Comparison of Early *versus* Late Use of Antibiotic Locks in the Treatment of Catheter-Related Bacteremia

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Background and objectives: This retrospective study compared the effectiveness of the timing of the antibiotic locks to clear catheter-related bacteremia in children on chronic hemodialysis.

Design, setting, participants, & measurements: The early antibiotic lock group received antibiotic locks along with systemic antibiotics from the very beginning of catheter-related bacteremia. The late antibiotic lock group was given only systemic antibiotics initially, and antibiotic locks were used late in the infection if the catheter-related bacteremia could not be cleared after resolution of symptoms.

Results: There were 264 catheter-related bacteremias in 79 children during 6 yr of observation. Early antibiotic locks were able to clear catheter-related bacteremia and resolve the symptoms more effectively without the need for catheter exchange when compared with late antibiotic locks. A total of 84 catheter-related bacteremias required wire-guided exchange of the catheters. Late antibiotic locks required wire-guided catheter exchange more frequently than the early antibiotic locks. The post–catheter-related bacteremia infection–free survival of the catheters after wire-guided exchange were significantly longer than those of both antibiotic lock groups. Recurrence of catheter-related bacteremia within 45 d after wire-guided exchange occurred at similar rates compared with the antibiotic lock groups.

Conclusion: Antibiotic locks are significantly more effective in clearing catheter-related bacteremia when used early in infection, diminishing the need for catheter exchange. Wire-guided exchange has a late-onset advantage for infection-free survival compared with catheter *in situ* treatment. The recurrence rates in the first 45 d after catheter-related bacteremia are similar regardless of the treatment strategy.

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Antibiotic lock solutions (ABL) are high concentration of antibiotic with or without anticoagulant agent that is dwelled (locked) in the catheter lumen, exposing the internal lumen of the catheter to persistent antibacterial action. Biofilms that harbor microorganisms are demonstrated on external and internal surfaces of the indwelling catheters within as early as 24 h after their placement (1,2). The fibrinous-proteinous ultrastructure of the biofilm gives both protection and antimicrobial resistance to the microorganisms. Because the intraluminal concentrations of the systemic antibiotics never reach high enough concentrations above the minimal inhibitory concentration, treatment failure as well as the loss of the catheter becomes inevitable during treatment of catheter-related bacteremias (CRB). Clinical series involving tunneled-cuffed catheters used for hemodialysis or nutrition reported 44 to 100% success rates for clearing CRB with ABL along with systemic antibiotics (3–9). The success of these studies has led to the recommendation of the use of ABL for the management of uncomplicated catheter-related bacteremias from a consensus panel (10).

Despite the current recommendations for long-term vascular access in hemodialysis patients being arteriovenous (AV) fistula or AV graft, still in 60% of the newly diagnosed and 30% of the prevalent hemodialysis patients, tunneled cuffed long-term central venous catheters are used as vascular access because of the difficulties in creating and maintaining AV fistulas and grafts (11–17). This is even more prominent for the pediatric ESRD population (18–20). CRB that lead to septic shock and metastatic infections are the most feared complications of long-term catheter use, and systemic antibiotics cannot satisfactorily clear the infected catheters, requiring early catheter exchange, as recommended in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (11).

The aim of this study was to investigate the effect of timing of the use of ABL along with systemic antibiotics for CRB treatment on children who were receiving long-term hemodialysis. The tested hypothesis was that ABL would act synergistically with the systemic antibiotics in eradicating the CRB when used early in the course of CRB rather than when systemic antibiotics fail to control CRB initially. The infection-free

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outcomes of the two ABL groups were compared with the outcomes of the catheters that were submitted to wire-guided exchange (WGE) as a result of CRB. The WGE catheters did not receive any ABL but only systemic antibiotics. These new catheters had no reason to have intraluminal biofilm formation. The second tested hypothesis was that ABL can successfully clear the intraluminal space of an infected catheter. If so, then post-CRB infection–free survival of the catheters treated *in situ* should be similar to WGE catheters as a result of CRB. The study was designed as a retrospective chart review protocol.

Materials and Methods

Our institutional review board approved this study. Retrospective chart review was performed for 98 children who were undergoing long-term hemodialysis in the pediatric dialysis unit at the University of Miami/Holtz Children's Hospital from January 1999 through April 2005. All consecutive patients were included in the study, and 88 of 98 (90%) children were using tunneled cuffed catheter as vascular access at least for some portion of the study. Standard tunneled cuffed, silicone, double-lumen hemodialysis catheters (Hemo-Cath®; Medcomp, Harleysville, PA) were used for vascular access and were placed percutaneously by the interventional radiologist or by the pediatric surgeon in children who weighed <15 kg. A total of three pediatric surgeons and three interventional radiologists were involved in the placement and exchange of the catheters. The size and length of the catheters were based on the patient's size and ranged from 8 French, 18 cm to 14 French, 40 cm. The right internal jugular vein was used whenever possible.

