Should Central Venous Catheters Be Removed as Soon as Candidemia Is Detected in Neonates?

M. Gary Karlowicz, MD*; Laura Nickles Hashimoto, MD*; Robert E. Kelly, Jr, MD‡; and
E. Stephen Buescher, MD*

ABSTRACT. *Background.* **Controversy exists regarding the most appropriate acute management of central venous catheters (CVCs) in neonates with candidemia, with up to two thirds of neonatologists preferring to attempt antifungal therapy without removing CVCs.**

Objective. **To determine whether CVCs should be removed as soon as candidemia is detected in neonates.**

Methods. **A cohort study of candidemia and CVC was conducted in infants in a neonatal intensive care unit (NICU) over a 5-year period (1994–1998).**

Results. **Fifty infants had early-removal CVC (ER-CVC) within 3 days and 54 infants had late-removal CVC (LR-CVC) >3 days after the first positive blood culture for *Candida* species. All infants were treated with amphotericin B. There was no significant difference between infants in the ER-CVC and LR-CVC groups in terms of gender, ethnicity, birth weight, gestational age, age at candidemia, severity-of-illness scores, distribution of types of CVC, or in the distribution of *Candida* species causing candidemia. The ER-CVC group had significantly shorter duration of candidemia (median: 3 days; range: 1–14 days), compared with the LR-CVC group (median: 6 days; range: 1–24 days). The case fatality rate of *Candida albicans* candidemia was significantly affected by the timing of CVC removal: 0 of 21 (95% confidence interval [CI]: 0–14) infants died in the ER-CVC group in contrast to 9 of 23 (39%; 95% CI: 19–59) in the LR-CVC group.**

Conclusion. **Failure to remove CVC as soon as candidemia was detected in neonates was associated with significantly increased mortality in *C albicans* candidemia and prolonged duration of candidemia regardless of *Candida* species. *Pediatrics* 2000;106(5). URL: http://www.pediatrics.org/cgi/content/full/106/5/e63; *Candida, central venous catheter, neonate.***

ABBREVIATIONS. NICU, neonatal intensive care unit; CVC, central venous catheter; ER-CVC, early-removal central venous catheter; LR-CVC, late-removal central venous catheter; NTISS, Neonatal Therapeutic Intervention Scoring System; CI, confidence interval.

Several authors have expressed concern that systemic candidal infections are increasing in neonatal intensive care units.[1,2] We reported that the rate of candidemia in our neonatal intensive care unit (NICU) increased >11-fold in the 15 years from 1981 to 1995.[3] We also reported a significantly higher case fatality rate of 26% for candidemia caused by *Candida albicans*, compared with a 4% case fatality rate for *Candida parapsilosis*.[3] Increased and widespread use of central venous catheters (CVCs) in NICUs is believed to contribute to the increased incidence of candidemia as well as increased morbidity and mortality of candidal infections.[1,2]

The 1996 International Consensus Conference on the Management of Severe Candidal Infections strongly suggested that all intravascular catheters in patients with systemic candidal infections be removed, although the focus of the Consensus Conference was primarily adult patients.[4] Edwards and Baker[5] unequivocally stated that identification of candidemia in neonates "mandates removal of all intravascular devices," but no citation from the neonatal literature was given to support this recommendation. In fact, 2 case series have recently suggested that bloodstream infections in neonates, including candidemia, can resolve with antimicrobial therapy without removing CVC.[6,7] Therefore, it is not surprising that a recent survey by the Neonatal Candidiasis Study Group reported that only 35% neonatologists and 53% infectious disease specialists would immediately remove a CVC from a neonate with the first positive blood culture for *Candida* species.[8]

In our institution, the attitude toward removal of CVC at the time of diagnosis of candidemia varied among pediatric specialists, leaving the dilemma unresolved. Because we have extensive experience with candidemia in neonates, we sought to address this controversy by determining: 1) whether candidemia was prolonged when CVCs were not removed immediately; 2) whether the case fatality rate of candidemia was increased if CVCs were not removed as soon as candidemia was detected; and 3) whether the case fatality rates and duration of candidemia of different *Candida* species were affected differently by timing of removal of CVC.

METHODS

Study Population

A cohort study was conducted of all infants with candidemia and CVC in the NICU at Children's Hospital of The King's Daughters, Norfolk, Virginia, between January 1, 1994 and December 31,

1998. This hospital contains the regional referral nursery for southeastern Virginia and northeastern North Carolina. We excluded infants without CVCs and infants who died within 2 days of onset of candidemia because they were fulminant cases. Infants with fulminant candidemia were excluded because they died before *Candida* species were identified as the pathogens causing sepsis and, therefore, before a decision could be made regarding CVCs removal based on detection of candidemia.

