Central Venous Catheter Removal Versus In Situ Treatment in Neonates With Enterobacteriaceae Bacteremia

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ABSTRACT. Objective. To determine how often neonates with Enterobacteriaceae (ENTB) bacteremia can be treated successfully without removing central venous catheters (CVCs).

Methods. A retrospective cohort study was conducted of ENTB bacteremia in infants in a neonatal intensive care unit during a 7-year period (1994–2000). Cases of ENTB bacteremia were identified from a microbiology database and limited to late-onset cases occurring after 3 days of age.

Results. There were 53 cases of ENTB bacteremia in infants with CVCs. Blood cultures were positive for ENTB within a median of 10 hours (range: 5–43). Timing of CVC removal was at the discretion of attending neonatologists. Fifteen cases had early-removal CVC (ER-CVC) within 2 days, and 38 cases had late-removal CVC (LR-CVC) > 2 days after the first positive blood culture for ENTB. There were no significant differences between infants in the ER-CVC and LR-CVC groups for case fatality, recurrence, or duration of ENTB bacteremia. Although 16 (42%) of 38 (95% confidence interval [CI]: 26%–59%) LR-CVC cases required CVC removal to resolve ENTB bacteremia, 17 (45%) of 38 (95% CI: 29%–62%) LR-CVC cases were treated successfully without removal of CVCs. ENTB bacteremia was successfully treated without CVC removal in 85% of 13 LR-CVC cases with 1 day of bacteremia in contrast to 24% of 25 LR-CVC cases with > 1 day of bacteremia (relative risk: 3.5; 95% CI: 1.7–7.4). CVC removal was required to resolve ENTB bacteremia in 9 (82%) of 11 LR-CVC cases with severe thrombocytopenia compared with 7 (32%) of 22 LR-CVC cases without severe thrombocytopenia (relative risk: 2.6; 95% CI: 1.3–5.0).

Conclusions. Retention of CVCs was successful in 45% of cases of ENTB bacteremia in which it was attempted, but success was unlikely when bacteremia lasted > 1 day. ENTB bacteremia cases associated with severe thrombocytopenia rarely resolved unless CVCs were removed. Pediatrics 2003;111:e269–e274. URL: http://www.pediatrics.org/cgi/content/full/111/3/e269; Enterobacteriaceae, central venous catheter, infant, newborn.

ABBREVIATIONS. CVC, central venous catheter; ENTB, Enterobacteriaceae; NICU, neonatal intensive care unit; NTISS, Neonatal Therapeutic Intervention Scoring System; NEC, necrotizing enterocolitis; ER-CVC, early-removal central venous catheter; LR-CVC, late-removal central venous catheter; RR, relative risk; CI, confidence interval; ESBL, extended-spectrum beta-lactamase; NS, not significant.

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http://www.pediatrics.org/cgi/content/full/111/3/e269

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CVC in the neonatal intensive care unit (NICU) at Children’s Hospital of The King’s Daughters (Norfolk, VA), between January 1, 1994, and December 31, 2000. This hospital contains the regional referral center for southeastern Virginia and northeastern North Carolina. We excluded infants without CVCs, infants with CVCs and polymicrobial sepsis, and infants with CVCs who died within 48 hours of onset of ENTB bacteremia. The last were excluded because we believe that sepsis syndrome was already established when initial blood cultures were obtained in fulminant cases. We chose to focus on nonfulminant cases, in which management of CVCs may have an impact on the outcome of the bacteremia.

Definitions

ENTB bacteremia was defined as ENTB family growth from at least 1 blood culture from a peripheral or central venous sample. This included Klebsiella species, Enterobacter species, Escherichia coli, Serratia species, and Citrobacter species. Duration of ENTB bacteremia was defined as the interval from the first to the last blood culture positive for ENTB. CVCs were catheters whose tips were located in the superior vena cava, inferior vena cava, or right atrium. There were 3 types of CVCs: 1) peripheral CVCs, which were inserted by NICU staff; 2) surgical CVCs, which were inserted by NICU staff; and 3) umbilical CVCs, which were inserted by the pediatric surgery service. The Neonatal Therapeutic Intervention Scoring System (NTISS) was used as an indicator for severity of illness. An NTISS score was determined for the day of the first positive blood culture. The score is a total of points assigned from 1 to 4 for various intensive care therapies, with higher values indicating higher severity of illness. The retrospective study design did not permit systematic analysis of specific clinical features such as lethargy or feeding intolerance. History of necrotizing enterocolitis (NEC) was defined as any infant with a diagnosis of NEC within 3 months before ENTB bacteremia.