Hemodialysis Protocol and Catheter Care

Patients underwent dialysis three to four times per week, with hollow-fiber dialyzers appropriate for body size with Cobe (Gambro BCT, Lakewood, CO) or Baxter (Deerfield, IL) hemodialysis machines. A standard bicarbonate bath was used as dialysate. Intravenous antibiotics, vitamin D analogs, erythropoietin, and intravenous iron supplements were infused toward the end of dialysis as needed, through the catheter. Hemodialysis catheters were handled only during dialysis with no intervention between treatments. The exit site was cleaned with Betadine solution, and a chlorhexidine-impregnated dressing was applied weekly starting after July 2001. At the end of each hemodialysis session, each port of the catheter was filled with 5000 U/ml heparin solution according to the volume of the ports. Catheter malfunction was defined as the inability to get adequate clearance during a hemodialysis session. Poor control of hyperkalemia and hyperphosphatemia, persistent inappropriately high uremia, and excessive venous or arterial pressure alarms during treatment sessions all were evaluated as catheter malfunction. Poor blood flow was defined as increased resistance when either pulling blood from the catheter or pushing normal saline through the catheter at any point during a hemodialysis treatment. Catheter malfunction with or without poor blood flow was treated with installation of 2 mg/2 ml tissue-plasminogen activator (TPA) into each lumen for 1 h.

Definitions

1. CRB: Occurrence of a positive blood culture from the catheter with or without positive peripheral blood culture in a child with systemic symptoms (fever, chills, vomiting, hypotension) and no other source of infection identified. No surveillance blood cultures were obtained from the catheters during the study period.
2. Short-term success/clearance of CRB: At least two negative blood cultures from the catheter 1 wk apart in the index CRB with resolution of the systemic symptoms.
3. Late recurrence: Recurrence of CRB within 6 wk from the treatment of the index CRB, either with the same or a different microorganism.
4. Exit-site infection (ESI): Presence of purulent discharge, swelling, erythema, and tenderness at the exit site with or without a positive swab culture.
5. Polymicrobial CRB: Documented growth of at least two or more microorganisms in the first or sequential blood cultures during the index CRB.
6. Infection-free survival of a catheter after a CRB: The period between the final dose of antibiotics and the first subsequent positive blood culture obtained from that catheter. All blood cultures were obtained when CRB was clinically suspected. No surveillance blood cultures were obtained during the study period. Censored events were removal of that catheter for malfunction, obstruction or poor blood flow, transfer to another facility, elective removal of the catheter (AV fistula, AV graft, kidney transplantation), or end of study with functional catheter.

Late ABL Group

This group of children was treated in our center between January 1999 and December 2003. Blood cultures were obtained from both ports of the catheter when children presented with fever, chills, hypotension, or emesis during treatment. Peripheral blood cultures were obtained when possible. All children with symptoms were examined for a clear source of infection, and when none was found, they were presumed to be CRB. The initial empiric treatment was decided with the CRB history and antibiotic sensitivities of each patient. Cefazolin was the initial Gram-positive coverage and tobramycin was the initial Gram-negative coverage unless otherwise indicated by the attending physician. The systemic antibiotics were tailored according to the sensitivities of the CRB as soon as the blood culture results were available, typically at 48 to 96 h of treatment. Double coverage was not given unless the previous CRB was polymicrobial. Symptomatic CRB at 48 to 72 h of treatment went for catheter exchange with either WGE or removal and later replacement. CRB that was not symptomatic but persisted with positive blood cultures was treated with ABL, starting at 72 h to 7 d after the empiric treatment. Once started, ABL were used after every treatment until resolution of CRB. CRB that was not symptomatic and did not have persistent positive blood cultures were treated with systemic antibiotics until two negative blood cultures 1 wk apart were obtained. In the beginning of CRB treatment, blood cultures were obtained at every treatment until the first negative blood culture. Another blood culture was obtained 1 wk after the first negative blood culture. All children got treated for 2 full weeks with the appropriate antibiotics when two negative blood cultures were documented at least 1 wk apart. The total amount of treatment was 2 to 3 wk, and the use of ABL was three to five doses. Cefazolin, vancomycin, or tobramycin was mixed with either heparin or TPA when preparing the ABL, and it was a clinical decision. The antibiotic in the ABL was decided with the sensitivities of CRB. The final concentration of ABL was 5 mg/ml antibiotics. Heparin was at 5000 U/ml, and TPA was 2 mg/2 ml.

