

# Candidemia in Nonneutropenic Patients with an Intravenous Hyperalimentation Catheter: Good Prognosis of *Candida parapsilosis* Infection

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(Received: April 27, 1995)

(Accepted: June 16, 1995)

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Key words: candidemia, catheter-related infection

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## Abstract

Positive blood cultures reported between 1986 and 1993 at the Tokyo Metropolitan Komagome Hospital were evaluated and all patients with an intravenous hyperalimentation catheter who developed candidemia, a total of 94 patients, were analyzed further, while patients with neutropenia were excluded.

The primary diagnosis was malignancy in 87.2% of the cases, and *Candida albicans* and *C. parapsilosis* were the main organisms detected. A total of 17 patients died from candidemia. The patients who were positive for *C. parapsilosis*, however, all survived in spite of the fact that their main treatment was only removal of the catheter (20/32 cases), while eight of 25 patients who developed fungemia due to *C. albicans* died from the fungemia ( $p=0.001$ ). There were no significant differences in their risk factors.

Because of the better outcome for the patients who developed candidemia due to *C. parapsilosis*, we might be able to consider less aggressive treatment for such patients.

## Introduction

The increasing incidence of fungal infection in the immunocompromised host has become one of the leading causes of morbidity and mortality in recent years. Its growing importance is expanding to patients without neutropenia and management is becoming more difficult because of the difficulty in making a diagnosis. It may be too late to start appropriate treatment once the blood culture has become positive<sup>1)~4)</sup>. In many cases, therefore, effective treatment has to be started when fungemia is suspected, which is especially difficult in patients without neutropenia or any other significant risk factor.

The treatment of fungal infection in general is to remove a foreign body including a central venous catheter and start administration of antifungal agents, which should be continued for several weeks at least<sup>1)~6)</sup>. This will prolong the length of the patient's hospital stay with increasing hospital costs.

In reviewing the medical records of the patients with fungemia in our institution, a significantly better outcome was observed in a group of patients with a central venous catheter who were not neutropenic and were infected with *Candida parapsilosis*. This observation might help reduce the

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平成7年9月20日

hospital costs in taking care of such patients.

### Materials and Methods

Sequential positive blood cultures reported between 1986 and 1993 at the Tokyo Metropolitan Komagome Hospital were analyzed. The BacT/Alert system (Organon Teknika Co., Durham, NC, U.S.A.) or Bactec NR vials (Becton-Dickinson Diagnostic Instrument Systems, Sparks, Md, U.S.A.) were used for the blood culture. API 20 C AUX (BioMerieux S.A., Marcy-l'Etoile, France) was used to identify the fungi.

Medical records of the patients with blood cultures positive for *Candida* were reviewed, and those of all patients with an intravenous hyperalimentation (IVH) catheter were analyzed further. Patients with neutropenia (granulocyte count less than  $0.5 \times 10^9/L$ ) when their blood culture became positive for *Candida* were excluded from the analysis.

The methods of treatment and the outcome of the disease were evaluated retrospectively. Treatments selected by the responsible physicians were then divided into four groups: removal of the IVH catheter only, parenteral administration of antifungal agents without removal of the catheter, removal of the catheter and initiation of antifungal agents, and no specific treatment. The selection of antifungal agents including their dose and the duration of the treatment depended on the individual physician. If the patient died within a month after the first positive blood culture was obtained, the case was evaluated by one of the authors (H.A.) who was not told the identity of the responsible organisms. If the patients died while blood cultures remained positive or died from multi-organ failure due to fungal sepsis, the death was considered to have been caused by fungal infection.

#### Risk factor analysis

The APACHE-II severity of illness index was used to quantify the physiologic impairment of the patients<sup>7)</sup>. The APACHE-II score was calculated retrospectively from available data such as temperature, blood pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, potassium, creatinine, hematocrit, and white blood cell counts. Age and chronic health status were also calculated. Scoring was on the basis of the worst value available for the 24-hour period prior obtaining the first positive blood culture. Previous histories of using systemic antibiotics or corticosteroids within 2 weeks prior to, and the exposure to surgical procedures within 4 weeks prior to, the positive blood culture were also included in the evaluation.

#### Statistical analysis

Fisher's exact two-tailed test and unpaired t-test were used to compare proportions and means.

### Results

#### Patient characteristics

A total of 1185 patients at the Tokyo Metropolitan Komagome Hospital had positive blood cultures at least once between January 1986 and December 1993. In 151 patients (12.7%), the blood culture was positive for fungus. From these patients, a total of 153 fungi were obtained, and 125 of them from 123 patients were *Candida* species. Eleven patients developed candidemia during the study period while they were neutropenic and were excluded from further analysis, while another 18 patients with candidemia were also excluded because they did not have an IVH catheter.

