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PREFABL: predictors of failure of antibiotic locks for the treatment of catheter-related bacteraemia

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Abstract

Background. Antibiotic lock (ABL) solutions can effectively treat catheter-related bacteraemia (CRB) without the need for catheter exchange. This approach does not increase secondary infectious complications. We evaluated the risk factors that contribute to failure when CRB is treated with ABLs and systemic antibiotics in paediatric haemodialysis patients.

Methods. A retrospective chart review of 72 children on haemodialysis between January 2004 and June 2006 was

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performed. We evaluated risk factors for ABL treatment using patients' characteristics, CRB/catheter characteristics and patients' biochemical profiles. The first CRB of each catheter was included in the statistical analysis. Our end points were outcome at 2 weeks of treatment and at 6 weeks following treatment. Compound symmetry covariance structure was employed for statistical analysis.

**Results.** We treated 149 CRB in 50 patients. The incidence was 3.4 CRB/1000 catheter days. Thirty CRB failed to be cleared with the use of ABL and systemic antibiotics at 2 weeks of treatment (30/149, 20 vs 80%, P < 0.001). Twenty-four of these catheters required exchange. Thirty-nine of the treated catheters got re-infected within the next 6 weeks (39/125, 31 vs 69%, P < 0.001). CRB aetiology was the only statistically significant independent variable for 2-week outcome (P = 0.033). Coagulase-negative *Staphylococcus* CRB had higher odds of being cleared at 2 weeks compared with other CRB aetiologies. For the 6-week outcome, the statistically significant independent variables in the final model included age (P = 0.048) and serum phosphorous level (P < 0.001). Younger age and higher serum phosphorous levels were independent risk factors for failure at 6 weeks with re-infection. Area under the receiver operating characteristic (ROC) curve for the model of the 2-week outcome was 0.736 with the percentage of correct predictions at 81.2%. Area under the ROC curve for the model of the 6-week outcome was 0.689 with the percentage of correct predictions at 75.5%.

**Conclusions.** CRB can effectively be treated with ABLs and systemic antibiotics. CRB aetiology is the only independent variable of early treatment failure. Younger age and higher serum phosphorous levels are independent risk factors for re-infection at 6 weeks.

**Keywords:** antibiotic locks; catheter-related bacteraemia; haemodialysis; phosphorous; sepsis

**Introduction**

Catheter-related bacteraemia (CRB) is a well-documented and feared complication of haemodialysis patients using tunnelled-cuffed catheters (TCC) as long-term vascular access [1–3]. The reported incidence of CRB varies from 1.1 to 4.2/1000 catheter days, with 5% mortality rate for the adult population [4–6]. Systemic antibiotics infused through the infected catheters can clear about 35% of the CRB episodes with high rates of systemic infectious complications and unacceptably high rates of early recurrence of CRB [2,7–10]. The current K/DOQI guidelines recommend removal of the catheter/exchanging the catheter over a guidewire while on systemic antibiotics for the treatment of CRB [11]. This makes CRB the most common cause of catheter loss in this patient population [1,12]. Treatment of CRB without changing the catheter allows the patient not only to have less exposure to procedures/sedation and continue to get outpatient haemodialysis, but also saves the access site from premature stenosis secondary to multiple manipulations [13,14]. This goal has to be achieved with minimal risk to the patient.

The pivotal point in the CRB pathogenesis is the biofilm formation of the microorganisms in the presence of the foreign body which makes them further resistant to the effects of the systemic antibiotics [15]. These biofilms occupy both the internal and the external surfaces of the catheters and their presence can be demonstrated within the first 24 h of catheter placement [16,17]. Successful eradication of the biofilms may clear CRB without the need for catheter exchange and without increasing the complication risks. Antibiotic lock (ABL) solutions consist of high concentrations of an antibiotic mixed with/without an anticoagulant that is dwelled in the catheter lumen between haemodialysis treatments, providing persistent antimicrobial action in the vicinity of the biofilm. By increasing the intraluminal antimicrobial concentration to 100–1000 times above the minimal inhibitory concentration, ABL can more effectively clear CRB compared to systemic antibiotics alone. Clinical series involving different types of catheters, different treatment needs (haemodialysis vs parenteral nutrition) and different ABL types have reported 44–100% success rate for clearing CRB [18–24]. We have reported similar outcomes with ABL treatments in paediatric haemodialysis patients, noting that post CRB infection-free survival was comparable to the wire-guided exchanged catheters [25,26]. The positive impact of the above reports in the literature resulted in the recommendation of the use of ABL for the management of uncomplicated CRBs from an infectious disease consensus panel [27].