Early ABL Group

This group of children was treated in our center between January 2004 and April 2005. Similar to the historical group, blood cultures were obtained from both ports of the catheter when children presented with fever, chills, hypotension, or emesis during treatment. Peripheral blood cultures were obtained when possible. All children with symptoms

were examined for a clear source of infection, and when none was found, they were presumed to be CRB. The initial empiric treatment was broad-spectrum intravenous antibiotics: Vancomycin and levofloxacin, as well as empiric tobramycin-TPA ABL. Tobramycin was not infused systemically for this patient group. The maintenance doses of the antibiotics were infused for the next 6 to 7 treatment days (2 wk). In the beginning of CRB treatment, blood cultures were obtained at every treatment until the first negative blood culture. Another blood culture was obtained 1 wk after the first negative blood culture. All children got treated for 2 full weeks with the appropriate antibiotics when two negative blood cultures were documented at least 1 wk apart. In cases of polymicrobial CRB, both antibiotics were continued and an antifungal was added when necessary. The total duration of treatment was 2 wk from the initial diagnosis of CRB. ABL were used at the end of every hemodialysis treatment for the full duration of 2 wk treatment; tobramycin-TPA was used for Gram-negative CRB, and vancomycin-TPA was used for Gram-positive CRB. The final concentration of ABL was 5 mg/ml antibiotics. TPA was the only anticoagulant used for ABL in the time period; TPA concentration was 2 mg/2 ml. The treatment antibiotics were not altered according to sensitivities. Catheters were removed when there was malfunction, catheter breakage, cuff extrusion, persistence of symptoms beyond 48 h of treatment, recurrent CRB, growth of methicillin-resistant *Staphylococcus aureus*, or fungus that persisted with positive blood cultures into 1 wk of treatment. All catheter exchanges were done by WGE. There was no removal and later replacement of the catheters (R&R).

WGE Catheter Group

Catheters were exchanged when CRB was refractory to *in situ* treatment. The indications for catheter exchange were explained already in detail. Patients with WGE catheters continued their systemic antibiotic course to complete 2 wk but did not receive any ABL. The systemic antibiotics were used to prevent metastatic infectious complications. After the WGE, blood cultures were obtained at every treatment until the first negative blood culture. Another blood culture was obtained 1 wk after the first negative blood culture. All children got treated for 2 full weeks with the appropriate antibiotics when two negative blood cultures were documented at least 1 wk apart.

The treatment protocol for the R&R catheters was very similar. They were not included in the analysis because there was no R&R in the early ABL group.

Antibiotic Lock Solution

The goal was to prepare a 5-mg/ml antibiotic concentration in the ABL with each of the anticoagulants. They were prepared at bedside and installed into the catheter lumen according to the volume of the catheter. Combinations of antibiotics were not used with any of the ABL.

In vitro compatibility of the ABL was confirmed at our pharmacy. The ABL were prepared in a syringe and left at room temperature for 8 to 12 h to check for crystallization. The different types of ABL were approved after the documentation of no crystallization. We did not do any stability or bioactivity assessment of these ABL but extrapolated from the data accomplished for similar ABL in the literature (21,22).

The ABL were left to dwell in each of the catheter lumens after each treatment for 48 to 72 h, until the next treatment. They were drawn before the next treatment session. When the treatment of CRB was completed, heparin locks with 5000 U/ml solution equal to the volume of the lumens were used.

Outcome Parameters

The primary end points were successful clearance of CRB at the end of 2 to 3 wk of treatment and for the catheters to be infection-free at 6 wk after the completion of treatment. In both groups, ABL were used along with systemic antibiotics infused through the catheters. Secondary end points were being symptomatic at 48 h of treatment, catheter loss as a result of CRB, infection-free survival of the catheters after treatment of CRB, and determination of which CRB types/microorganisms were more susceptible to the use of ABL.

Data were obtained on serum albumin, serum hemoglobin, ferritin, intact parathyroid hormone, phosphorous, and calcium levels from the samples collected as monthly laboratory values without underlying CRB for all children during the protocol period. Patients' age, gender, cause of ESRD, cumulative catheter days when entering the protocol, and oral methylprednisolone (Medrol; Pfizer, New York, NY) treatments were also documented. Type of CRB (Gram-positive, Gram-negative, or polymicrobial), specific microorganisms of the CRB, post-CRB infection-free survival, and the outcome at the end of the infection-free period were also recorded.