Early removal of CVC (ER-CVC) was defined as removal of the CVC within 2 days of the first positive blood culture, and late removal of CVC (LR-CVC) was defined as removal of the CVC >2 days after the first positive blood culture for ENTB bacteria. The LR-CVC group included those infants who did not require catheter removal for resolution of the infection. For the sake of analysis, catheter exchange over a guidewire was considered to be catheter removal. Timing of CVC removal was at the discretion of the attending neonatologists. CVC “removal not required” was defined as cases in which there was successful treatment of ENTB bacteremia without removal of CVCs. This required at least 2 consecutively negative blood cultures and retention of CVCs for at least 7 days after the last positive blood culture. CVC “removal required” was defined as cases in which ENTB bacteremia did not resolve until CVCs were removed. A blood culture positive for the same organism after at least a 7-day interval with at least 2 negative blood cultures was considered a recurrence of bacteremia. ENTB bacteremia was considered contributory to case fatality when death occurred within 3 days of a blood culture positive for ENTB, by time-case relationship. Complications attributed to ENTB bacteremia were defined as the new diagnosis of abscess, endocarditis, meningitis, osteomyelitis, urinary tract infection, or thrombosis within 1 week of a positive blood culture.

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 resident physicians and/or NICU staff. The study database for retrospective analysis. The study was granted exemption by the Institutional Review Board of Eastern Virginia Medical School because it was a research study of existing data recorded in such a way that the subjects cannot be identified.

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 with an automated culture system. All positive vials were Gram-stained and subcultured for organism identification on sheep’s blood, chocolate, and MacConkey agars.

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 exact test or χ² test for trends as appropriate. Significance was declared at P < .05, and relative risks (RRs) with 95% confidence intervals (CIs) are shown.

RESULTS

Study Group

A total of 4032 infants were admitted to the NICU during the 7-year study period. There were 105 cases of ENTB bacteremia in 92 infants. Fifty-two cases were excluded: 22 did not have a CVC at the time of bacteremia (including 6 who died within 48 hours of the first positive blood culture), 28 had polymicrobial sepsis, and 2 had catheters but died within 48 hours of the first positive blood culture. Three infants in the LR-CVC group had >1 ENTB bacteremia, but all 3 infants had a different species that caused the second case. There were 2 cases of recurrence of ENTB bacteremia that presented as polymicrobial cases and were analyzed separately. In study infants, 29 peripheral CVCs, 19 surgical CVCs, and 5 umbilical CVCs were in place at the time of diagnosis of ENTB bacteremia.

Either gentamicin or tobramycin was used for empiric antibiotic treatment of suspected late-onset bacteremia caused by Gram-negative organisms. Blood cultures were positive for ENTB within a median of 10 hours (range: 5–43) after being obtained. Only 4 (7%) cases took >24 hours to become positive. Patient sera were assayed to ensure that aminoglycoside concentrations were in the therapeutic range. In our institution, the empiric treatment of suspected Gram-negative bacteremia was changed from gentamicin to tobramycin in January 1999 because internal data showed decreasing susceptibility of Pseudomonas species to gentamicin. There were 3 cases of ENTB bacteremia caused by organisms with intermediate susceptibility to the aminoglycosides—2 in the ER-CVC group and 1 in the LR-CVC group—but only 1 infant, from the ER-CVC group, required change of antibiotic therapy to imipenem to resolve the bacteremia. There were 2 cases of Klebsiella pneumoniae bacteremia whose isolates carried extended-spectrum β-lactamas (ESBL)—1 in the ER-CVC group and 1 in the LR-CVC group—and these cases resolved only after being treated with imipenem and/or amikacin. All other cases were caused by organisms that were susceptible to the initial empiric aminoglycoside.

The timing of obtaining repeat blood cultures after the first positive blood culture for ENTB varied be-
tween daily cultures until negative to repeat cultures whenever a previous culture became positive, ie, every 1 to 2 days. There was no difference between the ER-CVC and LR-CVC groups or the “removal required” and “removal not required” groups in frequency of blood cultures. It was not our routine to culture CVC tips on removal, except with some surgical CVCs.