Definitions

Candidemia was defined as *Candida* species growth from at least 1 blood culture from a peripheral or central venous sample.[3] Cultures with the same organism within 30 days of first isolation were considered 1 episode. Duration of candidemia was defined as the interval from the first to the last blood culture positive for *Candida* species.[9] There were 3 types of CVCs: 1) surgical CVCs, which were 4 French, double-lumen polyethylene CVCs inserted percutaneously by surgical staff; 2) peripheral CVCs, which were inserted by NICU staff; and 3) umbilical CVCs, which were inserted by resident physicians and/or NICU staff. Early removal of CVC (ER-CVC) was defined as removal of CVC within 3 days of the first positive blood culture, and late removal of CVC (LR-CVC) was defined as removal of CVC >3 days after the first positive blood culture for *Candida* species. Catheter exchange over a guidewire was considered to be catheter removal for sake of analysis. Timing of CVC removal was at the discretion of the attending neonatologists. The Neonatal Therapeutic Intervention Scoring System (NTISS)[10] was used as an indicator for severity-of-illness. An NTISS score on the day of the first positive blood culture for *Candida* was determined from the medical record of each patient. Candidemia was considered contributory to case fatality if: 1) an infant died within 3 days of a positive blood culture[3]; 2) there was autopsy evidence of disseminated candidiasis; or 3) death was attributable to complications of candidemia, eg, superior vena cava syndrome after an infected venous thrombus.

Database Management

The neonatology division maintains several databases that prospectively abstract information from the medical records of infants admitted to the NICU. Data are entered into databases by research nurses. Data entry is closely monitored and periodically reviewed by the senior clinical investigator (M.G.K.) for quality improvement purposes. Two separate NICU databases were used as information sources: a neonatal database that contains basic demographic, morbidity, and outcomes data; and a candidemia database containing clinical details about episodes of candidemia. A third database is prospectively maintained by the pediatric surgery service that tracks placement, removal, and complications of all CVCs inserted throughout the institution. These data are collected and entered by a central line nurse who is supervised by the surgeons. Data from the neonatal database, the candidemia database, the central line database, and manual review of medical records were entered into a single study database for analysis. The study was approved by the institutional review board of Eastern Virginia Medical School.

Microbiology

Blood cultures were collected and processed according to standard microbiologic techniques. BACTEC Peds Plus/F culture vials were used routinely and all cultures were monitored using an automated culture system. All positive vials were Gram-stained and subcultured for organism identification on sheep's blood, chocolate, and MacConkey agars. Presumptive identification of *C albicans* was based on germ tube formation. Other *Candida* species were identified based on the Minitek yeast carbon assimilation procedure.

Statistical Methods

Comparisons between groups were made with the unpaired *t* test for parametric data or with the Mann-Whitney *U* test for nonparametric data. Categorical data were analyzed with the Fisher's exact test or χ^2 test for trends as appropriate. Significance was declared at $P < .05$, and relative risks with 95% confidence intervals (CIs) are shown. Absolute risk increase was determined when a specific treatment increased the occurrence of an adverse outcome and was calculated by subtracting occurrence rate in

controls from the occurrence rate in the intervention group. Number needed to harm indicates how many patients need to receive a specific treatment to cause one additional adverse outcome. Number needed to harm was determined by dividing 1 by the absolute risk increase.[11]

RESULTS

Study Group

A total of 2952 infants were admitted to the NICU during the 5-year study. There were 113 infants (4%) with 114 cases of candidemia. Ten infants were excluded: 3 died within 2 days of onset of fulminant candidemia and 7 did not have CVCs when candidemia was detected. In study infants, 73 peripheral CVCs, 28 surgical CVCs, and 6 umbilical CVCs were in use at the time of diagnosis of candidemia. All cases of candidemia were treated with amphotericin B, which was usually started at .5 mg/kg every 24 hours and advanced daily by .25 mg/kg up to 1 mg/kg by day 3 of treatment.

C albicans caused all 3 cases of fulminant candidemia. Considering all cases of candidemia that occurred in the NICU during the study period, *C albicans* candidemia had a significantly higher case fatality rate (24%; 12 of 50) than did *C parapsilosis* (4%; 2 of 57; $P = .003$). When analysis is limited to the 1996–1998 cohort, the case fatality rate for *C albicans* candidemia was still significantly higher at 8 of 33 infants (24%), compared with 1 of 40 infants (3%) with *C parapsilosis* candidemia ($P = .009$).