The infection-free survivals of the WGE catheters during the study were used as the gold standard of survival and compared with the infection-free survivals of the catheters that were treated in the early ABL group and late ABL group. The WGE catheters did not receive any ABL but only systemic antibiotics. These new catheters had no reason to have intraluminal biofilm formation. The tested hypothesis was that ABL can successfully clear the intraluminal space of an infected catheter. If so, then post-CRB infection-free survival of the catheters treated *in situ* should be similar to WGE catheters as a result of CRB.

Statistical Analyses

Mean (SD), median (interquartile range), and percentage values were used to summarize baseline characteristics and outcome data. Results were expressed as the mean ± SD and median ± interquartile range when appropriate. $P < 0.05$ was considered significant. χ^2 tests were used to compare proportions. Paired t test and Fischer exact test were used to compare outcomes in the two groups. Infection-free survivals of the catheters treated with different modalities were compared using the Kaplan-Meier curves and the log-rank test. SAS9.1 PROC LIFETEST (SAS Institute, Cary, NC)was used for creating the Kaplan-Meier curves. GraphPad statistical software (GraphPad, San Diego, CA) and SAS9.1 were used for statistical analysis.

Results

There were a total of 98 pediatric hemodialysis patients in our center during the period of this analysis. Eighty-eight of these children underwent hemodialysis using a long-term catheter at least for part of the study period. There were 40 (41%)boys and 58 (59%) girls. The mean age was 13.7 ± 4.2 yr. Their racial distribution was 58 black, 31 Hispanic, and nine white. Ten patients were using AV graft/fistula as their vascular access throughout the study. The primary cause of ESRD was obstructive nephropathy/renal dysplasia-hypoplasia/neurogenic bladder in 33 patients, chronic glomerulonephritis in 28 patients, lupus nephritis/vasculitis in 14 patients, HIV nephropathy in 11 patients, and unknown/other in 12 patients. Table 1 describes the comparative demographics of the two ABL groups. Sixteen children contributed to both treatment periods; however, none of the catheters was overlapping in both treatment groups. The catheters from the late ABL period that were functioning and infection-free at the start of the early

Table 1. Comparative demographics for the early ABL and the late ABL groups[a]

Characteristics	Early ABL Group	Late ABL Group	*P*
Age (mean ± SD)	12.8 ± 5.2	13.9 ± 4.6	NS
Male gender (%)	39	44	NS
HIV primary cause (%)	11	15	NS
Medrol treatment	23	17	NS
Children with catheters (*n*/*N* [%])	48/51 (94)	60/72 (83)	NS
Serum hemoglobin (g/dl; mean ± SD)	10.8 ± 1.1	10.6 ± 0.5	NS
Serum albumin (g/dl; mean ± SD)	3.3 ± 0.4	3.4 ± 0.6	NS

[a]ABL, antibiotic lock.

ABL period were censored at that point. The average cumulative catheter days of these children before the study were 487 ± 86 d. There were a total of 259 catheters in the study period, with a distribution of 175 right internal jugular, 67 left internal jugular, 15 right subclavian, and two left femoral catheters.

This study involved 51,819 total catheter-days. There were 264 CRB in 79 children. The incidence of CRB was 5.1 per 1000 catheter-days during this period. Nine (9%) patients did not experience CRB. Their distribution was 176 (67%) Gram-positive CRB, 42 (16%) Gram-negative CRB, and 46 (17%) polymicrobial CRB. Coagulase-negative *Staphylococcus* species were the most common Gram-positive isolate (58%), followed by *Staphylococcus aureus* (14%) and *Enterococcus fecalis* (13%). Only 24% of the Gram-positive isolates were sensitive to oxacillin. Vancomycin sensitivity was 100%, including the *Enterococcus* species. The most frequent Gram-negative isolate was *Enterobacter/Acinetobacter* species (40%), followed by *Klebsiella* species (26%) and *Pseudomonas/Stenotrophomonas* species (21%). Tobramycin sensitivity in the Gram-negative isolates was 81%, and 90% of *Stenotrophomonas maltophilia* was resistant to tobramycin. Table 2 provides information on the distribution of the microorganisms for the two ABL groups and their antibacterial sensitivity patterns.

