

Oral amphotericin B for the prevention of *Candida* bloodstream infection in critically ill children*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Identify the role of the length of intensive care unit stay in the development of *Candida* bloodstream infection in critically ill infants and children.
2. Identify the important sites for *Candida* colonization and their relationship to *Candida* bloodstream infection in the pediatric intensive care unit.
3. Understand the role of oral Amphotericin B treatment in the prevention of *Candida* bloodstream infections in critically ill infants and children.

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Objectives: To determine the efficacy of oral amphotericin B for the prevention of *Candida* bloodstream infection in the pediatric intensive care unit.

Design: Retrospective, nonrandomized, historic-control study.

Setting: Multidisciplinary pediatric intensive care unit at a university-affiliated children's medical center.

Patients: Study group included all patients admitted to the pediatric intensive care unit from January 1, 1998, to December 31, 1999, who required mechanical ventilation and who were admitted for >7 days. The control group included all patients admitted for >7 days who needed mechanical ventilation from January 1, 1994, to December 31, 1997.

Interventions: Oral amphotericin B suspension, 50 mg every 8 hrs, administered to all study group patients soon after initiation of mechanical ventilation and terminating after weaning.

Measurements: The rates of *Candida* bloodstream infection were compared between the study and control groups.

Main Results: *Candida* species were isolated from blood cultures in 5 of 185 (2.1%) and 21 of 196 (10.7%) patients in the study and control groups, respectively ($p = .0038$). There was also a statistically significant ($p = .017$) decrease in *Candida* bloodstream infection rate in all patients admitted to the pediatric intensive care unit for >7 days during the study period compared with the *Candida* bloodstream infection rate during the control period.

Conclusion: Prophylactic administration of oral amphotericin B may lead to a significant decrease in the rate of *Candida* bloodstream infection in ventilated pediatric intensive care unit patients. (*Pediatr Crit Care Med* 2006; 7:115–118)

KEY WORDS: candidemia; *Candida*; amphotericin B; pediatric intensive care unit; preventive; nosocomial

Candida bloodstream infection (CBSI) is becoming an increasingly important nosocomial infection (1, 2). *Candida* species is the fifth most common cause of bloodstream infections among patients in pediatric intensive care units (PICUs) (2–

4). The rate of CBSI among patients in the PICU has been reported to be 0.2% to 4.3% (2–5). The National Epidemiology of Mycosis Survey (or NEMIS) showed that the average rate of CBSI is 0.98% in ICU patients, and there are wide interinstitutional variations, from 0.29% to 2%

(6, 7). CBSI accounted for 4.9–9.3% of all blood stream infections in PICUs (3, 4, 8). Nosocomial CBSI is associated with increased morbidity and mortality during hospitalization compared with other non-fungal bloodstream infections (8–10). This is especially true for patients who

*See also p. 184.

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require prolonged hospital stay, central venous catheters, total parenteral nutrition, mechanical ventilation, and broad-spectrum antibiotic and corticosteroid therapy (2, 5, 8–11).

Candida colonization is a significant risk factor in most reports (2, 7, 9, 10). It is presumed that the origin of invasive candidiasis is often a colonized gastrointestinal tract (8, 9, 12, 13). Therefore, prophylactic administration of oral amphotericin B, a potent, nonabsorbable anticondandidal medication, may decrease the load of *Candida* in the intestine and the rate of CBSI. Prophylactic administration of fluconazole to very-low-birthweight infants resulted in decreased risk of colonization and invasive fungal infection (14, 15). Several studies have shown that oral amphotericin B may be effective in the prevention of fungal infection in patients with neutropenia secondary to chemotherapy, patients after bone-marrow transplantation, and patients with immune deficiency (16–18).

In our PICU, prophylactic treatment with oral amphotericin B to all ventilated patients was initiated as a new policy in January 1998. The present study summarizes 2 yrs of this policy. The aim of this study was to determine the efficacy of oral amphotericin B solution for prevention of CBSI in ventilated patients hospitalized in the PICU as compared with historic controls.

METHODS

Patients. All patients admitted to the PICU between January 1, 1998, and December 31, 1999 (study period), who required mechanical ventilation and had a PICU stay of >7 days were enrolled in the study. Patients who had a diagnosis of CBSI at admission or who were being treated with amphotericin B or other systemic antifungal medications were excluded. This retrospective study was reviewed by the institutional review board and is in accordance with the ethical standards with institutional review board criteria.

Setting. The study was performed in a multidisciplinary PICU at Schnieder Children's Medical Center of Israel, a 250-bed tertiary care facility. The number of yearly admissions to the PICU is 700–800 patients.

Design. The study was divided into two periods: January 1, 1998, to December 31, 1999 (study period), and January 1, 1994, to December 31, 1997 (historic control period). To compare the rate of CBSI between similar populations between the periods, we defined a group of patients at high risk: patients who were admitted to the PICU for >7 days and who required mechanical ventilation. The fol-

lowing risk factors for CBSI during the control and study periods were compared: duration of PICU stay, duration of ventilation, need for total parenteral nutrition, presence of central venous catheters, and antibiotic therapy.

