence of local or diffuse bronchopneumonia on imaging. Of the 30 patients described by Masur et al. [1], 10 were suspected to have had hematogenous spread of infection to the lungs, 16 were suspected to have had infection spread to the lungs by way of aspiration, and four patients had uncertain routes of infection. Although the specific primary sources of hematogenous dissemination of *Candida* were not described in this study, one can hypothesize that these can include anything from intraabdominal abscess, to right-sided endocarditis with septic emboli occurring in the setting of intravenous drug abuse, to septic thrombophlebitis occurring in the setting of contaminated central venous catheters.

From Masur et al.'s [1] data, it appears that *Candida* pneumonia is a rare phenomenon that typically occurs in the setting of severe underlying malignant disease in patients who develop severe sepsis and/or multiorgan system failure. The caveat to this description is the fact that the data were collected predominantly from a referral center that specializes in the diagnosis and treatment of hematologic/oncologic disorders. It is certainly the case that referral bias could have skewed these results.

The next prominent autopsy series was published by Mohsenifar et al. [2] in 1979. This was a retrospective study of 20 cases of pulmonary candidiasis diagnosed at autopsy between 1974 and 1978 in the Department of Medicine at the UCLA School of Medicine. As was the case in the series by Masur et al. [1], patients were included only if there was histologic evidence of invasive candidiasis in pulmonary tissue; they were excluded if postmortem culture of lung tissue revealed growth of *Candida* but histologic evidence of invasion was lacking. Of these 20 cases, all patients clinically displayed cough with purulent sputum production and hypoxemia; four patients had occasional hemoptysis. Sixteen of the 20 patients had serious underlying diseases requiring immunosuppression (ie, steroids) or cytotoxic therapy (ie, chemotherapy). The remaining four patients had complicated medical disease requiring prolonged courses of broad-spectrum antibiotics. Fourteen of the 20 patients had low leukocyte counts, 10 of the 20 patients had an underlying malignant condition, 16 of the 20 patients had diffuse involvement of the lungs on radiograph, and four patients had lobar infiltrates.

This study was consistent with that published by Masur et al. [1], suggesting again that the vast majority of cases of invasive *Candida* pulmonary infection occur in patients who are significantly immunosuppressed. Contrary to Masur et al.'s [1] data, however, it appears that these cases do not universally occur in patients with underlying malignant conditions. In fact, patients receiving high-dose steroids for nonmalignant conditions and patients with complicated medical illness requiring pro-

Table 2. *Candida* species isolates

***Candida pneumonia* (Haron et al. [3])**

C. albicans: 10/13 (77%)

C. tropicalis: 1/13 (8%)

C. albicans + *C. tropicalis*: 1/13 (8%)

C. parapsilosis: 1/13 (8%)

***Candida empyema** (Ko et al. [4])**

C. albicans: 47%

C. tropicalis: 22%

C. glabrata: 22%

C. parapsilosis: 3%

C. guilliermondii: 3%

C. humicola: 1.7%

C. famata: 1.7%

*n = 60 isolates.

longed courses of broad-spectrum antibiotics seem to be at risk as well.

The final large autopsy series was published by Haron et al. [3] and described a series of 31 patients treated at the University of Texas, M.D. Anderson Cancer Center between 1966 and 1986 who were found at autopsy to have primary *Candida* pneumonia. The authors reviewed a total of 7725 autopsies, from which there were 351 cases of autopsy-proven invasive pulmonary *Candida* infection (incidence of 4.5%). It is important to note that, unlike the previous autopsy studies, the authors of this study excluded 320 patients with evidence of invasive pulmonary *Candida* infection that was not primary (ie, it was secondary to hematogenous dissemination). All 31 patients with primary *Candida* pneumonia had underlying malignancy (48% with hematologic malignancy, 52% with solid tumors). Thirteen patients (42%) had adequate neutrophil counts (ANC > 1000) throughout their hospitalizations; nine patients (29%) had severe neutropenia (ANC < 100). The majority of these patients presented with dyspnea and/or tachypnea (97%), fever (87%), and hypoxemia (90%). Sixty-one percent of patients displayed altered mental status and there was clinical evidence of aspiration in 26% of patients. Seven patients (23%) were found to have *Candida* esophagitis. Approximately half of the patients included in the series had diffuse bilateral pulmonary infiltrates, whereas the other half had infiltrates limited to one or more lobes.