Clinical Features of Candidemia in Infants With ER-CVC and LR-CVC

Fifty infants had ER-CVCs within 3 days of the first positive blood culture for *Candida* species. Six ER-CVCs were exchanged over a guidewire. Fifty-four infants had LR-CVCs >3 days after the first positive blood culture for *Candida* species. Two LR-CVCs were exchanged over a guidewire. The frequency of obtaining blood cultures after the first positive blood culture varied between daily cultures until negative to repeat blood cultures whenever a previous culture became positive, ie, every 2 to 3

TABLE 1. Clinical Characteristics of Candidemia in Infants With ER-CVCs and LR-CVCs

Clinical Features	ER-CVC n = 50	LR-CVC n = 54	P Value
	No. (%)	No. (%)	
Male gender	29 (58)	35 (65)	.55
Black ethnicity	36 (72)	32 (59)	.22
	Median (range)	Median (range)	
Birth weight (g)	800 (426–3190)	738 (437–2840)	.35
Gestational age (wk)	26 (23–40)	25.5 (23–40)	.45
Age at detection (d)	27 (14–171)	26.5 (7–152)	.54
NTISS	22 (14–37)	24 (15–49)	.08
	Distribution	Distribution	
Type of CVC			
Peripheral CVC	34	39	.71
Surgical CVC	14	14	
Umbilical CVC	2	4	
Candida species			
C albicans	21	23	.94
C parapsilosis	26	28	
C glabrata	2	3	
C tropicalis	1	0	

days. There was no difference between the ER-CVC group and the LR-CVC group in frequency of blood cultures. Table 1 shows that there was no significant difference between infants in the ER-CVC and LR-CVC groups in terms of gender, ethnicity, birth weight, gestational age, age at candidemia, or NTISS scores. NTISS scores could not be determined in 2 infants in the ER-CVC group and 2 infants in the LR-CVC group because of incomplete medical records. Table 1 also shows that there was no difference in the distribution of types of CVC or in the distribution of Candida species causing candidemia in each group. Table 2 lists the reasons for ER-CVC.

Outcomes of Candidemia in Infants With ER-CVC and LR-CVC

Table 3 compares outcomes for infants in the ER-CVC and LR-CVC groups. Candidemia survivor length of stay was similar in both groups of infants. The ER-CVC group had significantly shorter duration of candidemia (median: 3 days; range: 1–14 days), compared with the LR-CVC group (median: 6 days; range: 1–24 days; $P = .0002$). Both C albicans and C parapsilosis showed similar shorter duration of candidemia with ER-CVCs. C parapsilosis candidemia had significantly shorter duration in the ER-CVC group (median: 3 days; range: 1–14 days), compared with the LR-CVC group (median: 6.5 days; range: 1–24 days; $P = .005$). C albicans candidemia also had significantly shorter duration in the ER-CVC group (median: 3 days; range: 1–14 days), compared with the LR-CVC group (median: 5.5 days; range: 1–23 days; $P = .03$). Only 5 of 54 cases (9%) of candidemia resolved without removal of CVC within 7 days of the last positive blood culture.

There were at least 2 negative blood cultures before candidemia was considered resolved, in all but 7 of 93 survivors of candidemia. Seven infants had only 1 negative blood culture, including 5 from the ER-CVC group and 2 from the LR-CVC group. Both ER-CVC and LR-CVC infants were treated with amphotericin B for a median of 15 days after the last positive blood culture for Candida species (Table 3). Infants who died from candidemia were treated with amphotericin B for a shorter duration than were those who survived, because they lived for a median of only 8 days (range: 5–36 days) after onset of candidemia.

Thirty-two infants with candidemia had other organisms isolated from the Candida positive blood cultures or from blood cultures obtained between cultures positive for Candida species. There were 16 infants in the ER-CVC group and 16 in the LR-CVC

group. Five infants had 2 different pathogens in addition to Candida species. Pathogens included coagulase-negative staphylococci (22 cases), Enterococcus species (7 cases), Staphylococcus aureus (3 cases), Klebsiella species (2 cases), and 1 case each of Enterobacter cloacae, Serratia marcescens, and Pseudomonas fluorescens.