There have been attempts to explain the risk factors for failure while treating CRB with ABL. The CRB type, the specific pathogen, different types of ABL and intrinsic patient characteristics have been reported as such in the literature [22,28–30]. This investigation was conducted to determine the risk factors contributing to treatment failure in the paediatric haemodialysis patients when CRB was treated with ABL and systemic antibiotics without immediate catheter exchange. The study was designed as a retrospective chart review protocol.

**Materials and methods**

The institutional review board at University of Miami approved this study. Retrospective chart review was performed on 72 chronic haemodialysis patients who were treated at the paediatric dialysis unit at the University of Miami/Holtz Children's Hospital from January 2004 to June 2006. All consecutive children in the unit were included in the review. TCC were used as vascular access for 61/72 (85%) children for a minimum of 90 days during this period. These were silicone double-lumen haemodialysis catheters (TCC) (Hemocath®, Medcomp, Harleysville, PA, USA). The right jugular vein was used whenever possible.

**Haemodialysis protocol and catheter care**

Patients were dialysed three to four times per week, with hollow-fibre dialysers appropriate for body size with Cobef® (Gambro Inc., Lakewood, CO, USA) or Baxter® (Deerfield, IL, USA) haemodialysis machines. The exit site was cleaned with chlorhexidine-based solution or povidone-iodine solution and chlorhexidine-impregnated dressing was applied weekly. Catheter malfunction was diagnosed when goal blood flow rate could not be maintained or urea reduction rate was <65%. Catheter malfunction was initially treated with installation of 2 mg/2 mL TPA into each lumen for 1–2 h.
Definitions

(a) CRB was defined as the 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 and hypotension) and no other source of infection identified. No surveillance blood cultures were obtained from the catheters during the study period.

(b) Exit site infection was defined as the presence of purulent discharge, swelling, erythema and tenderness at the exit site with or without a positive swab culture.

(c) Polymicrobial CRB was defined as the documented growth of at least two or more microorganisms in the first or sequential blood cultures during the index CRB.

Diagnosis and management of CRB

CRB was suspected when children presented with fever, chills, hypotension or emesis prior to or during dialysis treatment, and blood cultures were obtained from both ports of the catheter. Peripheral blood cultures were obtained when possible, but were not required for CRB diagnosis. All symptomatic children were examined for a clear source of infection, and if none were found, they were presumed to be CRB. The initial treatment consisted of vancomycin and levofloxacin. The choice of antibiotics was based on our retrospective data on CRB aetiology and sensitivities [2]. The maintenance doses of the antibiotics were infused for the next six to seven treatment days (2 weeks) until two blood cultures from the catheter, 1 week apart, demonstrated no growth. Gram-positive CRB was treated with vancomycin and gram-negative CRB was treated with levofloxacin. Both antibiotics were continued for polymicrobial CRBs and an antifungal was added if necessary. The total duration of treatment was 2 weeks from the initial diagnosis of CRB. The treatment antibiotics were not altered according to sensitivities. The protocol was discontinued if the blood cultures demonstrated no growth at 5 days observation. Following the eradication of CRB, no surveillance blood cultures were obtained in asymptomatic children.

Catheters were removed if there was malfunction, catheter breakage, cuff extrusion, persistence of symptoms beyond 48 h of treatment, recurrent CRB and/or growth of methicillin-resistant *Staphylococcus aureus* or fungus that persisted with positive blood cultures into a week of treatment. All catheter exchanges were done by wire-guided exchange by the interventional radiologist.

Antibiotic lock solutions

The final antimicrobial concentration was 5 mg/mL for the ABL. Tobramycin and vancomycin were the antibiotics used in the ABL. TPA (2 mg/2 mL) and heparin (5000 units/mL) were the two different anticoagulants used in this period.