Antemortem sputum culture was positive in 17 of 19 patients. Postmortem culture of lung tissue was obtained from 15 patients, 13 of which were positive (10 *Candida albicans*, 1 *C. tropicalis*, 1 *C. albicans* and *C. tropicalis*, 1 *C. parapsilosis*) (Table 2). Histopathologic findings were most commonly bronchopneumonia (81%); intra-alveolar exudates (52%) and intra-alveolar hemorrhage (52%) were also common. Evidence of aspirated material was found in

10% of cases. Only one patient displayed evidence of intravascular involvement. Upon review of all data, the death of 84% of these patients (26 of 31) was felt to have been secondary to primary *Candida* pneumonia ($n = 21$) or to concomitant *Candida* and bacterial pneumonia ($n = 5$).

As was the case with the series by Masur et al. [1], this series also included patients from a specialized referral center, skewing the population to include only those patients with an underlying malignancy. A substantial fraction of these patients had clinical evidence of aspiration prior to death, although, unlike in the study by Masur et al. [1], this was confirmed by histology in only a fraction of cases.

What can we gather from these autopsy studies? *Candida* pulmonary infection, whether primary or secondary, does seem to exist in certain distinctly immunocompromised populations. Most patients with postmortem evidence of invasive pulmonary disease had antemortem clinical evidence of pneumonia, characterized by pulmonary infiltrates, fever, and hypoxemia. This diagnosis is rare (with an incidence of 3%–4.5% based upon previous studies [1,3]) and seems to occur predominantly in patients with underlying malignancy, although it can also occur in patients who are immunosuppressed for other reasons.

In considering these data, we realize that the groups from which these data were obtained are not necessarily representative of everyone in an inpatient hospital setting. Further, given advancements in the diagnosis and treatment of malignant and rheumatologic conditions with cytotoxic and/or immunosuppressive therapy, and given the increase in the number of patients who have undergone solid organ transplantation, the populations of patients included in these studies are not necessarily representative of the population we care for today.

Other Clinical Presentations of *Candida* Pulmonary Infection

Candida pulmonary infection is not necessarily limited to pneumonia. Alternative presentations of this disease, including *Candida* empyema and a variety of postsurgical *Candida* infections in lung transplant patients, are described below.

Candida empyema: fungal empyema thoracis

As reported by Ko et al. [4], the incidence of fungal empyema thoracis has increased in recent years. This entity is defined by the following criteria: 1) the presence of an exudative pleural effusion with isolation of fungal species, 2) the presence of significant signs of infection, and 3) repeat isolation of fungal species from the pleural effusion or the isolation of fungal species from other specimens such as blood or sputum. Of the 67 patients described by Ko et al. [4], 90% had underlying medical disease and 84% developed nosocomial infection (most acquired in the intensive care unit). Regarding the microbiology of these infections, 82% of the clinically

significant isolates were *Candida* species (47% *C. albicans*, 22% *C. tropicalis*, 22% *C. glabrata*, 3% *C. parapsilosis*, 3% *C. guilliermondii*, 1.7% *C. humicola*, and 1.7% *C. famata*) (Table 2). Most of the patients with fungal empyema thoracis received systemic antifungal therapy (73%), 57% underwent closed drainage therapy, 16% required pleural irrigation, and 9% required decortication. The crude mortality, despite these therapies, was 73%. Through multivariate analysis, it was shown that patients with an underlying immunocompromised state and patients with respiratory failure had an increased risk of death (RR of 1.58; $P < 0.005$ and RR of 2.31; $P < 0.001$, respectively).

Spectrum of *Candida* pulmonary infections in lung transplant recipients

Candida species have also been implicated in pulmonary infections in patients who have undergone lung transplantation. As lung transplant is becoming a more common therapeutic option for patients with end-stage lung disease, these infectious complications must be considered by the providers caring for these patients.

The spectrum of post-lung transplant pulmonary complications secondary to *Candida* is quite broad. Kanj et al. [5], in a review of a series of patients undergoing lung and heart-lung transplantation from 1992 to 1995 who later developed fungal infection, reported three different manifestations of *Candida* pulmonary infection.

First, disease can be manifest by *Candida* pneumonia, with resulting disseminated disease. This particular manifestation was described in a patient who, on postoperative day 5, in the setting of profound respiratory failure requiring extracorporeal membrane oxygenation, was found to have pulmonary hemorrhage and focal necrosis in the left lung with no rejection; culture of lung tissue grew *C. albicans*. The patient was treated with fluconazole but ultimately developed cultures positive for *C. albicans* from blood, sputum, bronchoalveolar lavage (BAL), and peritoneal fluid. Despite therapy being switched to amphotericin B, the extent of the patient's infection worsened and the patient ultimately died.