A total of 94 patients with candidemia were analyzed. Their mean age was 62.4 years (range 24-91). The primary diagnosis was malignancy in 87.2% of the patients, while 65.8% of them (57.4% of the total) had gastrointestinal cancers (Table 1). *Candida albicans* and *C. parapsilosis* were the main organisms detected in patients with candidemia. In detail, *C. albicans* was responsible more frequently in patients under surgical care, and *C. parapsilosis* and *C. guilliermondii* tended to occur

Table 1 Characteristics of the patients who developed candidemia

<i>Candida</i> species	Patients (S/M)	Age		Primary disease		
		average	range	Malignancy		Others
				GI	Others	
<i>C. albicans</i>	25 (15/10)	62.9	24-80	12	8	7
<i>C. parapsilosis</i>	32 (13/19)	63.8	43-79	24	9	0
<i>C. glabrata</i>	14 (5/9)	64.9	43-91	7	3	4
<i>C. tropicalis</i>	12 (5/7)	56.1	28-73	6	4	2
<i>C. guilliermondii</i>	11 (2/9)	60.7	39-78	5	4	3
Total	94 (40/54)	62.4	24-91	54 (57.4%)	28 (29.8%)	16 (17.0%)

S/M: Number of patients in surgical service/medical service; GI: gastrointestinal.

in the medical services, although the difference was not statistically significant.

#### Treatment and outcome

A total of 17 patients died from candidemia and 14 of them died within 10 days after the first positive blood culture was obtained. Another four patients died within a month, but their deaths were not considered to be due to fungemia. Two patients died from their primary diseases even though they responded to removal of the IVH catheter and antifungal agents (both patients had candidemia due to *C. parapsilosis*). Two other patients died from aspiration pneumonia (*C. parapsilosis*, 1; *C. glabrata*, 1). There were no reported cases of late candidal infection including symptomatic endophthalmitis and myelitis.

Patients whose catheter was not removed had a worse outcome than those whose catheter was removed ( $p < 0.001$ ). Regarding antifungal agents, miconazole or fluconazole was administered intravenously to 38 patients, while only five patients received amphotericin B intravenously. There was no significant correlation between the antifungal agent used and patient mortality ( $P = 0.190$ ). *C. albicans* versus *C. parapsilosis*

The outcomes of the infection were then compared according to the species of fungus and treatment regimen. The patients who were infected with *C. parapsilosis* all survived, even though their main treatment was only removal of the catheter (20/32 cases). The patients who received antifungal agents with or without removal of the catheter also survived the candidemia. On the other hand, of the 25 patients who developed fungemia due to *C. albicans*, eight died from fungemia and three of the 20 whose catheter was removed died. Even when antifungal agents were used, five of 12 patients died from fungemia (Table 2). Two patients died even before the positive blood culture was reported. Catheter tips of 18 patients with fungemia due to *C. albicans* and 28 patients with *C. parapsilosis* were

Table 2 Outcome for the patients who developed candidemia according to the treatment regimen

<i>Candida</i>	Cases (death)	Treatment regimen [Cases (death)]			
		Removal of catheter	Antifungals	Both	None
<i>C. albicans</i>	25 (8) *	11 (1)	3 (3)	9 (2)	2 (2)
<i>C. parapsilosis</i>	32 (0) *	20 (0)	1 (0)	10 (0)	1 (0)
<i>C. glabrata</i>	14 (3)	4 (0)	1 (0)	4 (1)	5 (2)
<i>C. tropicalis</i>	12 (5)	3 (1)	2 (1)	5 (1)	2 (2)
<i>C. guilliermondii</i>	11 (1)	1 (0)	3 (1)	5 (0)	2 (0)
Total	94 (17)	39 (2)	10 (5)	33 (4)	12 (6)

\* $P = 0.001$  by Fisher's exact two-tailed test.

Table 3 Risk factors for candidemia in the patients with fungemia due to *C. albicans* and *C. parapsilosis*

Factor	<i>C. albicans</i> (n=25)	<i>C. parapsilosis</i> (N=32)	P value
APACHE-II score	13.7±4.9	12.3±4.7	0.287
Recent use of antibiotics	16 (66.7)	16 (50.0)	0.420
Recent use of corticosteroids	6 (24.0)	6 (18.8)	0.747
Recent surgery	7 (28.9)	7 (21.9)	0.758

P values were calculated by Fisher's exact two-tailed test and unpaired t-test.

( ) percentage.

cultured and 10 and 22 samples, respectively, were positive.

The mortality rate for patients who developed candidemia due to *C. parapsilosis* was, therefore, significantly lower than that for those infected with *C. albicans* ( $P=0.001$ ). Risk factors, such as APACHE-II scores, recent histories of using antibiotics, corticosteroids and/or surgical procedures, were then analyzed and no significant differences between the two groups were found (Table 3).