Tobramycin-based ABL was used as initial empiric treatment of all CRBs. Following the identification of the microorganism, vancomycin-based ABL was used for gram-positive CRB and tobramycin-based ABL for gram-negative CRB. Vancomycin-based and tobramycin-based ABLs were alternated for polymicrobial CRB. The ABLs did not contain more than one antibiotic. One dose of empiric ABL and six doses of CRB-specific ABLs constituted our protocol (2 weeks) and each ABL was installed in the catheter at the end of the haemodialysis treatment. The catheters were locked with heparin at the end of 2 weeks when the CRB was cleared.

In vitro compatibility of the ABL was confirmed by our pharmacy. The ABL was prepared in a syringe and left at room temperature for 8–12 h to observe for signs of crystallization. The four different types of ABL, vancomycin–TPA, vancomycin–heparin, tobramycin–TPA and tobramycin–heparin, were approved after documentation of no crystallization. Our protocol was extrapolated from published data [29,31].

Outcome parameters

The primary end points in this study were clearance of CRB at the end of 2 weeks of treatment without the need for catheter removal and being infection-free at 6 weeks following the completion of treatment. The risk factors that interfered with these successful outcomes were investigated by constructing statistical models to explain the observed data.

Statistical methods

Descriptive statistics were calculated for all variables and included frequencies and percentages for nominal and ordinal variables, as well as means and standard deviations (SD) for continuous variables. All results were expressed as the mean ± SD. P-values of <0.05 were considered significant. Chi-square tests were used to compare proportions. Paired t-tests and Mann–Whitney tests were used to compare outcomes for different groups.

Generalized linear models were constructed using a hierarchical method to determine which variables, if any, were significant predictors of the outcome variables. Statistical selection methods (stepwise selection and backward conditional selection) were employed in order to determine which of the independent variables were significant predictor variables. The criteria for inclusion and exclusion of a numeric variable using the stepwise method were 0.05 and 0.05, respectively. The criterion for inclusion of a nominal variable using the backward conditional method was 0.05.

Model diagnostics were computed in order to identify outliers and influential observations, and multicollinearity was also assessed for the models. Three highly influential observations (out of 149 observations in the data) were eliminated from the final models. The independent variables (predictors) in our final models exhibited no multicollinearity. All statistical tests were two-tailed, and the Type I error rate was specified to be 0.05.

The data were analysed using SAS 9.1® (SAS Institute, Cary, NC, USA). The SAS procedure PROC GLIMMIX was used to model the variable ‘2-week outcome’. ‘Two-week outcome’ was a binary variable with two levels: cleared and not cleared. Similarly, PROC GLIMMIX was also used to model the binary variable ‘6-week outcome’ [32].

Data were collected at several times from the patients. For any particular patient, the data collected at these times were not independent of data collected at previous times [33]. However, each patient was considered to be independent of all other patients in the study. In order to account for the lack of independence of the data collected within each patient, several covariance structures were considered and analysed, including compound symmetry (CS) covariance structures and autoregressive (AR) covariance structures, among others [34]. The determination of which covariance structure best fits the data was made using the Akaike Information Criterion (AIC) and the Schwarz Information Criterion (BIC). Thus, the final models that we developed possessed two components: the statistically significant independent variables in the model that predict the outcomes and a determination (or description) of the pattern of dependence of observations within each patient (the covariance structure).

The potential independent variables that were examined include serum haemoglobin, albumin, ferritin, phosphorous, calcium × phosphorous product and intact parathyroid hormone (PTH) levels from the monthly scheduled labs without diagnosed CRB for all children during the study period. Patient’s age, cumulative catheter days coming into the study, concurrent immunosuppressive treatments (yes/no), HIV status (yes/no) and ABL prophylaxis (yes/no) were also included in the analysis. Finally, the CRB type, specific aetiology of CRB, presence of exit site infection, antibiotic sensitivity characteristics of CRB–oxacillin sensitivity (yes/no) and tobramycin–gentamicin sensitivity (yes/no), the type of ABL (heparin or TPA) and whether the catheter was newly placed (within 90 days) or not were also examined in the statistical model for failure of ABL treatments.