Next, *Candida* infection in the post-lung transplant setting can take the form of disseminated candidiasis originating from the donor lung. This manifestation was described in a patient who, on postoperative day 5, underwent cardiopulmonary arrest with follow-up bronchoscopy yielding a BAL culture positive for *C. albicans*. The patient was treated initially with vancomycin and ceftazidime; because of persistent fever and leukocytosis, fluconazole was started on postoperative day 7. Subsequent cultures from blood and peritoneal fluid were positive for *C. albicans*. Karyotypic analysis revealed that the *C. albicans* grown from the transplant recipient's cultures matched the *C. albicans* that was isolated from the donor lung prior to transplant. As the donor was on mechanical ventilation for only 1 day prior to death, it was suspected that the donor lungs were simply

colonized with *Candida*. In the setting of profound immunosuppression in the recipient, the presence of this *Candida* was enough to set up a rapidly evolving pneumonia.

The final manifestation of *Candida* pulmonary infection that has been described in patients after lung transplant is infection and subsequent poor healing of the bronchial anastomosis sites. The patient described by Kanj et al. [5] was a patient with an uncomplicated postoperative course who presented on postoperative day 11 with dyspnea on exertion and bilateral pulmonary infiltrates. Bronchoscopy revealed stenotic bronchial anastomoses with erythematous mucosa and possible tissue necrosis. Endobronchial biopsy revealed coagulation necrosis with fungal forms; BAL cultures grew *C. albicans*. This patient was initially treated with both intravenous and inhaled amphotericin B. After discharge, the patient completed a 4-month course of fluconazole and once-weekly nebulized amphotericin B, with ultimate resolution of the abnormalities at her anastomoses.

Clinical Manifestations of Disease: How Severe Is *Candida* Pulmonary Infection?

The previously described autopsy studies are valuable in that they allow for characterization of *Candida* pulmonary infection (ie, who gets it, what it looks like) based upon strict histologic criteria. The pitfall of these studies, however, is that it is impossible to determine a true mortality rate for *Candida* pulmonary infection given the fact that the mortality rate of the patients included in these autopsy studies is 100%.

What is the mortality rate associated with *Candida* pulmonary infection? This question is difficult, if not impossible, to answer given the broad spectrum of disease and the lack of clarity in making a definitive diagnosis. Chen et al. [6], however, in a report of a series of invasive fungal infections, attempted to characterize patient outcomes and prognostic factors.

Chen et al.'s [6] study reviewed all cases of pulmonary fungal infection from January 1988 to December 1997 from a university-affiliated tertiary medical center in Taiwan. In this series, acute invasive fungal infection was defined as "patients with rapid progression of disease clinically or radiographically, and at least one of the following: 1) fungal invasion of lung parenchyma noted by pathologic examination or 2) fungal isolation from sterile site such as blood or pleural effusion." Of 140 patients with pulmonary fungal infection included in the study, 20 patients (14%) had evidence of infection with *Candida* species (9 *C. albicans*, 4 *C. tropicalis*, 4 *C. glabrata*, and 2 *C. parapsilosis*). Of these 20 cases of invasive *Candida* infection, 12 were cases of *Candida* pneumonia and eight were cases of systemic disease (ie, presence of pneumonia plus fungemia). The mortality rate for these patients was 70% (compared with 36.4% for all 140 patients included

in the series). Although it was suggested that invasive *Candida* infection is not as common as infection by *Aspergillus* species or *Cryptococcus* species, it did appear that *Candida* infection is associated with a significantly higher mortality rate.

Chen et al. [6] not only demonstrated the severity of *Candida* pulmonary infection, but also demonstrated an increase in the frequency of the disease. Although they reported five, eight, and six cases identified in 1988, 1989, and 1990, respectively, there were more than 15 cases identified annually from 1994 to 1997. This finding was corroborated by Schwesinger et al. [7] in their case series describing candidiasis and aspergillosis identified on autopsy from 1994 to 2003. A total of 2027 autopsies were performed at a mid-sized hospital and several outlying regional hospitals in Germany. The population included in this study was more general than those populations included in Masur et al.'s [1] and Haron et al.'s [3] studies (which included a disproportionate number of severely immunosuppressed patients.) The rate of candidiasis increased dramatically from the years 1994 to 1998 to the years 1999 to 2003 ($P < 0.0001$). During the period from 1994 to 1998, 4.4% of autopsies revealed candidiasis and 42% of these had lung/trachea involvement. During the period from 1999 to 2003, 10.4% of autopsies revealed candidiasis (or candidiasis plus aspergillosis) and 37.5% of these had lung/trachea involvement. This suggests an incidence of *Candida* pneumonia in a general hospitalized population of 1.8% (from 1994–1998) that increased to 3.9% (from 1999–2003).

