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Early Central Venous Catheter Replacement After Candida in Pediatric Intestinal Failure Patients

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ABSTRACT

Background: Deferred central venous catheter (CVC) replacement places children with intestinal failure (IF) at risk of complications. We hypothesized that early CVC replacement after uncomplicated candidemia is safe and beneficial.

Methods: We performed a retrospective review of children with IF. Patients were divided into early (<7 days after their first negative culture), and late (≥7 days after their first negative culture) CVC replacement following uncomplicated candidemia. We calculated the median time to CVC removal, clearance of infection, CVC replacement or exchange, and duration of the initial hospitalization. The proportion of patients readmitted within 30 days was also calculated, taking note of the number of candida reinfections.

Results: Early replacement occurred in 18 encounters and late replacement in 21 encounters. The median time in both groups to CVC removal was 3 days ($P = 0.949$), and clearance of infection was 4 days ($P = 0.466$). The median time to CVC replacement or exchange in the early group was 4 days, compared to 10 days in the late group ($P < 0.001$). The median duration of the hospitalization in the early group was 12 days compared to 21 days in the late group ($P = 0.011$). In total 39% of patients from the early group were readmitted within 30 days compared to 57% from the late group ($P = 0.359$). None of the patients were reinfected with candida within 30 days.

Conclusion: Early CVC replacement after uncomplicated candidemia in children with IF decreases hospital stay without increased risk of readmission or reinfection.

Key Words: pediatric intestinal failure, prolonged parenteral nutrition, central venous catheter, candidemia

What Is Known

- Children with intestinal failure (IF) receiving parenteral nutrition through a central venous catheter (CVC) are at increased risk of catheter-related candidemia.
- Deferred CVC replacement places children with IF at risk of complications.

What Is New

- Children with IF studied retrospectively at 1 hospital who underwent early (<7 days after the first negative blood culture) CVC replacement after clearance of uncomplicated candidemia had shorter hospital stays compared to children who underwent late (≥7 days from the first negative blood culture) CVC replacement.
- Early CVC replacement was not associated with an increased risk of hospital readmission or reinfection with candida among children with IF who underwent early CVC replacement.

Translational Impact

- Providers may consider early replacement of a CVC following clearance of uncomplicated candidemia in pediatric patients with IF.
- Large randomized controlled trials are needed to confirm these findings.

INTRODUCTION

Children with intestinal failure (IF) receiving parenteral nutrition through a central venous catheter (CVC) are at increased risk of catheter-related candidemia (1). The Infectious Diseases Society of America (IDSA) recommends the removal of both short- and long-term catheters in patients with catheter-related bloodstream infection (CRBSI) due to fungi (1). More specifically, the IDSA 2016 guidelines strongly recommend early removal of a CVC when the infectious source is presumed to be the CVC, as CVC retention with candida worsens outcomes (2,3); these guidelines were endorsed by the American Academy of Pediatrics and the Pediatric Infectious Diseases Society (2).

In addition to source control, antifungal treatment and blood culture-confirmed clearance are recommended for all cases of CRBSI due to candida (1). If there are no obvious serious infectious complications, patients are recommended to receive 2 weeks of treatment after documented bloodstream clearance of candida species (2). Evidence-based guidelines for the prevention of CRBSIs, published by the Centers for Disease Control and Prevention, also exist for persons responsible for surveillance and control of infections in hospital, outpatient, and home healthcare settings (4).

In contrast, little is known about the optimal timing for the replacement of a CVC in the setting of candidemia (5–7). As a result,

Received June 8, 2023;accepted July 20, 2023.

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Daphna Katz, MD, accepts full responsibility for the conduct of this study.

This project was supported by Grant Number 1UL1TR000460, University of Miami Clinical and Translational Science Institute, from the National Center for Advancing Translational Sciences and the National Institute on Minority Health and Health Disparities. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

The authors report no conflicts of interest.

JPGN Reports (2023) 4:4(e358)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000358

practices greatly vary between practitioners. Often, replacement is deferred until completion of antifungal therapy due to fear of reinfection of the catheter with circulating organisms (6). This poses a challenge for children with IF who are dependent on daily parenteral nutrition, need a secure access point for antibiotic administration, and require multiple blood draws for laboratories. Moreover, as children with IF are frequently admitted, prolonging hospitalizations to complete antifungal therapy, or scheduling a follow-up admission for long-term CVC replacement negatively impacts associated healthcare costs and patients' and caregivers' quality of life.

The goal of this study was to determine whether outcomes among pediatric patients with IF treated for uncomplicated candidemia differ following early (<7 days after the first negative blood culture) versus late (≥7 days from the first negative blood culture) CVC replacement. We hypothesized that early CVC replacement following clearance of uncomplicated candidemia leads to a shorter initial hospitalization, and does not increase the short-term risk of hospital readmission or candida reinfection.