**Poly microbial Cases**

Twenty-eight infants with CVC and ENTB bacteremia had polymicrobial sepsis, with other pathogens isolated from the ENTB-positive blood cultures or from blood cultures obtained between cultures positive for ENTB. These cases were analyzed separately and were excluded from the comparison of the ER-CVC and LR-CVC groups. Five infants had 2 different pathogens in addition to ENTB. Pathogens included *Enterococcus* species (10 cases), coagulase-negative staphylococci (9 cases), *Staphylococcus aureus* (6 cases), *Candida* species (6 cases), and *Streptococcus agalactiae* (2 cases). Case fatalities occurred in 3 (11%) of 28 polymicrobial cases. Polymicrobial sepsis was treated successfully without CVC removal in only 3 (11%) of 28 cases. There was successful treatment of ENTB bacteremia without removing CVC in only 1 (11%) of 9 cases with simultaneous coagulase-negative staphylococcal bacteremia.

**Clinical Features of ENTB Bacteremia in Infants With ER-CVC and LR-CVC**

The study group consisted of 53 cases. In 15 cases, CVCs were removed within 2 days (ER-CVC) of the first positive blood culture for ENTB. In 38 cases, CVCs were retained for >2 days (LR-CVC) after the first positive blood culture for ENTB. Table 1 shows that there were no significant differences between the ER-CVC and LR-CVC groups with respect to gender, ethnicity, history of NEC, birth weight, gestational age, infant age at detection of bacteremia, or distribution of ENTB species. Only 4 infants had NEC at the time of bacteremia, and all 4 were in the LR-CVC group. At the onset of bacteremia, the ER-CVC group had significantly older CVCs (median: 18 days; range: 3–48) than the LR-CVC group (median: 7 days; range: 1–48; *P* = .02). Infants in the ER-CVC group had significantly lower NTISS scores (mean: 16.1; standard error of the mean: ±1.8) than infants in the LR-CVC group (mean: 21.9; standard error of the mean: ±1.3; *P* = .02). Significantly more surgical CVCs were in the ER-CVC group (60%) compared with the LR-CVC group (26%; *P* = .02).

**Outcomes of ENTB Bacteremia in Infants With ER-CVC and LR-CVC**

Table 2 compares the outcomes for the ER-CVC and LR-CVC groups. There were no significant differences in recurrence of ENTB bacteremia, case fatality, length of stay, or duration of bacteremia. There were no additional case fatalities when the definition was expanded to death within 7 days of the last positive blood culture.

Nineteen infants had surgical CVCs: 9 in the ER-CVC group and 10 in the LR-CVC group. ER-CVCs were exchanged over a guidewire in 5 cases with no subsequent blood cultures positive for ENTB. A CVC was inserted into a new site in the other 4 ER-CVC cases; 2 had no subsequent blood cultures positive for ENTB, but 2 had to be removed 2 to 6 days later because of persistently positive blood cultures for ENTB. There was successful treatment of the ENTB bacteremia without removal of surgical CVCs in 5 of 10 LR-CVC cases. These CVCs were retained for a median of 22 days (range: 9–28) after the last blood culture positive for ENTB. Three surgical LR-CVCs were exchanged over a guidewire with successful resolution of the ENTB bacteremia within 1 day of the exchange. A surgical CVC was placed in a new site in 1 LR-CVC case but was removed 4 days later because of persistently positive blood cultures. ENTB bacteremia resolved in 1 infant with a surgical LR-CVC that was replaced with peripheral venous catheters for 4 days before a new surgical CVC was inserted.

**TABLE 1. Clinical Characteristics of ENTB Bacteremia in Infants With ER-CVC and LR-CVC**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>ER-CVC (n = 15)</th>
<th>LR-CVC (n = 28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (n)</td>
<td>8 (53%)</td>
<td>19 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Black ethnicity (n)</td>
<td>10 (67%)</td>
<td>25 (66%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of NEC (n)</td>
<td>4 (27%)</td>
<td>15 (39%)</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g; median [range])</td>
<td>954 (547–3190)</td>
<td>875 (519–3120)</td>
<td>.26</td>
</tr>
<tr>
<td>Gestational age (wk; median [range])</td>
<td>27 (24–38)</td>
<td>26 (23–34)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at detection (d; median [range])</td>
<td>62 (9–216)</td>
<td>25 (5–195)</td>
<td>.09</td>
</tr>
<tr>
<td>CVC days before ENTB bacteremia</td>
<td>18 (3–48)</td>
<td>7 (1–48)</td>
<td>.02</td>
</tr>
<tr>
<td>(median [range])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTISS (mean [SEM])</td>
<td>16.1 (1.8)</td>
<td>21.9 (1.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Distribution of CVCs (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral CVC</td>
<td>5 (33)</td>
<td>24 (63)</td>
<td>.02</td>
</tr>
<tr>
<td>Surgical CVC</td>
<td>9 (60)</td>
<td>10 (26)</td>
<td></td>
</tr>
<tr>
<td>Umbilical CVC</td>
<td>1 (7)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Distribution of ENTB species (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>8</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><em>Serratia</em> species</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter</em> species</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