What is the etiology of the increased incidence of invasive candidiasis?

There is no clear-cut answer to this question; however, it is appealing to suggest that this is because we are caring for a sicker population of patients. Because of advances in many aspects of medical care, we are not only caring for a group of patients with a greater burden of underlying disease, but we are also keeping these patients alive for longer periods of time. We care for a population of patients with more advanced malignancy, often requiring aggressive chemotherapy regimens, leading to depressed neutrophil count or function. We care for a population with an increasing rate of solid organ transplants, leading to increased use of aggressive immunosuppression, which, in turn, leads to impaired T-lymphocyte function. Given the prominent role that T-lymphocytes play in immune defense against *Candida* (evidenced by the increased incidence of chronic candidal infection in patients with T-lymphocyte deficiency states, such as DiGeorge syndrome or AIDS), impaired T-lymphocyte function can lead to an increased risk of candidiasis. Finally, we care for a population of critically ill patients that is often treated aggressively with broad-spectrum antibiotics, potentially leading to changes in a patient's normal flora, with poten-

tial for overgrowth of *Candida* in the gastrointestinal tract. We are able to keep these complicated patients alive longer now than 10 or 20 years ago, thereby allowing increased opportunity for the establishment of invasive *Candida* infection.

Although the incidence of *Candida* pneumonia is on the rise, it is a diagnosis that might often be missed

In a comparison of premortem clinical diagnoses in critically ill patients and subsequent autopsy findings in 100 patients who died in a mobile intensive care unit in 1996, Roosen et al. [8] determined that the diagnosis of 16 cases of fungal pneumonia was missed; five of these cases were felt to represent “major missed diagnoses” (ie, diagnoses that if known before death “would have led to a change in management with potential for cure or prolonged survival”). It is important to note that the precise etiology of these fungal pneumonias (ie, *Candida* vs other fungi) was not described in the study. These five “major missed” cases all occurred in patients who were immunosuppressed (or functionally immunosuppressed): two patients with chronic obstructive pulmonary disease on chronic corticosteroid therapy, one patient after lung transplant, one patient with decompensated liver cirrhosis, and one patient after recent chemotherapy for non-Hodgkin’s lymphoma. Further, this study demonstrated that 31% of fungal infections in immunosuppressed patients were missed, despite a high index of suspicion and an aggressive diagnostic approach.

***Candida* Pneumonia Is a Severe Disease: How Do We Make the Diagnosis?**

It is clear that *Candida* pneumonia, when it occurs, is a devastating disease with increasing incidence, but how do we make the diagnosis? The autopsy data described here are not robust enough to clearly inform us of how culture data from respiratory tract specimens should be interpreted. What, then, should we make of respiratory tract cultures that are positive for *Candida* species?

There are no specific criteria used in practice to diagnose *Candida* pulmonary infection

Perhaps some of the lack of clarity in how to handle the presence of *Candida* in a respiratory tract sample is rooted in the fact that there is no precise set of criteria for interpretation of respiratory tract samples with *Candida* species.

At the present time, respiratory tract samples with *Candida* species are most often obtained from mechanically ventilated patients. With this in mind, before attempting to determine whether the presence of *Candida* species in these patients represents colonization or pneumonia, it is important to consider the current characterization of ventilator-associated pneumonia (VAP).

There is no standard set of criteria for the diagnosis of VAP, but it is generally recognized as the development of a clinical pneumonia (new or progressive pulmonary infiltrates, fever, leukocytosis, or purulent tracheobronchial secretions) that has developed more than 48 hours after the initiation of mechanical ventilation [9]. Given the lack of concrete criteria for use in the definition/diagnosis of VAP, accurate epidemiologic data are limited; in most reports, however, VAP frequency is typically said to be between 8% and 28% [10].

The bacteriologic strategy to diagnose pneumonia and identify pathogens in VAP often relies upon use of bronchoscopy with BAL or protected specimen brush (PSB). BAL studies have typically relied upon a diagnostic threshold of 10^4 or 10^5 colony-forming units (CFU)/mL of bacteria; PSB studies have typically relied upon a diagnostic threshold of 10^3 CFU/mL [11]. It is important to note that there is no similar threshold established for diagnosis of *Candida* pulmonary infection.