### Discussion

A total of 94 cases of candidemia among nonneutropenic patients with IVH catheters were documented during the 8-year period ending in December 1993, at the Tokyo Metropolitan Komagome Hospital. Many of the patients had gastrointestinal malignancies as the primary disease because this institution specializes mainly in care of adult patients with malignant diseases. During the study period, only 11 patients developed fungemia while they were neutropenic. However, this is not due to a low incidence of neutropenic episodes in our institution. For example, in the hematology division, almost 400 chemotherapy-induced neutropenic episodes of more than 10 days' duration were observed in patients with hematological malignancies during the same period<sup>8</sup>). The low incidence of neutropenic patients among those with candidemia is probably due to early initiation of antifungal treatment for patients suspected of having fungemia.

The mortality rate for the patients who developed candidemia was 18.1% (17/94). This rate might be lower than reported figures but the criteria for selection of the patients in our series should also be considered<sup>9</sup>). The mortality rate for the patients whose IVH catheter was removed was lower than that for the others, but this could be due to the poor general condition of the patients in the latter group, which prevented physicians from removing the catheter. Another four patients died but their deaths were considered not to be due to fungemia. Three of them had candidemia due to *C. parapsilosis*, but all of them were afebrile after removal of the catheter and/or initiation of antifungal treatment and their deaths were attributed to the primary disease or pneumonia.

When the mortality rate for the patients with fungemia due to *C. parapsilosis* was compared with that due to *C. albicans*, the former was found to be significantly lower than the latter ( $P=0.001$ ). The difference was significant even if three patients who were considered to have died of causes other than fungal infection were included in the analysis ( $P=0.04$ ). The mortality rate for the patients with fungemia due to *C. parapsilosis* was not compared with that for patients infected with other specific *Candida* species because of the small number of patients to be compared. But if the mortality rates for the patients with *C. parapsilosis* and those with all other *Candida* species were compared, the difference between them was still statistically significant ( $P=0.001$ ).

This difference, however, was not explained by the patients' status. The APACHE-II score of the patients in these two groups did not show any significant differences even though the score was

calculated retrospectively. The analysis of other risk factors, such as the use of corticosteroids or antibiotics within 2 weeks prior to, or a history of a surgical procedure within a month prior to, positive blood cultures, also failed to show any significant differences.

The fact that 76.8% of the cultures of catheter tips of 28 patients with fungemia due to *C. parapsilosis* were also positive for fungi makes it rather difficult to consider the possibility of contamination while obtaining the specimen. In general, these patients' symptoms resolved promptly after the removal of the catheter, which also suggests the existence of active infections due to fungi. Therefore, the difference in the mortality rates between these two groups seems to be due to the differences in the characteristics of the fungi themselves.

By using multivariate analysis, Komshian et al. showed that the mortality was not significantly affected by the species of *Candida*<sup>9)</sup>. The mortality rate due to *C. parapsilosis* (44%) was somewhat lower than that due to *C. albicans* (59%), even though the difference was not statistically significant. Those authors also found that *C. parapsilosis* fungemia rarely occurs in the setting of neutropenia, and that the portal of entry is most often an indwelling cannula. However, they did not limit their analysis to nonneutropenic patients, which makes it difficult to compare their data with ours. On the other hand, the association of *C. parapsilosis* with cannula sepsis, especially in the presence of hyperalimentation, has been well established<sup>10)</sup>. The incidence of fungemia due to *C. parapsilosis* in nonneutropenic patients may therefore increase in future.

Fungal infection is one of the leading causes of morbidity and mortality in immunocompromised hosts, and its importance is now expanding to patients without neutropenia. Management of the disease is therefore becoming more difficult. Although our data do not guarantee the safety of patients with fungemia due to *C. parapsilosis* after removal of the catheter, they might support the idea that observation only, without administering antifungal agents, might be sufficient for them as long as they are not neutropenic and have remained stable without any sign of active infection after removal of the catheter<sup>11)~6)</sup>. This strategy definitely requires that a more careful, possibly prospective, study be conducted but this study would be worth doing to reduce the length of hospitalization of the patients and also to reduce hospital costs in treating them.

### Acknowledgments

The authors thank Kuniko Nakamura for preparation of the manuscript.

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## IVH カテーテルを有する患者にみられた candida 血症の検討

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都立駒込病院で、1986年から1993年に血液培養から *Candida* が同定された症例のうち、IVH カテーテルが挿入されており、かつ neutropenia (顆粒球  $500/\mu\text{l}$  以下) のない94症例を対象とし、菌種と治療による予後の差について検討した。

同定された菌種は *Candida albicans* 25例 (うち真菌血症が直接死因となったと思われる死亡例 8), *C. parapsilosis* 32例 (0), *C. glabrata* 14例 (3), *C. tropicalis* 12例 (5), *C. guilliermondii* 11例 (1) であり、*C. parapsilosis* による死亡率が

*C. albicans* に比べ低かったが、両群の患者の危険因子については、解析しえた限りでは差は認められなかった。

カテーテルに合併した candida 血症に対しては、カテーテルの抜去と十分な抗真菌剤による治療が必要とされているが、本院での治療結果を見る限り、*C. parapsilosis* による真菌血症は、顆粒球が十分に有ればカテーテルの抜去のみでも対処できる可能性が示唆された。