There were 31 ESI during the study period. Late ABL group had significantly more ESI (25 *versus* 6; $P < 0.05$). Despite the decrease in ESI, there was no difference in the rate of CRB between the late and early ABL groups (4.8 *versus* 5.8 CRB/1000 catheter-days, respectively; $P > 0.05$). Twenty-nine of 31 infections were documented by skin swab cultures. Two of them were culture negative but improved with systemic antibiotic coverage targeting Gram-positive microorganisms. Gram-positive ESI constituted 76% of the culture-proven cases. *Corynebacterium* species (42%) and coagulase-negative *Staphylococcus epidermidis* (49%) were the leading causes. Four ESI were associated with CRB, all in the late ABL group. Gram-negative microorganisms were cultured in 30% of the ESI, mostly as polymicrobial infections. The application of chlorhexidine-impregnated dressing at the exit site significantly decreased the ESI incidence (20 *versus* 11; $P < 0.05$), and all four CRB associated with ESI occurred in patients without chlorhexidine dressing on. A subanalysis of the late ABL group was completed to determine whether the use of chlorhexidine dressing had an

Table 2. Cumulative CRB demographics and incidence of various CRB types and their antimicrobial sensitivity patterns compared between the early ABL and the late ABL groups[a]

Parameter	Early ABL Group	Late ABL Group	*P*
Total no. of CRB	76	188	NA
Total catheter-days	12,931	38,888	NA
CRB/1000 catheter-days	5.8	4.8	NS
Gram-positive CRB (*n* [%])	49 (65)	126 (67)	NS
oxacillin sensitivity (%)	18	24	NS
vancomycin sensitivity (%)	100	99	NS
Gram-negative CRB (*n* [%])	15 (20)	26 (14)	NS
tobramycin sensitivity (%)	87	78	NS
cefotaxime sensitivity (%)	74	68	NS
levofloxacin sensitivity (%)	100	100	NS
Polymicrobial CRB (*n* [%])	12 (15)	36 (19)	NS
tobramycin sensitivity (%)	37	28	NS
cefotaxime sensitivity (%)	54	61	NS
levofloxacin sensitivity (%)	100	100	NS
vancomycin sensitivity (%)	100	100	NS

[a]CRB, catheter-related bacteremia; NA, not applicable.

impact on CRB incidence. The CRB incidence before the chlorhexidine dressing was part of the care was comparable to CRB incidence while the chlorhexidine dressing was used routinely (4.2 *versus* 5.5 CRB/1000 catheter-days, respectively; $P > 0.05$). All ESI responded to antibiotic treatment with complete resolution.

Early ABL were able to clear CRB ($P < 0.05$) and resolve the symptoms more effectively ($P < 0.0001$) without the need for catheter exchange when compared with late ABL. The recurrence of CRB at 6 wk and after CRB infection–free survivals were not statistically different between the two groups. Table 3 summarizes the outcomes. In both groups, polymicrobial CRB were significantly less likely to be successfully treated by catheter *in situ* methods compared with Gram-positive and -negative CRB ($P < 0.01$). In the late ABL group, both Gram-negative and polymicrobial CRB were more likely to be symptomatic at 48 h of treatment compared with Gram-positive CRB ($P < 0.01$). For the early ABL, only polymicrobial CRB were more likely to be symptomatic at 48 h ($P < 0.05$). No specific microorganism was more likely to persist with symptoms at 48 h of CRB for either ABL group.

In the late ABL group, there were 41 heparin-based ABL and 32 TPA-based ABL. The success rates for clearing CRB was similar for the heparin- and TPA-based ABL (26 [63%] of 41 *versus* 17 [53%] of 32, respectively; $P > 0.05$). There was no difference for recurrence at 45 d (13 [50%] of 26 *versus* 7 [41%] of 17, respectively; $P > 0.05$) or after CRB infection–free survival (57.4 ± 6.7 *versus* 71.4 ± 9.5 d, respectively; $P > 0.05$). The slight advantage of survival with the TPA-based ABL did not reach statistical significance. Gram-positive CRB was more likely to be treated with systemic antibiotics alone (odds ratio 3.3; 95% confidence interval 1.6 to 7.0; $P < 0.001$) (20).

Recurrence of CRB within the first 6 wk after the completion of treatment was more likely to be with a different microorganism in the early ABL group (14[78%] of 18; $P < 0.05$) and with the same microorganism for the late ABL group (32 [65%] of 49; $P < 0.05$). None of the secondary CRB was due to *Candida* species. When CRB was symptomatic at 48 h of treatment, recurrence at 6 wk was more frequent with persistent use of TPA-ABL/AB in the early group ($P < 0.05$). There was no statistically meaningful correlation of failure at 6 wk for the late ABL group.