The most common etiologic microorganisms, as documented in a combination of 24 studies [10], are gram-negative bacilli, which account for 58% of recovered organisms. *Pseudomonas aeruginosa* is the most commonly recovered microorganism (24.4%), whereas Enterobacteriaceae (including *Klebsiella*, *Escherichia coli*, *Proteus*, *Enterobacter*, and *Serratia*) are next most commonly recovered microorganisms (14.1%); *Staphylococcus aureus* accounts for 20.4% of recovered microorganisms. Fungi (not further characterized in these studies, but presumably including *Candida* species) constitute only 0.9% of all recovered microorganisms suspected to be the etiologic agent responsible for VAP. (Note that these estimates are based on studies that do not necessarily include rigorous histologic analysis of tissue, perhaps accounting for the somewhat lower incidence of fungal VAP reported here as compared with that described in some of the previously mentioned studies.)

Defining *Candida* colonization versus infection in immunocompetent patients

In order to better determine the significance of positive pulmonary cultures when histologic data are not available, investigators have sought to better characterize *Candida* colonization versus infection in immunocompetent patients.

Wood et al. [12••] conducted a retrospective study exploring the significance of *Candida* species isolated from BAL fluid of intensive care unit (ICU) trauma patients. This study included all patients in a trauma ICU with *Candida* species isolated from diagnostic BAL cultures during a 3-year period; all patients had clinical signs and symptoms of VAP, with fever, elevated leukocyte count, purulent sputum, and/or new or evolving infiltrate on chest radiograph. Of 1077 BAL cultures, 85 (8%) grew *Candida* species (no colony counts $> 10^5$ CFU/mL); this was representative of a total of 64 episodes of possible *Candida* VAP. (For the purposes of this study, the physicians did not use

a standard definition for *Candida* VAP; rather, *Candida* species isolated from a BAL was considered to be possible *Candida* VAP.) Physicians treated their patients with antifungal therapy only if their clinical suspicion was such that the presence of *Candida* on BAL was representative of true infection. Given these study guidelines, physicians treated only two of the 64 cases of possible *Candida* VAP with antifungal therapy. Despite the paucity of aggressive treatment for possible candidal VAP, no patients developed subsequent candidemia and 74% of follow-up BALs were negative for *Candida* species. Further, overall mortality among the patients with BAL positive for *Candida* species was similar to that among matched patients without *Candida* in respiratory tract samples.

In a more rigorous study, researchers examined 25 mechanically ventilated patients who died while in the ICU [13]. All of these patients were mechanically ventilated for more than 72 hours; none were immunosuppressed, had a diagnosis of hematologic malignancy, or were neutropenic (ANC < 1000). Twenty of 25 patients had clinically suspected pulmonary infection on the day of death; 21 of the 25 patients had pulmonary infiltrates 24 hours before death. The presence of *Candida* species from quantitative cultures (obtained via endotracheal aspirate, protected specimen brush, and BAL) was assessed; these findings were then correlated with microbiologic and histologic data from immediate postmortem lung biopsies (obtained via thoracotomy guided by fiberoptic bronchoscopy, and via thoracotomy by blinded approach). Forty percent of the patients (10 patients) included in this study had pulmonary biopsy cultures positive for *Candida* species; however, only two of these patients (8% of total group) had evidence of definite *Candida* pneumonia (one diagnosed based on histology, one diagnosed based on presence of *Candida* in pleural fluid culture).

How should we interpret these studies? It appears that *Candida* pneumonia is exceedingly rare in immunocompetent hosts. It is suspected that the isolation of *Candida* species from respiratory secretions might simply be the result of aspiration of colonized oropharyngeal or gastric contents [14]. At the present time, given the low frequency with which it is suspected that *Candida* species cause VAP in immunocompetent patients and the belief that presence of *Candida* species on endotracheal aspirates most often represents colonization, the current American Thoracic Society/Infectious Diseases Society of America guidelines for evaluation and treatment of VAP states that isolation of *Candida* species from ventilated patients “rarely requires treatment with antifungal therapy” [11].

Practice patterns are not necessarily consistent with these guidelines

Despite this evidence, many providers (in particular critical care specialists) do not feel comfortable disregarding the presence of *Candida* in respiratory tract samples. This has

been demonstrated in several clinical studies comparing the practice patterns of infectious disease specialists with critical care specialists.

