Candida in Lung Specimens from Non-Neutropenic ICU Patients: Infection or Colonization?

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■ Introduction

Candida is an opportunistic yeast normally found in the oral cavity and gastrointestinal tract. Its ability to multiply and to invade the bloodstream and deep tissues is increasing. This has produced new clinical patterns of systemic disease whose expression is dependent on the immune status of the host. Thus, presence of *Candida* is intimately linked to the effects of chemotherapy and radiation therapy for cancer, hematological malignancies, human immunodeficiency virus (HIV) infection, malnutrition, corticosteroid therapy, and broad-spectrum antibiotics.

New definitions have been developed for classifying invasive fungal infections in cancer patients and/or bone marrow transplant (BMT) recipients as 'proven', 'probable', or 'possible', with the goal of improving the cross-study comparability of clinical and epidemiological data [1]. A diagnosis of proven invasive candidiasis requires a positive blood culture, a positive culture from a normally sterile site (other than the urine and sinuses), or a histologically positive biopsy specimen.

The 'probable' and 'possible' categories are defined based on three groups of criteria:

- host factors: duration of neutropenia longer than 10 days, persistent fever despite broad-spectrum antibiotic therapy, recent use of immunosuppressants, history of definite or probable candidiasis, acquired immunodeficiency syndromes (AIDS), clinical evidence of graft-versus-host disease;
- microbiological criteria: positive blood culture, positive urine culture in a patient without a urinary catheter;
- Clinical criteria indicating lower respiratory tract infection, sinonasal infection or central nervous system (CNS) infection, with major and minor criteria; criteria for disseminated infection (extensive skin lesions, enophthalmos) or chronic infection (abscesses of the liver or spleen, alkaline phosphatase elevation).

'Probable' invasive candidiasis is defined as the combination of one host factor, one microbiological factor, and either one major or two minor clinical factors. 'Possible' invasive candidiasis is the presence of one host factor and either one major or two minor clinical factors. A positive blood culture should be interpreted according to host factors, neutrophil counts, whether the patient has a central line, and whether the blood was sampled from a peripheral vein or a catheter.

Many intensive care unit (ICU) patients have pulmonary specimens containing *Candida* counts above the significant 'thresholds' validated for distinguishing colonization from nosocomial pneumonia [2]. *Candida* colonization in ICU patients reflects

acquired immunodepression with alterations in both neutrophil function (killing of bacteria, production of oxidants) and alveolar macrophage function [3–5].

We will focus on the interpretation of specimens yielding *Candida* in non-neutropenic ICU patients. After reviewing the clinical and experimental literature, we will critically appraise this issue, taking care to separate the questions that have been answered from those that remain open. Finally, we will suggest a research agenda for improving our understanding of the continuum that extends from colonization to infection of the lower respiratory tract by *Candida* in non-neutropenic ICU patients.

■ *Candida* Infection in the ICU: Epidemiological Studies

We will consider two groups of epidemiological studies, those addressing nosocomial pneumonia in general and those focusing specifically on fungal infections in the ICU. In the former, an approach similar to the standard diagnostic strategy for bacterial nosocomial pneumonia revealed a high prevalence of respiratory tract specimens yielding *Candida* in concentrations above the threshold used to distinguish colonization from infection. The latter used a more specific approach to the diagnosis of *Candida* pneumonia and found that the incidence of this condition, although low, is on the rise.

The European Prevalence of Infection in Intensive Care (EPIC) study, a 1995 prevalence survey of nosocomial infection in European ICUs, found that pneumonia contributed 46.9% of all ICU-acquired infections and that 17% of ICU-acquired infections were related to yeasts, primarily *Candida* [2]. The National Nosocomial Infections Surveillance (NNIS) system in the United States showed that *Candida* species were responsible for 10.1% of all ICU-acquired infections between 1980 and 1990 [6]. Furthermore, the incidence of *Candida* infection in hospital patients increased steadily over the study period, 5-fold for candidemia, 2-fold for urinary tract infections, and 1.6-fold for pneumonia [6]. Other studies have reported nosocomial *Candida* pneumonia in patient subgroups sharing factors such as ICU admission or postoperative status [7–9]. *Candida* pneumonia has also been described in patients with diabetes mellitus or alcohol abuse; pharyngeal colonization by yeasts is also common in these patients [10, 11].