Table 3 shows that the LR-CVC group had 10 deaths attributable to candidemia in 54 cases (19%), in contrast to the ER-CVC group that had 1 candidemia death in 50 cases (2%; $P = .008$; odds ratio: 11.1; 95% CI: 1.4–90.6). Case fatalities, which were not related to candidemia, occurred with similar frequency in both groups of infants with 6 (12%) additional case fatalities in 50 ER-CVC infants and 7 (13%) additional case fatalities in 54 LR-CVC infants. The 11 infants with candidemia case fatalities included 9 with C albicans and 2 with C parapsilosis. Eight infants had blood cultures positive for candidemia within 3 days of death, including 2 with autopsy evidence of disseminated candidiasis. The other 3 infants died from complications of candidemia, including superior vena cava syndrome secondary to an infected thrombus unresponsive to thrombolytic therapy, anuric acute renal failure with bilateral renal fungus balls, and candidal peritonitis.

The timing of CVC removal had no impact on case fatality rates in infants with C parapsilosis candidemia: 1 of 26 (4%) died in the ER-CVC group and 1 of 28 (4%) died in the LR-CVC group. Therefore, the significantly increased case fatality rate in the LR-CVC group shown in Table 3 could not be attributed to C parapsilosis candidemia.

Table 4 compares the features and outcomes of C albicans candidemia in infants with ER-CVC and LR-CVC. The case fatality rate from C albicans candidemia was significantly affected by timing of CVC removal: 0 of 21 (95% CI: 0–14) infants died in the ER-CVC group in contrast to 9 of 23 (39%; 95% CI: 19–59) infants in the LR-CVC group ($P = .002$; odds ratio 28.2; 95% CI: 1.5–523). Absolute risk increase of death from C albicans candidemia was 39% when CVCs were not removed promptly, and the number needed to harm was 2.6 (95% CI: 1.7–5.2). Of note, both ER-CVC and LR-CVC groups had similar NTISS scores indicating that both groups had similar severity-of-illness when candidemia was detected. There was also no significant difference in candidemia survivor length of stay between the 2 groups.

DISCUSSION

Our key findings are that failure to remove CVCs as soon as candidemia was detected in neonates was associated with increased mortality in C albicans candidemia and with prolonged duration of candidemia regardless of Candida species. These results substantiate the recommendations of Edwards and Baker[5] that CVCs be removed as soon as candidemia is detected in neonates.

Candidemia was prolonged by a median of 3 days in study infants when CVCs were not removed immediately, regardless of Candida species. Prolonged duration of candidemia may have considerable clinical significance. The morbidity of prolonged candi-

TABLE 2. Reasons for ER-CVCs in Infants With Candidemia ($n = 50$)

Reason for Removal	No. (%)
Candidemia	22 (44)
Indeterminate	11 (22)
Occluded	5 (10)
Infiltrated	5 (10)
Dislodged	4 (8)
Non-Candida species	3 (6)

TABLE 3. Outcomes of Candidemia in Infants With ER-CVCs and LR-CVCs

Outcome	ER-CVC n = 50	LR-CVC n = 54	P Value
	Median (range)	Median (range)	
Candidemia survivor length of stay (d)	109 (34–322)	112 (38–454)	.34
Duration of candidemia (d)	3 (1–14)	6 (1–24)	.0002
Duration of amphotericin B therapy (d)	18 (5–60)	21 (5–51)	.14
	No. (%)	No. (%)	
Candidemia case fatality	1 (2)	10 (19)	.008

TABLE 4. Clinical Features and Outcomes of *C albicans* Candidemia in Infants With ER-CVCs and LR-CVCs

Outcome	ER-CVC n = 21	LR-CVC n = 23	P Value
	Median (range)	Median (range)	
NTISS	23 (14–37)	24 (15–35)	.44
Candidemia survivor length of stay (d)	105 (50–322)	104 (40–454)	.92
Duration of candidemia (d)	3 (1–14)	5.5 (1–23)	.03
	No. (%)	No. (%)	
Candidemia case fatality	0	9 (39)	.002

demia includes thrombocytopenia, thrombosis, osteomyelitis, renal fungus balls, as well as prolonged antifungal therapy and its potential toxicity.[1,2]

This study shows that candidemia caused by *C albicans* has a significantly higher case fatality rate than does *C parapsilosis,* with rates of 24% and 4%, respectively. When our analysis was limited to the previously unreported outcomes of the 1996–1998 cohort, the case fatality rate for candidemia caused by *C albicans* was identical (24%) and still significantly higher than the 3% rate for *C parapsilosis,* corroborating our previous observation[3] that *C albicans* candidemia has a higher case fatality rate. Our findings parallel an earlier smaller study of invasive neonatal candidiasis that also described a higher case fatality rate for *C albicans*, compared with *C parapsilosis*.[12]