The post-CRB infection-free survivals of early and late ABL groups were compared with the outcomes of the WGE catheters for CRB during the study period using a Kaplan-Meier survival curve (Figure 1). Catheters that were removed electively, transferred to other centers, or still functional at the end of the study period were censored. There were 84 CRB that required WGE during the study period. Late ABL required WGE more frequently than the early ABL (71 of 188 *versus* 13 of 76; $P < 0.0001$). The infection-free survival of the catheters after WGE was 119.0 ± 106.1 d. This is significantly longer than the infection-free survivals of both early ABL and late ABL, using log-rank test ($P < 0.0001$). The detailed infection-free survival data of these three groups are demonstrated in Table 4. There was no statistically significant difference in the infection-free survivals of the WGE catheters regarding their index CRB type. The WGE group achieved the infection-free survival advantage in the survival analysis after 45 d. This survival analysis is demonstrated in Figure 1. When the data were analyzed using <45 d of infection-free survival, there was no statistical difference between the three treatment groups ($P = 0.37$). Recurrence of CRB within 45 d after WGE occurred in 17 (20%) of 84 cases, at similar rates to the ABL groups. Neither the type of CRB nor the specific microorganism made any difference in the rate of recurrence within 45 d in the WGE group.

There were no episodes of catheter malfunction from premature occlusion or catheter breakdown during the course of TPA or heparin-ABL treatments. There were no adverse outcomes, such as prolonged bleeding, metastatic infections, or allergic reactions, in the patients who were treated with TPA or heparin-ABL. No deaths during the study period were related to CRB.

Discussion

This study demonstrated that early use of ABL along with systemic antibiotics can be more effective in resolving the symptoms and eradicating CRB without the need to exchange the catheters in the majority of the cases. Polymicrobial CRB is still more resistant to catheter *in situ* treatments. The similar outcomes for recurrence of CRB at 6 wk and post-CRB infection–free survivals for the early and the late ABL may be only a mispresentation. Early ABL were able to clear a higher percentage and possibly more aggressive CRB; therefore, the similar long-term outcomes indirectly suggest the better efficacy of this protocol. The infection-free survivals of the catheters that were WGE for CRB was longer than both ABL groups, but it is interesting that there was no difference between the incidence of recurrence in the first 6 wk (45 d) between the WGE and the ABL groups. The survival advantage of the WGE group was demonstrated for the period after 6 wk (45 d). The initial treatment trial with ABL and systemic antibiotics for CRB did

Table 3. Comparison of catheter outcomes for the two different treatment modalities

Parameter	Early ABL Group ($n = 48$)	Late ABL Group ($n = 60$)	P
CRB cleared with ABL (n/N [%])	63/76 (83)	107/188 (57)	<0.0500
CRB with catheter loss (n/N [%])	13/76 (17)	81/188 (43)	<0.0001
Symptoms at 48 h (n/N [%])	5/63 (8)	58/107 (54)	<0.0001
Recurrence at 45 d (n/N [%])	18/63 (29)	49/107 (46)	NS
Infection-free survival days (mean ± SD)	68.2 ± 45.8	68.6 ± 53.1	NS