In a study of fungal pneumonia conducted at the National Taiwan University Hospital, a 27-fold increase in nosocomial candidemia occurred between 1980 and 1994 [12]. The diagnosis of fungal pneumonia was based on examination of lung biopsies obtained by thoracotomy or thoracoscopy, percutaneous pleural or lung biopsies obtained under ultrasound guidance, or transbronchial biopsies. The number of cases of fungal pneumonia increased from 5 in 1988 to 30 in 1997. Over the 10-year study period, 140 cases of fungal pneumonia were identified, including 20 due to *Candida*. *Candida* was associated with 70% mortality, the highest rate among causes of fungal pneumonia; mortality was 40% for *Aspergillus* and 6.7% for *Cryptococcus*.

In patients with cancer, neutropenia, anticancer chemotherapy, hematological malignancies, or organ transplants, *Candida* pneumonia is a marker for severe immune system impairment accompanied with selective vulnerability to opportunistic infections [13–15]. In most patients, pneumonia occurs as a metastatic complication of candidemia, often at the terminal stage of a malignant disease with pro-

found immunodepression [16]. Positive specimens for *Candida* in these patients raise specific issues, which will not be discussed here.

■ *Candida* Colonization: Considerations Specific to ICU Patients

Studies in ICU and surgery patients have confirmed that a continuum exists from colonization to infection with *Candida*: colonization is an independent risk factor for systemic candidiasis [17–20]. Pittet et al. found that *Candida* colonization was an independent risk factor for deep-seated candidal infection and that routine serial testing for colonization at multiple sites (trachea, urine, skin, stool, surgical wounds, and drainage fluids) can be used to define a colonization index (number of positive sites/number of tested sites) [8]. A colonization index greater than 0.5 was associated with an increased risk of deep-seated candidal infection. This risk increase may, in theory, indicate systemic antifungal treatment [21]. Evidence from several studies indicates that candidemia carries a poor prognosis and, consequently, requires early diagnosis or prophylactic measures [19, 22–25]. The beneficial effects of prophylactic treatment have been documented in hematology patients [26–28] and suggested by several ICU studies [29–32]. Work is ongoing to validate pre-emptive antifungal treatment in patients with *Candida* colonization.

At the respiratory tract, the colonization/infection dichotomy is supported by evidence from autopsy studies (which are older) and clinical studies. Three autopsy studies in 91 cancer patients led to the same conclusions. In immunocompromised patients with systemic candidiasis and pulmonary manifestations, lung pathology consists of necrotizing vasculitis, where the vessels are lined with pus cells containing yeasts. In contrast, in patients without systemic candidiasis, the pulmonary lesions are more likely to consist of pneumonia with intra-alveolar involvement but no vasculitis [16, 33, 34]. Thus, candidal ‘pneumonia’ seems to exist as two variants. One is secondary to hematogenous dissemination with selective tropism for the blood vessels; this is probably true pulmonary candidiasis. In the other variant, *Candida* colonizing the oropharynx and gastrointestinal tract spreads along the respiratory tract, ultimately filling the alveoli, so that endobronchial specimens are positive but no clinical or pathological evidence of pneumonia is detectable (Fig. 1) [35, 36].

Clinical studies consistently support this distinction. We will focus on two studies that investigated the clinical relevance of ‘positive’ tracheal or protected distal specimens, bronchoalveolar lavage (BAL) fluid, or bronchial or transbronchial biopsies. Both studies included ICU patients who received mechanical ventilation for longer than 3 days [37, 38] and had no evidence of systemic candidiasis. In most patients, lung biopsies or lung autopsy specimens found tracheobronchial colonization without evidence of invasive candidiasis despite positive respiratory specimens. Thus, the usual diagnostic criteria for nosocomial pneumonia do not seem valid for pulmonary candidiasis. Among clinical studies, we will discuss the immediate postmortem study by El-Ebiary et al. [37] in 25 non-neutropenic ICU patients who received mechanical ventilation for longer than 72 hours and died in the ICU. The objective was to investigate correlations between qualitative or quantitative cultures positive for *Candida* and a diagnosis of pulmonary candidiasis. Immediately after death, endotracheal aspirate, protected specimen brush (PSB), BAL, blind transbronchial biopsies, and bronchoscopically guided biopsies were performed. Ten

Fig. 1. Pathophysiological concept of *Candida* pneumonia. *Candida* pneumonia seems to exist as two variants. Even when *Candida* concentrations in respiratory specimens are greater than the cut-off separating colonization from infection, the most likely diagnosis is lower respiratory tract colonization related to spread of *Candida* colonization from the digestive tract to the tracheobronchial tree [58]. Histology shows no evidence of infectious vasculitis related to *Candida* invasion. Conversely, when candidemia is suspected, pulmonary involvement can reflect invasive candidiasis of the lungs secondary to hematogenous dissemination of the organism

(40%) of the 25 patients had at least one biopsy yielding *Candida*, and *Candida* contributed 9% of isolates from biopsies. However, only two (8%) of these patients had definite pulmonary candidiasis. Alveolitis was found in several patients, but there was no evidence of a causal relation with *Candida* since other organisms were usually present also. Furthermore, *Candida* colonization seemed uniform throughout the tracheobronchial tree. Although the small number of patients is a limitation of this study, the data provide a description of *Candida* colonization in ventilated ICU patients and emphasize the poor correlation between respiratory samples yielding *Candida* (colonization) and invasive pulmonary candidiasis.