Results

There were 72 paediatric haemodialysis patients during the study. Long-term haemodialysis catheters (TCC) were used for at least 3 months for 61 of these children (85%). Nine children were dialysed through arteriovenous (AV) fistulas and two were using AV grafts as vascular access. Eleven of the TCC group have not experienced CRB during the study period and 50 had at least one CRB (50/61, 82%). The average cumulative catheter days of the children prior to the study was 504 ± 638 days (0–2498 days). Table 1 summarizes the patient demographics.
Primary aetiology for ESRD, Caucasian, Hispanic, African American, Mean age (years) 14.3 ± 9.7

Females, aCRB aetiology is a categorical variable with six levels. A single parameter estimate is not applicable.

Table 1. Demographics of patients

| Patients with long-term catheters, n (%) | 61/72 (85) |
| Females, n (%) | 41/72 (57) |
| Mean age (years) | 14.3 ± 9.7 |
| African American, n (%) | 40 (56) |
| Hispanic, n (%) | 21 (29) |
| Caucasian, n (%) | 11 (15) |

Primary aetiology for ESRD, n (%)

| Renal dysplasia/obstructive uropathy | 23 (32) |
| Chronic glomerulonephritis | 29 (40) |
| Vasculitis/lupus nephritis | 9 (13) |
| HIV nephropathy | 5 (7) |
| Other/unknown | 6 (8) |

Table 2. CRB characteristics

| Total CRB number | 149 |
| Gram-positive CRB, n (%) | 95 (64) |
| Gram-negative CRB, n (%) | 29 (19) |
| Polymicrobial CRB, n (%) | 25 (17) |
| Distribution by microorganism, n (%) |
| CNS species | 60 (40) |
| Staphylococcus aureus | 16 (11) |
| Enterococcus fecalis | 14 (9) |
| Enterobacter/Acinetobacter species | 18 (12) |
| Klebsiella species | 13 (9) |
| Pseudomonas/Stenotrophomonas species | 9 (6) |
| Candida species | 5 (3) |
| Other | 14 (10) |

There were 43,823 observed catheter days. We treated 149 CRB in 50 patients. The incidence was 3.4 CRB/1000 catheter days. Heparin-based ABL were used to treat 16 CRB, and TPA-based ABL were used for 133 CRB. Table 2 summarizes the CRB distribution.

The study included 187 long-term catheters. Thirty CRB failed to be cleared with the use of ABL and systemic antibiotics at 2 weeks of treatment (30/149, 20 vs 80%, P < 0.001). Seventeen of these required early exchange of the catheter within 48–72 h of treatment (17/149, 11 vs 89%, P < 0.001). Seven more catheters of the failure group received catheter exchange in the next 2–3 weeks and six catheters were able to be salvaged with prolonged antibiotic and ABL treatment despite failure to clear blood cultures at 2 weeks of treatment (6/30, 20 vs 80%, P = 0.0066). Thirteen catheters were removed prior to any CRB involvement.

Among the 125 CRB catheters that were cleared/still in-use at 2-week outcome, 8 catheters were lost to malfunction/thrombosis and 39 catheters were re-infected within the next 6 weeks (39/125, 31 vs 69%, P < 0.001). The re-infection occurred with a different microorganism in 25 of the CRB (25/39, 64 vs 36%, P = 0.0802). None of these re-infection CRBs were due to Candida species.

There were eight exit site infections diagnosed and treated. Seven were swab culture positive. They were Corynebacterium species [4], coagulase-negative Staphylococcus (CNS) [2] and Bacillus species [1]. One of the exit site infections was associated with CRB (Corynebacterium species). All eight infections were successfully treated with intravenous oxacillin or cefazolin.