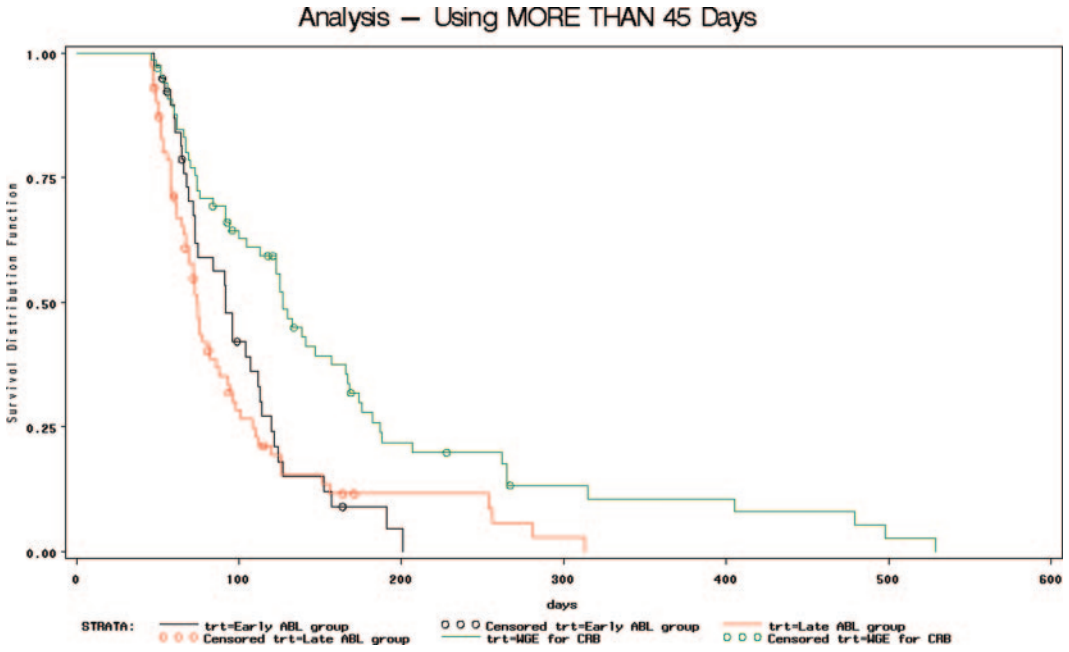

Figure 1. Kaplan-Meier curve for post–catheter-related bacteremia (CRB) infection–free survival of the wire-guided exchange (WGE) catheters compared with the two different antibiotic lock (ABL)-treated groups. WGE catheters had the advantage of longer post-CRB infection–free survival by log-rank test ($P < 0.0001$). Catheters that were removed electively or were still functional at the end of the study period were censored. Green, WGE; red, late ABL; blue, early ABL.

Table 4. Comparison of infection-free survivals of the three treatment strategies[a]

Parameter	Mean ± SD Days	Median ± IQR Days
Early ABL group ($n = 48$)	68.2 ± 45.8	61 ± 67
Late ABL group ($n = 60$)	68.6 ± 53.1	58 ± 42
WGE group ($n = 84$)	119.0 ± 106.1	92 ± 101

[a]WGE *versus* early ABL, $P = 0.0019$; late ABL *versus* WGE, $P < 0.0001$; early ABL *versus* late ABL, $P > 0.05$. IQR, interquartile range.

not result in metastatic infections, secondary *Candida* CRB, or any other infectious complications even in the cases that eventually needed catheter exchange. This is the first report comparing the timing of ABL for the treatment of CRB in the hemodialysis population.

CRB are not only the major limiting factor for long-term catheter survival but also a major cause of morbidity and mortality in the pediatric hemodialysis population (20,23–25). Hemodialysis patients have unique risk factors for CRB as a result of the ESRD, such as hypoalbuminemia, anemia, and parenteral iron treatments, and are susceptible to metastatic infections from the infected catheters because of the high blood flows required during renal replacement therapies (26–30). Systemic antibiotics alone can clear approximately 35 to 65% of the CRB episodes in the most successful series, with a very high rate of early recurrence of CRB (17,20,31,32). In our experience, CRB was successfully cleared in only 34% of the episodes with systemic antibiotics alone (20). The recently updated K/DOQI guidelines recommend removal of the catheter/exchanging the catheter over a guidewire while on systemic antibiotics, claiming that there is insufficient evidence for the use of ABL to give an evidence-based recommendation (11). The intraluminal presence of the biofilm is the reason for bacteremia, and the antibiotic levels around the biofilm are negligible with the use of systemic antibiotics alone. Scanning electron microscopic studies demonstrated the formation of biofilms on external and internal surfaces of indwelling catheters within 24 h after placement (1,2). The key to the success of the ABL is their ability to reach 100- to 1000-fold higher than minimal inhibitory concentration intraluminally in the vicinity of the biofilm (4–6). It is not clear whether dissolving the protein-fibrin matrix of the biofilm could provide extra success along with this high concentration of antimicrobials. In the early ABL group, TPA-based ABL were used because it was thought that the fibrinolytic properties of the agent may provide better clearance of CRB.

The success of the ABL protocol in the treatment of CRB was clearly associated with their early use. The early aggressive treatment of CRB by addressing the biofilm is crucial for success, as shown in our previous article (20). There is synergistic gain with the early start of ABL and systemic antibiotics when compared with late use of ABL. The significant decrease in the number of patients with symptoms at 48 h of treatment with early ABL decreases the morbidity associated with CRB. At the same time, the increased rate of clearing CRB without the need

for catheter exchange decreases the cost and the risks of exchanging the catheters and saves the other access sites for the coming years. In this study, the empiric ABL at the first treatment was tobramycin-TPA lock, because tobramycin had the better coverage for Gram-positive and -negative microorganisms. Along with parenteral vancomycin and levofloxacin, the goal was providing the empiric treatment as broadly as possible. This combination provided 100% coverage to the antimicrobial sensitivities in our unit (20). The choice of systemic antibiotics can be decided by the spectrum of microorganisms and their antibiotic sensitivity patterns for different hemodialysis units. Moreover, ABL with combination antibiotics can be investigated by *in vitro* protocols for empiric broad coverage.