Treatment Protocol. All 494 patients admitted to the PICU during the study period who required mechanical ventilation were treated with 50 mg of oral amphotericin B every 8 hrs, starting soon after initiation of mechanical ventilation and terminating soon after weaning.

Indications for Drawing Cultures. Routine urine and sputum cultures were taken twice a week from every patient via urine catheter or endotracheal tube.

In every suspicion for infection (fever, complete blood count abnormalities, change in clinical status), a peripheral blood culture, central venous catheter and arterial catheter blood cultures, and urine and sputum cultures were taken. Therefore, positive blood cultures were clinically significant.

Culture. For *Candida* isolation, 3–5 mL of whole blood was drawn for culture. Blood cultures that were positive for yeast by Gram-negative stain were further cultured on Sabourond agar and on CHROM agar *Candida*. *Candida* identification was done using the CANDIFAST test (International Microbiology) or the API ID 32C (BioMerieux).

Definitions. CBSI was defined as the isolation of *Candida* from at least one peripheral blood culture.

Chart Review. Data were retrieved from the patient's medical records and the microbiology laboratory data banks.

Analysis. The rates of CBSI during study and control periods were calculated by the number of patients with CBSI divided by the total number of patients in the group. Fisher's exact test was used for statistical analysis; $p \leq .05$ was considered statistically significant. Backward, stepwise, multivariate regression analyses were used for controlling the factors that are known to predispose to candidemia,

including the days in PICU, days of ventilation, central venous catheters, total parenteral nutrition, and antibiotic treatment.

RESULTS

During the study period, 223 patients were admitted for >7 days, of whom 185 patients required mechanical ventilation, and during the control period, 281 patients were admitted for >7 days, of whom 196 required mechanical ventilation. The rates of CBSI were 2.7% (5 of 185 patients) during the study period as compared with 10.7% (21 of 196 patients) during the control period ($p = .0038$). The average duration of PICU stay was 77.8 ± 66.9 and 63.4 ± 57.9 days ($p = .64$), and the duration of ventilation was 45.6 ± 42.6 and 29.25 ± 36.9 days ($p = .44$) in the study and the control groups, respectively. Figure 1 shows the breakdown of the risk groups during the study and control periods.

CBSI was found in 5 of 494 ventilated patients (1.01%) during the study period who were treated with oral amphotericin B. CBSI was diagnosed in 6 of 1,621 patients (0.37%) admitted to our PICU during the study period and in 22 of 2645 patients (0.83%) admitted during the control period ($p = .08$). However, there was a significant decrease in the rate of CBSI in all patients admitted to the PICU for >7 days, 2.7% (6 of 223 patients) vs. 7.8% (22 of 281 patients) ($p = .017$).

In multivariate regression analysis, the differences between the study and the control groups were not influenced by the days in the PICU, days of ventilation, central venous catheter, total parenteral nutrition, or antibiotic treatment

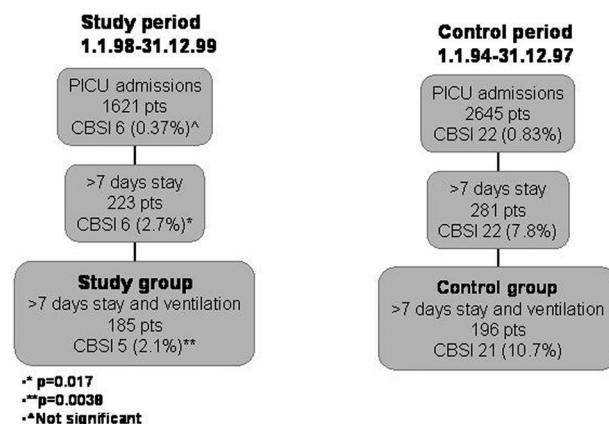


Figure 1. Breakdown of the risk groups and the rate of *Candida* bloodstream infection (CBSI). A significant decrease in the rate of candidemia between the study and the control group. * $p = .017$; ** $p = .0038$; [^] not significant. PICU, pediatric intensive care unit; pts, patients.

Table 1. Episodes of colonization of the various sites in both the study and control periods

Site	Control Group		Study Group	
	Total	Before Candidemia	Total	Before Candidemia
Central venous catheter ^a	7	2	2	0
Arterial catheter	1	1	0	0
Sputum	10	6	1	1
Urine	11	8	0	0
Skin wound	2	0	2	2

^a*Candida* isolation from central venous catheters concomitant with isolation of *Candida* from peripheral blood.

Table 2. Characterization of candidemic patients during the study period

Patient No.	Diagnosis	Infective Agent	Days After Admission	Prophylaxis
1	TEF, gastrostomy	<i>Candida albicans</i>	158	No ^a
2	70% surface area burn	<i>C. albicans</i>	24	Yes
3	Cardiac surgery	<i>C. albicans</i>	22	Yes
4	TEF, mediastinitis	<i>Candida parapsilosis</i>	2	Yes
5	Asphyxia	<i>Candida tropicalis</i>	6	Yes

TEF, tracheoesophageal fistula.