Investigators in Switzerland compared the management of suspected invasive *Candida* infection by infectious disease specialists and critical care specialists [15]. Sixty-five infectious disease specialists and 51 critical care specialists were presented with the following theoretical case: a 30-year-old man admitted to the ICU for multiple traumas requiring mechanical ventilation, later developing bilateral pulmonary infiltrates and fever, with BAL revealing 10^4 CFU/mL of *C. albicans* (in addition to 10^2 CFU/mL of *Pseudomonas* and 10^2 CFU/mL of *Acinetobacter*). Of the 65 infectious disease specialists, 94.9% of them considered the *Candida* to be a colonizer, whereas only 46.8% of the critical care specialists interpreted it as such. Given these alternative interpretations, it was not surprising that there was also a discrepancy in the rate of prescription of antifungals: 5.1% of ID specialists versus 51% of critical care specialists would have prescribed antifungals for these patients.

Should clinicians disregard the presence of *Candida* in respiratory tract specimens from immunocompetent patients?

At the present time, there are no convincing data to suggest that empiric treatment with antifungal agents is warranted in immunocompetent patients with respiratory tract specimens revealing *Candida* species. With that said, however, an immunocompetent patient with positive respiratory tract specimens in addition to positive blood cultures, pleural fluid cultures, or peritoneal fluid cultures should be treated for disseminated disease. The question of treatment in an immunocompetent patient with pulmonary infiltrates and *Candida* recovered on BAL (without positive culture data from any other source) is less straightforward. Because the data from Wood et al.’s study [12••] indicate that a lack of treatment for *Candida* pneumonia in immunocompetent patients with clinical evidence of pneumonia and *Candida* on BAL does not lead to increased mortality or increased rates of candidemia, we would not recommend antifungal therapy in these patients.

Given the fact that *Candida* pneumonia is exceedingly rare in immunocompetent patients, investigators have sought to determine the effect of limiting the identification of *Candida* species in respiratory tract samples. By not providing this potentially misleading culture data, it is theorized that inappropriate initiation of antifungal therapy in these patients would be limited.

There exist interesting data to suggest that limiting the identification of *Candida* species in respiratory tract samples may improve patient outcomes. Barenfanger et al. [16] reported their experience with limiting identification of rapidly growing yeasts (eg, *Candida* species) in respiratory tract secretions (including sputum samples, BAL specimens, or PSB specimens) and the subsequent impact

on patient, mortality, hospital stay, and cost of hospital stay. The study included 344 patients: 267 patients in a group in which yeasts were identified to the genus and/or species level (full identification group), and 77 patients in a group in which yeasts were identified as “yeasts, not *Cryptococcus*” (limited identification group). Of the patients included in the study, 90.1% were immunocompetent. The study revealed that in the limited identification group, antifungal medications were used less often (21% vs 39%; $P = 0.004$), patient hospital stay was shorter (10.1 vs 12.1 days per patient; $P = 0.02$), hospital stay costs were lower (\$6973 vs \$9407 per patient; $P = 0.03$), and mortality was lower (although not statistically significant at -14.3% vs 18.7%; $P = 0.34$). This argues that because of the little relevance of a respiratory tract specimen positive for *Candida* in an immunocompetent patient, limiting identification of the yeast may help to prevent unnecessary treatment. These results again lend credence to the idea that treatment of *Candida* identified in respiratory tract secretions from immunocompetent patients without clear evidence of disease is unwarranted.

Identification of *Candida* colonization versus infection in the immunocompromised host

If it is clinically reasonable to disregard respiratory tract samples positive for *Candida* in immunocompetent patients, how should we interpret respiratory tract samples positive for *Candida* in immunocompromised patients? This is a much less straightforward question.

It is agreed that *Candida* pneumonia occurs most commonly in organ transplant recipients, neutropenic patients, and in other immunocompromised hosts. Although it is more common in these patients, it is important to realize that it is still a very rare diagnosis. At the time of this writing, there were no current clinical data available to correlate the presence of positive respiratory tract specimens with clinical presentation and histologic evidence of pneumonia in today's immunocompromised patient population. However, it seems reasonable to suggest that the presence of *Candida* in a respiratory tract specimen from an immunocompromised patient and/or a patient with severe underlying malignancy who has clinical evidence of pneumonia be taken seriously. Although bacterial pneumonia would always be more common in such a scenario, if the patient's clinical condition deteriorates despite the use of broad-spectrum antibiotics and tissue biopsy cannot be performed, strong consideration should be given to the initiation of empiric antifungal therapy.