We also tried to determine which risk factors and variables predicted the ‘2-week outcome’ and the ‘6-week outcome’. For the binary dependent variable ‘2-week outcome’, the statistically significant independent variables in the final model included only the CRB aetiology (P = 0.037). Those catheters diagnosed as CNS CRB typically had higher odds of being cleared at 2 weeks of treatment than did other CRB aetiologies, such as Enterococcus species, Stenotrophomonas/Pseudomonas species and S. aureus, with odds of CNS patients being cleared ranging from 3.97 to 7.74. The outcome of patients with Klebsiella species CRB were not statistically significantly different from patients with CNS CRB (odds ratio 1.59). Patients with CNS CRB had 3.44 greater odds of being cleared than patients with Enterobacter/Acinetobacter species CRB, but this comparison was not statistically significant (at the 0.05 significance level). Table 3 summarizes the above data.

For the binary dependent variable ‘6-week outcome’, the statistically significant independent variables in the final model included age (P = 0.048) and serum phosphorous level (P < 0.001). For each year increase in age, the odds of being clear for CRB at 6 weeks decreased by 0.67. Alternatively, we could say that, for each unit increase in phosphorous level, the odds of being clear for CRB at 6 weeks increased by 1.15. Table 3 summarizes the above data.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Variables in final model</th>
<th>Estimate</th>
<th>Standard error</th>
<th>Odds ratio</th>
<th>P-value</th>
<th>Covariance structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘2-week outcome’ (cleared)</td>
<td>CRB aetiology*</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
<td>0.033</td>
<td>CSH</td>
</tr>
<tr>
<td></td>
<td>CNS vs Enterobacter/Acinetobacter</td>
<td>1.24</td>
<td>0.67</td>
<td>3.44</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CNS vs Enterococcus species</td>
<td>2.05</td>
<td>0.69</td>
<td>7.75</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CNS vs Klebsiella species</td>
<td>0.46</td>
<td>0.87</td>
<td>1.59</td>
<td>0.596</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CNS vs Staphylococcus aureus</td>
<td>1.38</td>
<td>0.68</td>
<td>3.97</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>‘6-week outcome’ (clear)</td>
<td>CNS vs Stenotrophomonas/Pseudomonas species</td>
<td>2.04</td>
<td>0.88</td>
<td>7.74</td>
<td>0.048</td>
<td>CSH</td>
</tr>
<tr>
<td></td>
<td>Age (per 1-year increment)</td>
<td>0.14</td>
<td>0.07</td>
<td>1.15</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phosphorous (per 1-mg/dL increment)</td>
<td>−0.40</td>
<td>0.12</td>
<td>0.67</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratios for ‘2-week outcome’ are odds of being cleared. Odds ratios for ‘6-week outcome’ are odds of persisting clear.

*CRB aetiology is a categorical variable with six levels. A single parameter estimate is not applicable. The bold values are the statistically significant P-values.
Table 4 summarizes the results of the statistical modelling for all the individual risk factors that were investigated in this study.

The overall catheter survival from children with no documented CRB (No-CRB group) were compared with the overall catheter survival from children with at least one documented CRB (At-least-one-CRB group) using the Kaplan–Meier survival curve (Figure 1). The No-CRB group had 24 catheters and the at-least-one-CRB group had 163 catheters. Catheters that were removed electively, still functional at the end of the observation period or of children that were transferred to other centres were censored. No-CRB group catheters seemed to have survival advantage over catheters from children with at least one CRB (267.5 ± 33.6 vs 222.1 ± 15.1 days). This difference in overall catheter survival did not reach statistical significance (P = 0.1042 by Wilcoxon test and P = 0.2768 by log-rank test). When the analysis was censored at 365 days, the difference in overall catheter survival between the two groups was still statistically insignificant (P = 0.1550 by Wilcoxon test and P = 0.1519 by log-rank test).

Area under the receiver operating characteristic (ROC) curve for the model of ‘2-week outcome’ was 0.736 with the percent of correct predictions at 81.2%. The false-positive rate was 25.0% and the false-negative rate was 18.6%. We then performed a lack of fit test for our model using the Hosmer–Lemeshow test. For the ‘2-week outcome’ model, the Hosmer–Lemeshow test revealed P = 0.9999, indicating that our model did not suffer from lack of fit. Area under the ROC curve for the model of ‘6-week outcome’ was 0.689 with the percent of correct predictions at 75.5%. The false-positive rate for this analysis was 0.0% and the false-negative rate was 25.0%. For the ‘6-week outcome’ model, the Hosmer–Lemeshow test revealed P = 0.1896, which indicates that our model did not suffer from lack of fit.