SEM indicates standard error of the mean; NS, not significant.
There was no significant difference in the percentage of infants with complications associated with ENTB bacteremia between the ER-CVC (13%; 2 of 15 infants) and LR-CVC (16%; 6 of 38 infants) groups. Two infants in the ER-CVC group had complications: 1 with urinary tract infection and 1 with meningitis. In the infant with meningitis, the CVC was removed after 1 day of bacteremia. The meningitis was detected after 5 days of persistent bacteremia, and tobramycin was replaced by cefotaxime for improved treatment across the blood-brain barrier. The bacteremia resolved the next day. Six infants in the LR-CVC group had a total of 9 complications, including 4 cases of meningitis; 2 cases of thrombosis; and 1 case each of osteomyelitis, lower extremity abscess, and urinary tract infection. Meningitis was detected at the time of bacteremia detection in 3 of the 4 cases. The fourth case of meningitis was detected after 3 days of bacteremia in an infant with ESBL-positive K. pneumoniae, which was resistant to the antibiotic being administered at the time. Both cases of thrombosis were clinically and radiographically detected 2 to 3 days after CVC removal. The infant with osteomyelitis had persistent bacteremia after having the CVC removed on day 4, and additional evaluation including a bone scan was performed on the final day of bacteremia (day 7). No antibiotic changes were made in this infant. The lower extremity abscess was detected at the same time the ENTB bacteremia was detected. The urinary tract infections were present at the time of detection of bacteremia. There was no echocardiographic evidence of endocarditis in 15 infants with persistent ENTB bacteremia.

Clinical Features of ENTB Bacteremia in LR-CVC Infants in Whom CVC Removal Was Required and in Infants in Whom CVC Removal Was Not Required

CVCs were left in place a median of 6 days (range: 3–12) in the LR-CVC group. Sixteen (42%) of 38 (95% CI: 26%–59%) LR-CVC cases required removal of CVCs to treat ENTB bacteremia successfully because the bacteremia did not resolve until CVCs were removed. These CVCs were removed in a median of 4 days (range: 3–12). Conversely, 17 (45%) of 38 (95% CI: 29%–62%) LR-CVC cases did not require removal of the CVC to treat ENTB bacteremia successfully. These CVCs were removed in a median of 14 days (range: 7–34). It is uncertain whether CVC removal was required in the remaining 5 LR-CVC cases (“removal required uncertain”). They did not meet the strict definition of successful treatment without removal of the CVC because the CVC was removed 3 to 6 days after the last positive blood culture.

We tried to determine whether clinical features on the first day of ENTB bacteremia identified which infants required CVC removal and which were successfully treated with gentamicin or tobramycin without CVC removal. Table 3 shows that there were no significant differences between the 2 groups with respect to birth weight, gestational age, age at detection, age of the CVC, NTISS score, presence of leukocytosis (white blood cell count >20 000/mm³), immature-to-total neutrophil ratio >0.2, or distribution of ENTB species. Table 3 also shows that severe thrombocytopenia (platelet count <50 000/μL) was present in 9 (56%) of 16 cases that required CVC removal, significantly more often than 2 (12%) of 17 cases that did not require CVC removal for resolution of ENTB bacteremia (RR: 4.8; 95% CI: 1.2–18.8; P = .01). CVC removal was required to resolve ENTB bacteremia in 9 (82%) of 11 LR-CVC cases with severe thrombocytopenia compared with 7 (32%) of 22 LR-CVC cases without severe thrombocytopenia (RR: 2.6; CI: 1.3–5; P = .01).