^aNot ventilated at the time of *Candida* bloodstream infection.

Table 1 summarizes the sites and time of *Candida* isolation colonizations during study and control periods. *Candida* species were isolated from central venous catheters in two (40%) and in seven (33%) patients with CBSI during the study and control periods, respectively. Overall, colonization with *Candida* preceded CBSI in 60% and 72.7% of the patients with CBSI in the study and control groups, respectively.

Disease-related data for the five patients with CBSI during the study period are shown in Table 2. One patient did not receive oral amphotericin B prophylaxis because she did not require mechanical ventilation at the time of CBSI. *Candida* species were isolated from peripheral blood culture of four patients, despite prophylactic treatment. *Candida albicans* was isolated from two of them, one had a third-degree burn on 70% of body surface area, and the other had undergone cardiac surgery, after which the chest wall was left open for 5 days due to severe hemodynamic instability. The third patient was a neonate in whom *Candida parapsilosis* was isolated from peripheral blood and from a central venous catheter. The patient had been in the PICU for only 2 days after 1 month of hospitalization in the neonatal ICU following tracheoesophageal fistula repair. He also had respiratory failure and suspected mediastinitis and was therefore treated with total parenteral nutrition and broad-spectrum an-

tibiotics. *Candida tropicalis* was identified in the fourth ventilated patient who had severe brain damage after resuscitation for severe airway obstruction. Thus, only three patients who received oral amphotericin B for >2 days before colonization had CBSI.

No significant adverse effects were noted in the ventilated study patients secondary to amphotericin B prophylaxis. In one patient with megalolarynx and megalotrachea, a small amount of the drug was aspirated from the tracheal secretion.

DISCUSSION

The present study demonstrates that the use of prophylactic amphotericin B may significantly decrease the rate of CBSI in patients admitted to the PICU for >7 days who also require mechanical ventilation. The rate of CBSI in all patients admitted to the PICU did not differ significantly between study and control periods, although there was a trend toward a lower rate of CBSI during the study period (0.37% vs. 0.83%, $p = .08$). The rate of CBSI in the present study was more than the 0.2% reported by Gray in PICUs and adult ICUs (3, 19) but much lower than the 4.3–3% rate in PICUs that was reported by others (2, 5).

One patient in the control group (4.8%) and one patient of the study group (20%) died within 7 days of the first positive culture, a period that is commonly

used to define death as a direct result of infection. Both patients had multiple organ failure before the CBSI. Therefore, it seems that none of the patients died as a direct result of CBSI during either the study or the control period. The rate of mortality within 7 days was 37.5% in recent studies (2, 3). Singhi et al. (2) reported 28% mortality of candidemic children in the PICU (18 out of 64 patients), all of whom were symptomatic. Eleven patients died within 72 hrs, before blood culture reports growing yeast became available; these patients were not started on antifungal therapy. The rate of late mortality in patients with CBSI was 38.1% (8 of 21 patients) in the control group and 40% (two of five patients) in the study group, respectively. This mortality rate is lower than that reported in two recent PICU studies (2, 3). Gray et al. (3) reported an overall 50% mortality (four of eight patients with CBSI). Our patients were at higher risk because all of them stayed in the PICU for >7 days and required ventilation.

A recent prospective survey of CBSI (9) showed a mortality rate of 12.7% in children (aged 0–9 yrs old, including premature infants). This study included asymptomatic patients. Another study reported that 21.7% of all deaths in the patient group were attributed to CBSI (19).

Several studies have proven the importance of *Candida* colonization as a risk factor for systemic infection, which in most cases is caused by endogenous organisms via translocation from the gastrointestinal tract (7–10, 20, 21). Tororano et al. (9) found that mucous membrane colonization preceded fungemia in 83% of CBSIs. *Candida* was isolated from the urine, sputum, or skin (burn or surgical wound) in 76% and 60% of CBSI patients in the control and study groups, respectively. It was isolated before CBSI occurred in most patients. Only three patients had CBSI, despite prolonged (>2 days) treatment with oral amphotericin B. Therefore, we speculate that amphotericin B should be given before colonization with *Candida* species. Because mechanically ventilated patients are at risk for CBSI and many of them will have more risk factors for CBSI during PICU stay, we decided to give prophylactic amphotericin B only to this group of patients and not to all PICU admissions.

Our study has the inherent limitations of a retrospective study. To avoid an inappropriate comparison between the pe-

riods, we determined the rate of CBSI in well-defined subgroups of patients. Patients in the control and study periods were similar for many risk factors of CBSI, including duration of PICU stay, duration of ventilation, use of total parenteral nutrition, antibiotic therapy, and central venous catheters and therefore could be compared.

In conclusion, oral amphotericin B may be an effective agent for the prevention of CBSI in patients hospitalized in the PICU, particularly if given before colonization with *Candida* species. A prospective, randomized, controlled study is needed to further establish the beneficial effect of prophylactic amphotericin B on the rate of CBSI in the PICU.

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