METHODS

We performed a retrospective chart review of all patients with IF ages 4 weeks to 22 years treated at Holtz Children's Hospital/Jackson Health System with approval (#20220569) from the University of Miami's Institutional Review Board. IF was defined using the criteria set forth by the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition: children who are dependent on parenteral nutrition for more than 60 days and/or have a remnant bowel length of less than 25% expected (8). Of note, there has since been a revised definition of IF published by the American Society for Parenteral and Enteral Nutrition Pediatric IF Section, which does not include remnant bowel length (9).

We reviewed 69 patients with IF with CVC in situ and included those admitted between January 2007 and July 2022 with a positive central or peripheral blood culture for candida. The included patients all had CVC replacement or exchange following at least 1 culture negative for 48 hours prior. Patients were excluded from the study if they were immunosuppressed, neutropenic (absolute neutrophil count less than 1500), or had active malignancy. Patients were additionally excluded for persistent fever >72 hours and those with complicated candidemia (ie, patients with endocarditis or septic thrombus). Patients with multiple encounters for candida infections were included if each candida infection occurred more than 6 months apart. As there was no institutional protocol, management in each case of CRBSI due to candida was determined based on IDSA guidelines, sometimes with the input of an infectious disease specialist, and with input from the surgeon or interventional radiologists performing the procedure.

We collected demographics, including gender, the etiology of IF, and whether patients were critically ill at presentation requiring admission to the pediatric intensive care unit. Using the number of days from the first negative culture until the CVC was replaced, we separated the encounters into 2 groups: those who underwent early replacement or exchange <7 days after their first negative culture, and those who underwent late replacement or exchange, ≥7 days after their first negative blood culture. We calculated the time to CVC removal and clearance of infection from the date of the first positive blood culture, and the time to CVC replacement/exchange from the date of the first negative blood culture. The duration of the initial hospitalization for each encounter was calculated from the date of admission to the date of discharge. Post-encounter data collection included hospital readmission within 30 days of discharge from the initial hospitalization for candida, and the reason for this readmission, noting reinfections with the same candida species within 30 days of the original infection.

The median time to CVC removal, clearance of infection, CVC replacement/exchange, and duration of the hospitalization were calculated along with the interquartile range for the early and late groups. A Shapiro-Wilk test for normality was performed, and the results demonstrated that the data were not normal. As a result, non-parametric tests were employed. A Mann-Whitney *U*-test was used to determine statistical significance. For proportions, a proportion test was used to determine significance.

RESULTS

A total of 21 patients, from whom there were 39 encounters of candida CRBSI were included in this study. Most patients in this study had IF due to short bowel syndrome and were not critically ill at the time of their candida infection (Table 1). Of the encounters, 46% underwent early CVC replacement or exchange, compared to 54% who underwent late replacement or exchange.

The median number of days in both groups from the first positive blood culture until the CVC was removed was 3 days (early group interquartile range [IQR], 2–5; late group IQR, 2–4.5; $P = 0.949$), and to clearance of infection was 4 days (early group IQR, 2–5; late group IQR, 3–6; $P = 0.466$) (Table 2). In contrast, the median number of days until the CVC was replaced or exchanged from the first negative blood culture was 4 days (IQR, 3–5.5) for patients with early

TABLE 1. Patient/encounter characteristics

Characteristics	n (%)
Gender	n = 21 (100%)
Female	5 (24)
Male	16 (76)
Etiology of intestinal failure	n = 21 (100%)
Surgical	17 (81)
Dysmotility	4 (19)
Critically ill at the time of presentation*	n = 39 (100%)
Yes	5 (13)
No	34 (87)

*Defined as requiring admission to the pediatric intensive care unit at presentation.

TABLE 2. Outcomes of pediatric patients with intestinal failure who underwent early (<7 days from the first negative blood culture) vs late (≥7 days after the first negative blood culture) central venous catheter replacement

Timing from first negative culture to CVC replacement or exchange	Early (<7 days) (n = 18)	Late (≥7 days) (n = 21)	*P* value
Median days to CVC removal	3 IQR, 2–5	3 IQR, 2–4.5	0.949
Median days to clearance of infection	4 IQR, 2–5	4 IQR, 3–6	0.466
Median days to long-term CVC replacement or exchange	4 IQR, 3–5.5	10 IQR, 8–13.5	<0.001
Median duration of hospitalization (days)	12 IQR, 9–20.5	21 IQR, 15–48	0.011
Proportion of patients readmitted within 30 days of the initial encounter	7/18 = 39%	12/21 = 57%	0.359
Number of reinfections with the same candida species within 30 days of the initial infection	0	0	n/a

CVC = central venous catheter; IQR = interquartile range.