The case fatality rates for candidemia in infants were *Candida* species-specific when removal of CVC was delayed >3 days after the first positive blood culture. The low case fatality rate of 4% for *C parapsilosis* was not increased with LR-CVC. In contrast, the case fatality rate for *C albicans* candidemia was increased significantly from 0% to 39% (95% CI: 19–59) in the LR-CVC group, compared with the ER-CVC group. Absolute risk increase of death from *C albicans* candidemia was 39% when CVCs were not removed promptly, and the number needed to harm was 2.6 (95% CI: 1.7–5.2). In other words, our data suggest that for every 3 infants with *C albicans* candidemia in whom CVCs were not removed as soon as candidemia was detected, another infant died.

Infants in the LR-CVC group were not sicker than infants in the ER-CVC group at initial detection of *C albicans* candidemia, because there was no difference in NTISS scores (Table 4). Similar initial severity-of-illness in both groups gives further support for the possibility of a causal role for delayed removal of CVCs in *C albicans* candidemia case fatality.

Although there were no deaths from *C albicans* candidemia in infants with ER-CVC, 3 infants were excluded because they died from fulminant *C albicans* candidemia within 2 days of the first positive blood culture. We excluded fulminant cases, because the focus of this study was the timing of the clinical decision to remove CVCs once it was known that *Candida* was growing from blood cultures. These infants died before clinicians were notified that *Candida* was the pathogen.

The explanations for why continued presence of a CVC increases the case fatality rate for candidemia caused by *C albicans* remain unclear. Perhaps it serves as a site for continued *Candida* growth and dissemination that is particularly difficult to treat with antifungal therapy alone. In contrast, the case fatality rate for *C parapsilosis* candidemia was not increased in infants with LR-CVC despite significantly increased duration of candidemia. The explanation for this effect may be that *C parapsilosis* is less virulent in experimental animals than is *C albicans*[13] and does not produce phagocytosis-resistant pseudohyphae.[14] *C parapsilosis* also does not adhere to and penetrate human endothelium as well as *C albicans*.[15] A combination of factors like these may explain the significantly increased case fatality rate for *C albicans* in infants in the LR-CVC group despite similarly prolonged duration of candidemia for both *C albicans* and *C parapsilosis* in infants with LR-CVC.

Only 5 infants (9%) in the LR-CVC group showed resolution of candidemia without removal of CVC. The 2 case series[6,7] reporting eradication of bloodstream infections in neonates without removing CVCs in >80% of cases were primarily concerned with bacterial infections, especially coagulase-negative staphylococcal bacteremia, and included only 7 cases of candidemia, the outcomes of which were not specified. Furthermore, cases of candidemia in children[16] and adults[9] with cancer have resolved after

removal of CVCs without antifungal therapy, although the best outcomes occurred when prompt removal of CVC was combined with antifungal therapy.

A limitation of our study is that it is based on clinical cohorts of infants rather than on a randomized, controlled trial. Although a fairly large study population of 104 cases was examined, the observation that a 39% increased risk of death in infants with *C albicans* candidemia occurred with LR-CVC results from analysis of the outcomes of only 44 cases. The uncertainty of this finding is reflected in the large 95% CI of 19% to 59%. Besides, a statistically significant association does not prove cause and effect. However, a strong association exists between LR-CVC and prolonged candidemia with either *C albicans* or *C parapsilosis*. And the observation that delayed removal of CVC is associated with prolonged candidemia and increased mortality in neonates is consistent with findings in children and adults with candidemia.[9,16,17] Although a large randomized, controlled trial would be more definitive in establishing a causal relationship between timing of CVC removal and mortality as well as duration of candidemia, at present such a trial has not been performed.

We acknowledge that some infants with candidemia may be too unstable to have their CVC removed or replaced. Yet, our findings strongly suggest that clinicians should attempt to remove a CVC as soon as candidemia is detected unless it cannot be removed or replaced because of severe generalized skin breakdown or unstable critical condition. In such circumstances, risk of removal or replacement of CVC may be greater than increased risk of mortality in cases of *C albicans* candidemia or greater than increased risk of morbidity from prolonged candidemia regardless of *Candida* species.

ACKNOWLEDGMENTS

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