### TABLE 2. Outcomes of ENTB Bacteremia in Infants With ER-CVC and LR-CVC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ER-CVC (n = 15)</th>
<th>LR-CVC (n = 38)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of ENTB bacteremia</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Case fatalities (n [%])</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay (d; median [range])</td>
<td>125 (19–253)</td>
<td>107 (17–343)</td>
<td>.31</td>
</tr>
<tr>
<td>Duration of bacteremia (d; median [range])</td>
<td>2 (1–7)</td>
<td>3 (1–18)</td>
<td>.48</td>
</tr>
</tbody>
</table>

### TABLE 3. Clinical Characteristics of ENTB Bacteremia in LR-CVC Infants in Whom CVC Removal Was Required Compared With Infants in Whom CVC Removal Was Not Required

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>CVC Removal Required (n = 16)</th>
<th>CVC Removal Not Required (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g; median [range])</td>
<td>895 (623–2284)</td>
<td>860 (519–3120)</td>
<td>.33</td>
</tr>
<tr>
<td>Gestational age (wk; median [range])</td>
<td>27 (24–33)</td>
<td>26 (23–34)</td>
<td>.24</td>
</tr>
<tr>
<td>Age at detection (d; median [range])</td>
<td>23 (5–118)</td>
<td>25 (8–195)</td>
<td>N.S.</td>
</tr>
<tr>
<td>CVC days before ENTB bacteremia detected (median [range])</td>
<td>6 (3–48)</td>
<td>7 (1–19)</td>
<td>N.S.</td>
</tr>
<tr>
<td>NTISS (mean [SEM])</td>
<td>23.4 (2.2)</td>
<td>20.6 (1.8)</td>
<td>.32</td>
</tr>
<tr>
<td>Severe thrombocytopenia (platelet count &lt;50 000/μL; n [%])</td>
<td>9 (56)</td>
<td>2 (12)</td>
<td>.01</td>
</tr>
<tr>
<td>Leukocytosis (white blood cell count &gt;20000/mm³; n [%])</td>
<td>5 (31)</td>
<td>6 (35)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Immature: total neutrophil &gt;0.2 (n [%])</td>
<td>9 (56)</td>
<td>13 (76)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Distribution of ENTB species (n)</td>
<td>E. coli 2, Klebsiella species 6, Enterobacter species 5, Serratia species 3, Citrobacter species 0</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>
Outcomes of ENTB Bacteremia in LR-CVC Infants in Whom CVC Removal Was Required and in Infants in Whom CVC Removal Was Not Required

Infants who were treated successfully without CVC removal had CVCs in place a median of 14 days (range: 7–32) after the last positive blood culture. There were no significant differences between the “removal required” and “removal not required” groups with respect to recurrence of ENTB bacteremia (1 in “removal required” group, 0 in “removal not required” group, and 1 in “removal required uncertain” group) or case fatality (2 in “removal required” group, 0 in “removal not required” group). Cases that required CVC removal had significantly longer duration of bacteremia (median: 6 days; range: 3–18) compared with cases that did not require CVC removal to resolve (median: 1 day; range: 1–3; P < .01). Eleven (85%) of 13 LR-CVC cases with ENTB bacteremia that lasted only 1 day (ie, blood cultures obtained 24–48 hours after initial blood culture were negative for ENTB) were treated successfully without removing CVCs. The success rate decreased to 60% (n = 6) in 10 cases with 2- to 3-day duration of bacteremia. None of 15 LR-CVC with >3 days of bacteremia resolved without CVC removal. Figure 1 illustrates that ENTB bacteremia was successfully treated without CVC removal in 85% of 13 LR-CVC cases with 1 day of bacteremia in contrast to 24% of 25 LR-CVC cases with >1 day of bacteremia (RR: 3.6; 95% CI: 1.7–7.4).

DISCUSSION

Our key findings are that ENTB bacteremia in neonates was successfully treated with gentamicin or tobramycin without removal of CVCs in 45% of cases in which it was attempted and that successful treatment of ENTB bacteremia of >1 day duration was unlikely without removal of CVCs. Our results suggest that CVCs may not need to be removed in all cases of ENTB bacteremia, especially in those with bacteremia lasting only 1 day. These results should be considered cautiously as they challenge expert opinion that isolation of a Gram-negative organism mandates removal of intravascular devices in neonates.7

It is interesting to compare our ENTB bacteremia data to the findings we reported on candidemia. Failure to remove CVCs as soon as candidemia was detected was associated with increased mortality in Candida albicans candidemia, prolonged duration of candidemia regardless of Candida species, and increased morbidity with prolonged candidemia (in which complications were a late finding).1 These conclusions supported the expert recommendation that CVCs be removed as soon as candidemia is detected in neonates. Failure to remove CVCs as soon as ENTB bacteremia was detected was not associated with increased mortality, increased recurrence, prolonged bacteremia, or increased morbidity.