Polymicrobial CRB were more resistant to successful clearance with catheter *in situ* methods in both ABL periods. One possible reason can be suboptimal coverage of the potential microorganisms by ABL. Because the ABL treatment for polymicrobial CRB was alternating Gram-positive and Gram-negative covering ABL during the treatment course, there was 50% reduction to the ABL exposure by both components of CRB. This is because we did not use the combination antibiotic protocol for the ABL, which will allow both Gram-positive and Gram-negative coverage at the same time—one more reason that it is important to get the stability studies for combination ABL in the future.

Recurrence within 6 wk of completion of treatment was accepted as a long-term end point in most of the protocols. A longer infection-free survival after treatment suggests eradication rather than suppression of the microorganisms in the catheter. Even though both ABL groups had similar rates of recurrence at the 6-wk mark, early ABL recurrence was with a different microorganism, whereas late ABL had it with the same causative agent as the index CRB. This suggests the suboptimal eradication of the CRB with late ABL as well as the polymicrobial nature of most CRB even though the index blood cultures are dominated with one microorganism. After the dominant microorganism is eliminated in the biofilm by the appropriate therapies, the suppressed microorganisms find the opportunity for fast replication, presenting with early recurrent CRB. It is more challenging to explain the very similar early recurrence rates after WGE catheters. The only common point of infection focus between the two ABL groups and the WGE catheters is the extraluminal but intravascular space around the catheter. The fibrin sheath that occupies this space for most of the catheters may as well be a reservoir for CRB. This may contribute to approximately 20% of the CRB cause because that is the rate of early recurrence for all three ways of treatment. Neither the systemic antibiotics nor ABL can effectively reach that space, making it more difficult to decrease the early recurrence rates for catheters. The possible areas of entry to the extraluminal intravascular area may be through the exit-site migration, contamination at the time of placement, or hematogenous spread during bacteremic episodes; however, even though this may provoke the use of removing and later placing the catheters at another site, that practice will deplete the possible access sites fast and will not work for the benefit of the patient on long-term care. At the same time, putting the extra effort to remove the fibrin sheaths at the time of WGE does hold the promise to decrease the early recurrence at the WGE groups.

In this study, the longer post-CRB infection–free survival advantage for the WGE catheters was demonstrated in the analysis after 6 wk. As discussed, there were similar early recurrence rates for the WGE catheter and ABL groups; however, the inferior results of the ABL groups should not bring WGE as the first option. There is not only cost and the risk of anesthesia and intervention but also damage at the vessel with every manipulation, which decreases the longevity of the access site. The promise of the ABL is fast control of CRB with total clearance of the catheters. If this can be demonstrated in large, randomized, controlled studies, then ABL may offer longer overall catheter survivals without secondary infectious complications.

The retrospective design of the study is its major limitation. The different treatment strategies were historically compared rather than a controlled, randomized manner. There are several unique aspects of our study. There were significant cumulative catheter days before the study for most of our patients. There were no exclusions, and all consecutive CRB were included in the protocol. The decision to exchange the catheter was a clinical decision rather than protocol; therefore, the results might be more likely to be reproducible if used in real-life situations. Because TPA is approximately 75 to 100 times more expensive than heparin, citrate, or ethanol as ABL solution, it is unlikely for TPA-ABL to gain generalized acceptance in everyday practice unless long-term outcomes offer cost-effective benefits.

Conclusions

Our study suggests that early ABL use can control the symptoms and clear the CRB in the majority of cases. This will decrease the need for catheter exchange/removal. ABL did not increase the serious complication rates, both infectious and noninfectious (occlusion, malfunction, catheter breakage, bleeding) during this protocol. The similar 6-wk recurrence rates for both ABL treatment groups and the WGE group suggest the extraluminal fibrin sheath as a possible focus of infection for some of the CRB. Because of its promise to preserve vascular access sites, the importance of catheter *in situ* treatment cannot be overemphasized in the hemodialysis population. Every manipulation in a vessel generates inflammation and sclerosis that contributes to the loss of the access site. The use of ABL along with systemic antibiotics holds the promise to preserve the access sites without increasing the risk for complications. The efficacy and the cost-effectiveness of different ABL need to be investigated in prospective, randomized, controlled trials.

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Disclosures

None.

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