■ Experimental Models of Pulmonary Candidiasis

Host defence mechanisms against *Candida albicans* have been investigated in several animal models, which are summarized in Table 1.

Knockout Mice for the Interferon Gamma Gene

Evidence for a key role of phagocytic cells stimulated by interferon (IFN)- γ has been obtained in knockout mice for the IFN- γ gene. As early as the second day after an intraperitoneal injection of *C. albicans*, a lymphoid infiltrate was seen

Table 1. Experimental models of *Candida* pneumonia

Reference	Year of publication	Experimental model	Route of <i>Candida</i> administration	Pulmonary involvement
[59]	1976	Mice	Intravenous	<i>C. albicans</i> multiplies at a faster pace in the kidneys than in the lungs
[60]	1991	Rats with obstructive jaundice	Intravenous	Increased pulmonary localization of <i>C. albicans</i> 3 weeks following ligation and division of the distal common bile duct
[61]	1992	Neutropenic rats (cyclophosphamide)	Intraperitoneal	Compartmentalized TNF production in the lower respiratory tract. Increased mortality, shock and ALI
[62]	1993	Rats with dual infection (<i>E. coli</i> and <i>C. albicans</i>)	Intravenous in association with <i>E. coli</i> injection	Increased lung distribution of <i>E. coli</i> following dual injection
[63]	1994	Neutropenic rats (cyclophosphamide) treated with GM-CSF	Intraperitoneal	Reduced incidence of shock and ARDS in GM-CSF treated rats. Decreased mortality. No hemorrhage, alveolar disruption, or fungi in lung parenchyma
[64]	1994	Murine BAL fluid was tested for anti-candidal activity	<i>Ex vivo</i> experiments	Heat-stable, soluble factor(s) suppress candidal colonization of the lower respiratory tract
[39]	1998	Mice KO for interferon γ -gene	Intraperitoneal	Extensive perivascular lymphoid infiltrate by day 3, diffuse pneumonia by day 28. Excess mortality
[41]	1999	Wild mice (control group)	Intratracheal	Normal lungs, normal clearance of <i>C. albicans</i>
[41]	1999	Mice deficient in MPO (homozygous mutant)	Intratracheal	Delayed clearance of viable <i>C. albicans</i> . Edema and massive infiltration of alveolar and peribronchiolar spaces with neutrophils by 120 hours. Excess mortality
[41]	1999	Mice deficient in MPO (homozygous mutant)	Intraperitoneal (high dose)	Increased <i>Candida</i> dissemination All animals dead by 2 days
[42]	2001	Alveolar macrophage-depleted mice	Intravenous	Increased cfu numbers of <i>C. albicans</i> , reduced pulmonary edema, BAL neutrophilia, MPO activity and MIP-2 expression in lung homogenates. Reduced mortality

KO: Knockout; BAL: bronchoalveolar lavage; MPO: myeloperoxidase; ALI: acute lung injury; cfu: colony forming unit; ARDS: acute respiratory distress syndrome

around the pulmonary blood vessels. Subsequently, the infiltrate cleared and diffuse pneumonia developed, without necrotizing vasculitis in the lungs, although necrotizing vasculitis was found in other organs (spleen, liver, heart, and brain). Mortality was considerably higher in the knockout mice than in the controls [39].

Myeloperoxidase-deficient Mice

Although mononuclear phagocytes are important in combating *C. albicans*, neutrophils also play a crucial role. Myeloperoxidase is an enzyme found mainly within neutrophils. It converts hydrogen peroxide (H_2O_2) to hypochlorite (HOCl), a highly cytotoxic compound involved in the neutrophil respiratory burst that releases reactive oxygen species (ROS), which are the key to the antimicrobial effects of neutrophils. Aratani et al. reported increased susceptibility to *C. albicans* in myeloperoxidase-deficient mice. Although *Staphylococcus aureus* clearance was normal in these mice, after instillation of *C. albicans* pneumonia was more likely to develop, and once developed to be fatal [40, 41].