Discussion

In this retrospective study, we were able to demonstrate distinct risk factors in the paediatric haemodialysis population for failure to clear CRB with ABL treatment and for early recurrence after CRB was treated with ABLs successfully. CRB aetiology was the only independent variable determining the likelihood of treatment failure, and CNS was more likely to be cleared when compared to any other microorganism. For those CRB that were treated with ABL with success at 2 weeks, the likelihood of early recurrence for CRB was higher for younger patients and for patients with higher serum phosphorous levels at routine monthly laboratory evaluation. CRB

Table 4. Examination of the potential predictors of ABL treatment success/failure for 2-week outcome and 6-week outcome end points identified by PROC GLIMMIX multivariate analysis

<table>
<thead>
<tr>
<th>Predictor of failure for ABL treatment</th>
<th>2-week outcome</th>
<th>6-week outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRB/catheter characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRB aetiology</td>
<td>0.0328</td>
<td>0.3078</td>
</tr>
<tr>
<td>Previous catheter days</td>
<td>0.3210</td>
<td>0.1003</td>
</tr>
<tr>
<td>CRB type</td>
<td>0.3749</td>
<td>0.2319</td>
</tr>
<tr>
<td>New catheter (yes/no)</td>
<td>0.9073</td>
<td>0.1543</td>
</tr>
<tr>
<td>Oxacillin sensitivity (yes/no)</td>
<td>0.8996</td>
<td>0.7229</td>
</tr>
<tr>
<td>Tobramycin/gentamicin sensitivity (yes/no)</td>
<td>0.1715</td>
<td>0.8791</td>
</tr>
<tr>
<td>Type of ABL (heparin/TPA)</td>
<td>0.9459</td>
<td>0.6447</td>
</tr>
<tr>
<td>Exit site infection (yes/no)</td>
<td>0.6550</td>
<td>0.4677</td>
</tr>
<tr>
<td>Patients’ biochemical profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum haemoglobin</td>
<td>0.2213</td>
<td>0.2205</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.7947</td>
<td>0.8459</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>0.9766</td>
<td>0.7293</td>
</tr>
<tr>
<td>Serum phosphorous</td>
<td>0.9305</td>
<td><strong>0.0009</strong></td>
</tr>
<tr>
<td>Phosphorous × calcium product</td>
<td>0.7730</td>
<td>0.6818</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>0.1669</td>
<td>0.5937</td>
</tr>
<tr>
<td>Patients’ characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.7835</td>
<td><strong>0.0487</strong></td>
</tr>
<tr>
<td>Immunosuppression (yes/no)</td>
<td>0.2823</td>
<td>0.2317</td>
</tr>
<tr>
<td>HIV infection (yes/no)</td>
<td>0.4969</td>
<td>0.5739</td>
</tr>
<tr>
<td>ABL prophylaxis (yes/no)</td>
<td>0.6573</td>
<td>0.9159</td>
</tr>
</tbody>
</table>

The bold values are the statistically significant P-values.

In this retrospective study, we were able to demonstrate distinct risk factors in the paediatric haemodialysis population for failure to clear CRB with ABL treatment and for early recurrence after CRB was treated with ABLs successfully. CRB aetiology was the only independent variable determining the likelihood of treatment failure, and CNS was more likely to be cleared when compared to any other microorganism. For those CRB that were treated with ABL with success at 2 weeks, the likelihood of early recurrence for CRB was higher for younger patients and for patients with higher serum phosphorous levels at routine monthly laboratory evaluation. CRB

Fig. 1. Kaplan–Meier curve for overall catheter survival of the catheters from children with no documented CRB compared with the catheters from children with at least one CRB. The catheters in the No-CRB group had better overall catheter survival, but this did not reach statistical significance (P = 0.1042 by Wilcoxon test).
aetiology or type (gram positive, gram negative or polymicrobial) did not have any impact at '6-week outcome'. The impact of high serum phosphorous was independent of serum intact PTH levels and phosphorous × calcium product.