TABLE 3. Reasons for readmission within 30 days for patients who underwent early (<7 days from the first negative blood culture) vs late (≥7 days after the first negative blood culture) central venous catheter replacement or exchange

Reason for hospital readmission	Early CVC readmission (n = 7/18)	Late CVC readmission (n = 12/21)
Catheter-related bloodstream infection with a new organism	3	4
Rule out sepsis/viral infection	1	4
Central line malfunction	1	3
Other	2	1

CVC = central venous catheter.

replacement, compared to 10 days for the late group (IQR, 8–13.5; $P < 0.001$).

Patients with early CVC replacement or exchange had a significantly shorter hospitalization, with a median of 12 days (IQR, 9–20.5) compared to a median of 21 days (IQR, 15–48) in the late group ($P = 0.011$). Early replacement or exchange was not more likely to result in hospital readmission within 30 days, as 39% of patients were readmitted compared to 57% from the late group ($P = 0.359$). The main reasons for readmission included CRBSI with a bacterial organism, sepsis rule out/ viral infections, and CVC malfunction (Table 3).

No patients in this study were reinfected with the same candida species within 30 days of the initial infection, regardless of the timing of CVC replacement or exchange.

DISCUSSION

This is the first study to our knowledge investigating the optimal timing of CVC replacement in pediatric patients with IF and candidemia. Pediatric IF is a small, but high-risk group associated with increased healthcare utilization and caregiver stress. In a study of adult patients with IF, the mean hospital cost for an individual patient admission was estimated to be $34 130 (10). Prolonged hospitalizations in pediatric IF patients are also associated with a large financial and emotional burden on caregivers (11,12). Strategies to reduce the duration of hospitalizations are needed to curb continuously rising healthcare costs and to improve patients' and caregivers' quality of life.

The limited existing literature on CVC replacement with candidemia involves mostly critically ill adults with inconsistent results. In a retrospective cohort study of 228 patients (median age greater than 70 years) with candidemia at 1 center, CVC replacement less than 2 days after removal was an independent risk factor for 30-day mortality. Many of these patients, however, had an active malignancy, and clearance of candidemia before CVC replacement was not documented (5). In contrast, in a retrospective chart review of 336 adult patients at 2 centers with CRBSI, there was no difference between early (after less than or equal to 3 days) and late (greater than 3 days) replacement of the CVC. This study was not specific to fungal infections, but the authors concluded that the replacement of a CVC in the setting of CRBSI, in general, should not be delayed in patients who require a long-term CVC (6). Fungal infection, compared to bacterial infection, was found to be an independent risk factor for recurrent CRBSI after CVC reinsertion in a retrospective cohort study of 53 patients who underwent reinsertion of a nontunneled CVC after CRBSI, and from which 16 patients had a recurrent/persistent infection. However, this study did not find an association between the timing of the reinsertion of a CVC and the risk of recurrent/persistent catheter-related infection (7). Similarly, in another retrospective review in mostly adult ICU patients, there was no association between the timing of CVC replacement and increased risk of recurrent infections (13).

Our study was conducted in a noncritically ill pediatric IF cohort, who all demonstrated clearance of candidemia before CVC replacement or exchange with at least 1 culture negative for a minimum of 48 hours prior. Patients in both groups underwent early removal of their CVC (median 3 days in both groups), as per IDSA guidelines, and similarly cleared their infection shortly after (median 4 days in both groups). However, patients in the late group waited significantly longer for CVC replacement. Likely as a result of the longer wait time, our study found that deferred replacement or exchange of a CVC after uncomplicated candidemia is associated with a longer hospital admission.

We did not find an increased risk of readmission with early CVC replacement. Similar rates of readmission were seen among both groups, given that pediatric IF is a high-risk population. A temporary CVC was necessary in some patients to ensure secure access for antifungal treatment and parenteral nutrition, which incur additional risks. Early long-term CVC replacement is therefore beneficial to reduce hospitalization duration and cost and to minimize interruptions in antimicrobial treatment and parenteral nutrition, without increasing patients' risk of readmission. Importantly, no patients in our study were reinfected with the same candida species within 30 days of the initial infection, regardless of the timing of their CVC replacement or exchange. This finding supports the early replacement of a CVC after documented clearance of candidemia.

The results of this study are limited by the fact that it was conducted retrospectively with a relatively small sample size. However, given the rarity of pediatric IF, this pilot study adds to the published literature on the management of CRBSI in this high-risk population. Future randomized controlled trials involving multiple centers should be conducted to confirm our findings.

CONCLUSION

Early CVC replacement after clearance of uncomplicated candidemia in pediatric patients with IF shortens hospitalizations with no increased risk for readmission or CVC reinfection with candida. Future randomized controlled trials are needed to confirm these findings.

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