Role of the Alveolar Macrophage in Defence Mechanisms against Candida

Another study established a role for alveolar macrophages in neutrophil recruitment induced by *Candida* instillation. This role is mediated by the cytokine macrophage inflammatory protein (MIP)-2, which is a chemoattractant for neutrophils. Mice deficient in alveolar macrophages were less likely to die than control mice during candidemia. [42] Yet, *Candida* concentrations were higher in the deficient mice. Neutrophil counts in BAL fluid were lower in the deficient mice than in the controls. Neutrophil recruitment was related to secretion of MIP-2 by alveolar macrophages [42].

In general, experimental models for invasive candidiasis have been developed only in immunocompromised animals [43, 44]. Defence mechanisms against *Candida albicans* and the pathophysiology of systemic candidiasis have been only partly elucidated [45–47]. Phagocyte dysfunction is associated with susceptibility to systemic fungal infections. Phagocytosis of *C. albicans* is optimal after opsonization, which is required for phagocytosis by mononuclear cells [45–47], via a mechanism strongly dependent on nitric oxide (NO) [48]. The pivotal role for dendritic cells in the phagocytosis of *C. albicans* has been established recently [49]. Experimental models have been used to develop agents that are active on *C. albicans* yet have limited toxicity to the patient; efforts have also been made to enhance the antifungal effects of the immune system [50, 51]. Thus, human recombinant myeloperoxidase, IFN- γ , or granulocyte/macrophage colony-stimulating factor (GM-CSF) stimulate mononuclear phagocytes and enhance *C. albicans* phagocytosis and killing [50–52].

■ Conclusion of the Literature Review

Positive specimens for *Candida* are common in patients with immunodepression or prolonged broad-spectrum antibiotic therapy [37, 38]. Invasive pulmonary candidiasis is an exceedingly rare entity that seems to represent the pulmonary expression of hematogenous dissemination. It is intimately linked to profound immuno-

depression, generally systemic (bone marrow failure, chemotherapy, HIV infection) but occasionally local (prolonged intubation in the ICU), and occurring mainly in terminally ill patients with several interlinked conditions (host factors, treatments, risk factors) [16]. Nevertheless, endobronchial specimens yielding *Candida* in counts above or below positivity thresholds remain clinically relevant: they indicate 'relative' immunodepression, particularly in ICU patients or after surgery (postaggression immunodepression). In this situation, curative antifungal treatment should be discussed. Because a respiratory specimen yielding *Candida* indicates bronchial colonization, a search for colonization at other sites is in order, to allow estimation of the colonization index, which is known to correlate well with secondary emergence of systemic candidiasis [8, 21, 30, 31].

Although we will not review the details of antifungal treatment, we will point out that treatment decisions depend on patient-related factors, the nature and severity of clinical manifestations, blood culture results, whether bone marrow failure is present, and whether other sites are colonized (colonization index). The recommendations issued by the British Society for Antimicrobial Chemotherapy Working Party can be used to select the antifungal agent [53, 54]; however, it should be borne in mind that the experts who developed these recommendations did not include the lungs among the targets of deep-seated candidal infection.

■ Suggested Research Agenda

Below is a suggested research agenda designed to help clinicians interpret pulmonary specimens yielding *Candida* in non-neutropenic ICU patients.

Epidemiological Questions

- What is the epidemiology of lower respiratory tract colonization by *Candida* in the ICU (host factors, *Candida* species involved)?
- What are the risk factors for acquiring *Candida* colonization of the lower respiratory tract? Identification of these risk factors would define a patient subset likely to benefit from prophylactic antifungal treatment strategies.

Impact of Lower Respiratory Tract Colonization by *Candida* in ICU Patients

- What are the morbidity and mortality attributable to *Candida* colonization of the lower respiratory tract?
- Is it possible to create, under experimental conditions, a model of invasive systemic candidiasis developing from lower respiratory tract *Candida* colonization in immunocompetent animals?
- How specific is lower respiratory tract *Candida* colonization? Does colonization at this site provide additional information over colonization at other sites? Does it have specific meaning in mechanically ventilated patients, given the described risk of translocation of bacteria colonizing the lower respiratory tract [55–57]?

Does Lower Respiratory Tract *Candida* Colonization *per se* Indicate Pre-emptive Antifungal Treatment in Patients on Mechanical Ventilation?

The value of pre-emptive or preventive treatment has been established in high-risk ICU patients [30] and is being evaluated in patients with multiple-site *Candida* colonization. The problem here is to discuss pre-emptive antifungal treatment in non-neutropenic patients with lung specimens yielding *Candida*, adjusting on the colonization index. The variable of interest will not necessarily be the mortality rate or incidence of candidemia; treatment efficacy could be evaluated based on criteria such as morbidity (ICU length of stay, mechanical ventilation duration), acquisition of bacteria with multiple drug resistance, emergence of resistance to the antifungal agent used, or selection of resistant *Candida* species.

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