In clinical medicine, it is very important to predict the outcome with the initial presentation and, therefore, be able to prevent unwanted results. The outcome of any infection may be affected by the infecting microorganism. CNS is a skin habitant and may be evaluated as a contaminant in temporary catheters. We have reported CNS as the most likely aetiology in our previous reports and persistently treated it in asymptomatic children [2,25]. Since we did not get surveillance blood cultures, we have no data to show the colonization rate of CNS in asymptomatic children. In this study, we show that the best outcome for ABL treatment for CRB can be achieved for CNS infections. Klebsiella species has very similar outcomes. However, other aetiologies are at higher risk to fail ABL treatments and that probably will be the case for Enterobacter/Acinetobacter species in a bigger cohort, even though we were not able to reach statistical significance. This finding is only to provide clinicians with pointers of what to expect as CRB outcome, and is by no means suggesting not to use ABL for CRB other than CNS. Overall, by treating all CRB with ABL, we achieved 80% success rate at 2 weeks and 69% of those catheters were still infection-free at 6 weeks. The decision for catheter exchange should be made with the clinical symptoms at 48–72 h of treatment [25].

Following a successful ABL treatment, younger children were more likely to have recurrence of CRB compared to older ones. This may be related to more frequent dialysis requirements of younger patients, inability of these patients to care for their catheters between treatments or even the unique haemodialysis properties such as higher portion of extracorporeal volume during treatment. Unfortunately, younger patients are less likely to have AV fistulas due to the technical difficulties. Considering them as high risk for CRB recurrence, younger patients may benefit from prophylactic use of ABL while using long-term catheters.

The pathophysiologic explanation for hyperphosphataemia as a risk factor for recurrence of CRB at 6 weeks may be multifactorial. Hyperphosphataemia may just be a surrogate marker of uraemia. End-stage renal failure patients are well documented to have an increased susceptibility to overwhelming infections due to impaired innate and acquired immunity [35]. Uraemia impairs cell-mediated immunity and reduces CD4/CD8 T-cell ratios [36,37]. It can also adversely affect neutrophil and phagocyte functions [38,39]. Moreover, high phosphate levels were demonstrated to induce mitochondrial reperfusion injury by in vivo studies [40]. Alternatively, hyperphosphataemia may be the presenting sign of secondary hyperparathyroidism, and excessive serum PTH levels or the lack of vitamin D may be responsible for decreased immune system activity [41,42]. Interestingly, neither calcium × phosphorous product nor intact PTH levels had any impact on the CRB risk in our study. This may suggest that serum phosphate levels have a direct impact on CRB risk, but this hypothesis needs to be studied by more appropriately designed studies to answer the question [43].

Several studies have looked into the predictors of treatment failure for CRB. Marr et al. wrote the seminal paper on attempted catheter salvage in haemodialysis patients with CRB. They reported only 32% success rate. They noted that hypertension, diabetes mellitus, injection drug use or immunocompromised state were not predictors of failure [7]. Ashby et al. later reported that catheter salvage was successful in 66% of a selected group of low-risk patients [44]. These patients made up 74% of their whole population, which actually brings their salvage rate to 48.8% (74 × 0.66 = 48.8). They suggested that the long duration of systemic antibiotic treatment may improve the catheter salvage rates and catheter salvage may be less successful if the CRB was a recurrence rather than the index CRB. In their multivariate analysis, Mokrzycki et al. demonstrated that attempted catheter salvage and S. aureus CRB were the only predictors of treatment failure [45]. Several other studies have suggested S. aureus as a predictor of failure for CRB treatment, even when ABLs are used [22,46]. Our paper presents the comparative risks for treatment failure for the various CRB aetiologies, and this was never reported before.

There were multiple factors described mainly for CRB risk in the literature and, therefore, these were included in our analysis. Catheter characteristics such as being a new catheter or the duration of previous catheter days had no impact on our two end points. Biochemical profile findings such as serum albumin and haemoglobin levels were again not showing any significant impact on the ABL treatment outcomes. Finally, either iatrogenic immunosuppression or HIV infection had no effect on ABL success. We had a small percentage of congenital HIV infection in our cohort. None of them were diagnosed as AIDS, with low or undetectable viral loads and all of them having CD4 counts above 200 cells per cubic millimetre. The failed kidney transplantation patients with intact allografts were on low-dose oral steroid treatment. Our lupus cases were clinically quiescent, not requiring significant maintenance immunosuppression. We observed only one extrarenal lupus exacerbation during the study period. Overall, neither of these patient groups was immunocompromised enough to significantly increase the risk of failure of CRB treatment.