The incidence of complications was similar in both ER-CVC and LR-CVC groups. Careful examination of the specific cases suggests that attempts to retain CVCs were not to blame for the complication in most instances. Both urinary tract infections and the lower extremity abscess were detected on day 1 of bacteremia. Meningitis was present on day 1 of bacteremia in 3 cases. A fourth case of meningitis was detected in an infant who was receiving inappropriate treatment for an ESBL-positive organism for many days. Early-removal of CVCs and the presence of prolonged bacteremia in these scenarios would have had no effect on the development of the complication. In 1 instance, meningitis itself seemed to have been responsible for prolonged bacteremia in an infant whose CVC had been removed on day 1. Once appropriate treatment for meningitis was administered, the bacteremia resolved. It is more difficult to understand the relationship of CVC retention and the development of abscess, endocarditis, osteomyelitis, and thrombosis as these diagnoses may remain clinically dormant initially and are not pursued until bacteremia has persisted for an unusual length of time. It is unknown whether the cases of osteomyelitis and thrombosis were present earlier in the course of bacteremia. There were no cases of endocarditis in our study group.

It is possible that prolonged ENTB bacteremia in neonates could be avoided if clinical or laboratory features on the first day of ENTB bacteremia identified which infants required CVC removal and which would be successfully treated without CVC removal. Our data showed that ENTB bacteremia cases with severe thrombocytopenia rarely resolved unless CVCs were removed. This is a unique finding when compared with our data from coagulase-negative staphylococcal bacteremia, which did not show any difference in thrombocytopenia between the “removal required” and “removal not required” groups.4 It is possible that thrombocytopenia in neonates with ENTB bacteremia is a marker for an infected catheter-related thrombus, which may serve as a nidus of infection until CVCs are removed.

Polymicrobial cases were excluded from our study group, but it is important to note that CVCs probably need to be removed as soon as polymicrobial sepsis with ENTB bacteremia is detected. It is unlikely that ENTB bacteremia will clear in these cases, even when the second organism is a coagulase-negative staphylococcus.

Our findings suggest that CVCs should be removed in cases of ENTB bacteremia that last >1 day because only 24% of infants with ENTB bacteremia
Enterobacteriaceae bacteremia that lasts >1 day were treated successfully without removal of CVCs. Approximately 80% of infants with ENTB bacteremia that lasted >1 day required CVC removal before resolution of bacteremia was achieved. The risk of prolonged ENTB bacteremia must be weighed against the risk of removal or replacement of the CVC. We acknowledge that some infants with ENTB bacteremia may be too unstable to have their CVC removed or replaced.

Delaying CVC removal, pending results of blood cultures obtained 24 to 48 hours after the initial blood culture, may increase the total duration of antibiotic exposure for 1 to 2 additional days and may increase antibiotic pressure. The risk that this small increase in duration of antibiotic therapy might pose for development of antibiotic resistance is not known but would need to be balanced against the anesthesia and procedure risks associated with CVC removal and replacement. We suppose that the risks of CVC removal and replacement are greater than those of 1 to 2 additional days of antibiotic therapy, but this remains to be fully explored.

A limitation of our study is that it is retrospective and based on clinical cohorts of infants rather than on a randomized, controlled trial. Although a fairly large study population was examined, some of our conclusions were drawn from analysis of the 38 cases in the LR-CVC group. A large, randomized, controlled trial would be more definitive in determining when CVCs should be removed in neonates with ENTB bacteremia, but at present such a trial has not been performed.

Our findings suggest that CVCs that are important for clinical treatment of a neonate may not need to be removed as soon as ENTB bacteremia is detected. It may be reasonable to decide whether to remove a CVC in an infant who is responding well to antibiotic therapy based on the results of blood cultures obtained 24 to 48 hours after the initial blood culture. Because it is unlikely that successful treatment will be achieved without CVC removal in infants with ENTB bacteremia that lasts >1 day, it is our recommendation that CVCs be removed immediately if subsequent blood cultures show persistence of bacteremia despite appropriate antibiotic treatment. This practice may decrease the risk of prolonged ENTB bacteremia in infants with CVCs. Likewise, CVCs should probably be removed in cases associated with severe thrombocytopenia and in cases associated with polymicrobial sepsis because ENTB bacteremia was unlikely to resolve without CVC removal when these factors were present.

Acknowledgments

We thank Marilyn Reininger, RN, for maintaining the neonatal database and Belinda J. Bordeaux, RN, for maintaining the CVC database.

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Central Venous Catheter Removal Versus In Situ Treatment in Neonates With Enterobacteriaceae Bacteremia
Pediatrics 2003;111:e269
DOI: 10.1542/peds.111.3.e269

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DOI: 10.1542/peds.111.3.e269

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