The gold standard for diagnosis of *Candida* pulmonary infection is histologic evidence of disease obtained via lung biopsy (transbronchial, thoracoscopic, or even thoracotomy approach). This constitutes an invasive approach that is not necessarily feasible to perform in all patients, particularly in those who are critically ill. Given the difficulty with identifying colonization versus infection based

on respiratory tract cultures alone, there has been some interest in development of an adjunctive test to aide in the diagnosis of true invasive *Candida* pulmonary disease.

It has been proposed that the assessment of *Candida* colonization index, a measure of the burden of body sites colonized with *Candida* species, might be useful in the determination of risk of development of invasive infection. This has been studied predominantly in non-neutropenic patients who are critically ill. Although it appears that *Candida* colonization identified in multiple body sites (ie, urine, respiratory secretions, gastric secretions) or in a single body site on numerous occasions is potentially predictive of the development of future *Candida* infection [17,18], calculation of a *Candida* colonization index will not aid in the definitive diagnosis of a current invasive pulmonary infection. What calculation of a *Candida* colonization index might do, however, is provide some guidance to clinicians regarding which patients might benefit from early empiric treatment with antifungals to prevent the development of future invasive infection.

Another potential adjunctive diagnostic test involves measurement of a serum level of (1→3)- β -D-glucan (BG), a polysaccharide that is a major cell wall constituent characteristic of fungi, including *Candida* species. Although this diagnostic test has not been studied extensively in cases of *Candida* pneumonia specifically, there are data to suggest that the BG assay may have high specificity and high positive predictive value in detecting invasive fungal disease that is not necessarily limited to the respiratory tract [19]. What is unclear, however, is whether this test has a high enough sensitivity when considered in the context of *Candida* pneumonia. As the cost of a missed diagnosis of *Candida* pneumonia is high, any diagnostic test relied upon should have a very high sensitivity. In the 333 patients included in the study by Ostrosky-Zeichner et al. [19], the BG assay had a sensitivity ranging from 57.1% to 79.1%, depending on the BG cutoff value used.

While the BG assay is not reliable enough to rule in or rule out the diagnosis of *Candida* pneumonia at the present time, some investigators and clinicians speculate that use and validation of this assay in quantification of BG in BAL fluid, thereby potentially leading to an increase in the sensitivity and specificity of the diagnostic test, may serve as a valuable diagnostic adjunct in the future. There is some thought, as well, that assay of fungal metabolites such as D-arabinitol, a metabolite of several pathogenic *Candida* species, could ultimately play a similar role.

Putting It All Together

Candida pulmonary infection is a rare entity, but there is evidence to suggest that it does exist in very specialized patient populations. As has been described in the preceding text, the diagnosis of *Candida* pulmonary infection is a difficult one to make without histologic proof of disease. Given

Table 3. Criteria for probable invasive *Candida* pulmonary disease**

Host factors
Recent history of neutropenia ($< 0.5 \times 10^9$ neutrophils/L for > 10 d) temporally related to the onset of fungal disease
Receipt of an allogeneic stem cell transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for > 3 wk
Treatment with other recognized T-cell immunosuppressants, such as cyclosporine, TNF- α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 d
Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
Clinical criteria for persistent lower respiratory tract infection
The presence of pulmonary infiltrates (diffuse or lobar) in setting of fever, hypoxemia, or sputum production despite appropriate broad-spectrum antibiotic therapy
Mycologic criteria
Direct test (cytology, direct microscopy, or culture)
Fungal elements in sputum, BAL fluid, or bronchial brush with recovery by culture of <i>Candida</i>
Indirect test
β -D-glucan detected in serum $\pm$ BAL fluid
*Probable invasive fungal disease requires presence of at least one of each criteria (host factors, clinical criteria, mycologic criteria).
†Treatment with antifungal therapy should be strongly considered if criteria for probable invasive <i>Candida</i> pulmonary disease have been met and the patient has persistent clinical evidence of pneumonia despite appropriate broad-spectrum antibiotic therapy in the setting of respiratory tract cultures positive for <i>Candida</i> species.
BAL—bronchoalveolar lavage; TNF—tumor necrosis factor.
(Adapted from De Pauw et al. [20••].)

the high mortality associated with *Candida* pulmonary infection, however, clinicians must be able to identify those patients who are likely to have disease so that treatment can begin in an appropriate time frame. With this in mind, our recommendations for treatment of *Candida* pulmonary infection are described in the following text.