We utilized elaborate statistical modelling for our risk factor analysis. We examined several possible covariance structures to account for the dependencies in the data within each patient. These included CS, heterogeneous compound symmetry (CSH), AR and heterogeneous AR covariance structures. During our analysis, the AIC and the BIC indicated that the CSH covariance structure was the best fit for our database.

There are several limitations of our study. First of all, it is a retrospective analysis, but the patients were treated according to the unit’s protocol. Secondly, we included multiple catheters and CRBs from the same patients and the intrinsic characteristics of the patients may have overwhelming influence on our final analysis. Most of our CRBs were diagnosed with blood cultures only from the catheters, without peripheral blood cultures confirming the bacteremia. We did not do any surveillance blood cultures and have no data for the colonization of the catheters. The big majority of the locks were TPA-based ABL and,
therefore, the influence of the TPA locks compared to heparin-based ABLs in eradicating the intraluminal biofilm cannot be excluded. The information on the use and the dosing of vitamin D preparations might have provided some light on the relationship of high phosphorous levels and recurrence of CRB, but we lacked that information during the writing of this paper.

**Conclusion**

In conclusion, this study suggests that there are unique risk factors for failure of CRB treatment by ABLs in the paediatric haemodialysis population. Regardless of any baseline characteristics, the majority of CRBs can be treated with ABLs and systemic antibiotics without the need to exchange the catheters. CNS is the most likely CRB aetiology to be cleared after 2 weeks of treatment. *Stenotrophomonas/Pseudomonas* species and *Enterococcus* species have the highest odds ratio for failure with ABL treatment. Following the early successful treatment of CRB, younger patient age and higher serum phosphorous levels are independent risk factors for early recurrence of CRB. Neither serum PTH levels nor phosphorous × calcium product was statistically significant in predicting early CRB recurrence. None of the other potential predictors of outcome including CRB/catheter characteristics, biochemical profiles of the patients during monthly labs or patient characteristics were able to reach statistical significance for either ‘2-week outcome’ or ‘6-week outcome’. More aggressive serum phosphorous management in haemodialysis patients may decrease CRB incidence. Both of the above findings and suggestions need to be tested in large prospective cohorts to be able to make recommendations/changes in daily haemodialysis practice.

**Conflict of interest statement.** None declared.

**References**

Background. The protein-bound uraemic toxin \( p \)-cresol is associated with immunodeficiency in haemodialysis (HD) patients. We investigated the effect of serum \( p \)-cresol, indoxyl sulphate and other variables on clinical outcomes in HD patients during a 20-month follow-up.

Methods. We enrolled 100 stable HD patients from a single medical centre. The primary outcomes were infection-related hospitalization, cardiovascular events and all-cause mortality. Serum total and free \( p \)-cresol and indoxyl sulphate levels were measured using ultra-performance liquid chromatography. Biochemical data were collected concurrently.

Results. Multivariate logistic regression analysis revealed that infection-related hospitalization correlated with free \( p \)-cresol (adjusted odds ratio: 1.70, \( P = 0.01 \)) and highly sensitive C-reactive protein (hsCRP) (adjusted odds ratio: 2.07, \( P = 0.01 \)); cardiovascular event was associated with free \( p \)-cresol (adjusted odds ratio: 1.78, \( P = 0.01 \)) and nPCR (adjusted odds ratio: 0.01, \( P = 0.02 \)); and all-cause mortality was related to albumin (adjusted odds ratio: 0.04, \( P = 0.01 \)). The Kaplan–Meier method showed that free and total \( p \)-cresol were significantly associated with cardiovascular events (log-rank \( P < 0.01 \) and log-rank \( P < 0.01 \), respectively). Serum free \( p \)-cresol seemed to have a trend to

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Serum protein-bound uraemic toxins and clinical outcomes in haemodialysis patients

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Abstract

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