Who should we treat?

Immunocompetent patients

Do not treat a patient with respiratory secretion cultures positive for *Candida* unless there is evidence of disseminated disease (ie, positive blood cultures, pleural fluid cultures).

Immunocompromised patients

Treat if there is evidence of disseminated disease, if histology from lung biopsy (thorascopic, transbronchial, etc) reveals parenchymal involvement/invasion with yeasts, or if the patient has probable invasive *Candida* infection (Table 3) [20••]. For example, treat if a highly immunosuppressed patient has persistent clinical evidence of pneumonia (fever, respiratory failure/insufficiency, sputum production) despite appropriate broad-spectrum antibiotic therapy in the setting of respiratory tract cultures positive for *Candida* species.

Treatment of *Candida* empyema

Because *Candida* empyema is still a rather rare diagnosis, rigorous data do not exist to suggest optimal management regarding antifungal therapy and drainage strategy. For

this reason, it seems reasonable at the present time to apply the current guidelines regarding management of bacterial empyema, realizing that these guidelines and management concepts rely heavily upon expert opinion and are not firmly rooted in evidence-based medicine [21].

In keeping with the American College of Chest Physicians consensus statement [22] regarding medical and surgical treatment of parapneumonic effusion, any pleural effusion with positive culture/gram stain or any pleural effusion yielding pus (ie, empyema) requires drainage (either with therapeutic thoracentesis, tube thoracostomy, video-assisted thorascopic surgery, or surgery with thoracotomy) because of high risk of poor clinical outcome. The more difficult decision, however, involves determining which patients would benefit from surgical intervention as opposed to tube thoracostomy. Although randomized controlled trial data are lacking, the existing data suggest that of patients with large, loculated pleural empyemas, video-assisted thorascopic surgery is superior to chest tube drainage with regard to hospital stay and duration of chest tubes [23].

So where does this leave us regarding the management of *Candida* empyema? In our opinion, all *Candida* empyemas require drainage of some sort. However, given the fact that in our clinical experience, most *Candida* empyemas do not develop thick rinds and multiple loculations (as occur frequently with bacterial empyema), tube thoracostomy (kept in place until there is minimal pleural fluid output) plus systemic antifungal therapy is often adequate.

With what should we treat?

There are three classes of drugs that are effective against *Candida* species. These are the azoles (fluconazole and voriconazole), echinocandins (caspofungin, micafungin, anidulafungin), and amphotericin B (both amphotericin B deoxycholate and the lipid formulations of amphotericin B). Aerosol agents like amphotericin B and lipid products of amphotericin B have been effectively used for prophylaxis in certain high-risk patients [24,25], but there are no substantial data on their use for treatment of fungal pneumonias. For treatment of *Candida* infection at the site of bronchial anastomosis in lung transplant patients, aerosol agents have been used successfully, but nearly always in concert with systemic antifungal therapy. Regarding systemic therapy, amphotericin B lipid complex obtains higher pulmonary tissue concentrations than liposomal amphotericin B [26], but there are no studies to show that this pharmacokinetic difference has a therapeutic advantage.

The two primary classes of drug for invasive candidiasis are azoles (fluconazole or voriconazole) and the echinocandins (caspofungin, micafungin, and anidulafungin). Both possess excellent penetration into lung tissue and fluids [27,28]. Although no specific studies in *Candida* pneumonia are available, it is reasonable to assume that depending on the susceptibility of the *Candida* species and the early institution of therapy, both classes should be effective in treatment of pulmonary candidiasis. As has been demonstrated in the setting of candidemia [29], the most important factor with regard to outcome in the setting of *Candida* pneumonia will likely be early diagnosis and institution of antifungal therapy.

Conclusions

Recent data have suggested that in immunocompetent patients, the presence of *Candida* colonization of the respiratory tract may be associated with a prolonged ICU and/or hospital stay, an increased risk of *Pseudomonas* VAP [30], and a potentially increased hospital mortality [31]. At the present time, however, it is unclear if the presence of *Candida*, in and of itself, is the potential cause of increased mortality. Rather, the presence of *Candida* could simply be a marker of increased host T-lymphocyte suppression, which ultimately may serve as the driving force behind increased mortality. As this story continues to unfold, it will be interesting to see if empiric therapy with antifungals in these patients will affect the described end points. If so, this could potentially alter treatment recommendations for immunocompetent patients.

Disclosures

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