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Peripherally inserted central catheters are associated with lower risk of bloodstream infection compared with central venous catheters in paediatric intensive care patients: a propensity-adjusted analysis

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Abstract

Purpose: Central line-associated bloodstream infection (CLABSI) is an important cause of complications in paediatric intensive care units (PICUs). Peripherally inserted central catheters (PICCs) could be an alternative to central venous catheters (CVCs) and the effect of PICCs compared with CVCs on CLABSI prevention is unknown in PICUs. Therefore, we aimed to evaluate whether PICCs were associated with a protective effect for CLABSI when compared to CVCs in critically ill children.

Methods: We have carried out a retrospective multicentre study in four PICUs in São Paulo, Brazil. We included patients aged 0–14 years, who needed a CVC or PICC during a PICU stay from January 2013 to December 2015. Our primary endpoint was CLABSI up to 30 days after catheter placement. We defined CLABSI based on the Center for Disease Control and Prevention's National Healthcare Safety Networks (NHSN) 2015 surveillance definitions. To account for potential confounders, we used propensity scores with inverse probability weighting.

Results: A total of 1660 devices (922 PICCs and 738 CVCs) in 1255 children were included. The overall CLABSI incidence was 2.28 (95% CI 1.70–3.07)/1000 catheter-days. After covariate adjustment using propensity scores, CVCs were associated with higher risk of CLABSI (adjHR 2.20, 95% CI 1.05–4.61; $p = 0.037$) compared with PICCs. In a sensitivity analysis, CVCs remained associated with higher risk of CLABSI (adjHR 2.18, 95% CI 1.02–4.64; $p = 0.044$) after adding place of insertion and use of parenteral nutrition to the model as a time-dependent variable.

Conclusions: PICC should be an alternative to CVC in the paediatric intensive care setting for CLABSI prevention.

Keywords: Peripherally inserted central catheter, Central venous line, Infection, Paediatric intensive care unit

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Take-home message: PICCs could be used as an alternative to CVCs in Paediatric ICUs. We observed that in four PICUs from Brazil, PICCs were commonly used instead of CVCs. We showed for the first time in a multicentre study that PICCs were associated with a protective effect in CLABSI prevention in paediatric critical care setting.

Introduction

Central line-associated bloodstream infection (CLABSI) is an important cause of complications in paediatric intensive care units (PICUs). Even though the rate of CLABSI has decreased in developed countries, mainly due to the large-scale implementation of bundles for its prevention [1, 2], it is still a common problem, especially in the most severely ill population. The burden is even worse in undeveloped and developing countries, and becomes more relevant if we consider that CLABSI increases length of stay (LOS), antibiotic use, hospital costs and morbidity [3, 4].

The use of peripherally inserted central catheters (PICCs), inside and outside the PICU, is increasing worldwide, probably due to the low risk of mechanical complications during placement [5]. It has also been suggested that PICC use is associated with a reduction in the incidence of CLABSI. PICCs have had the advantage over central venous catheters (CVCs) in reducing CLABSI in specific paediatric populations, such as outpatients who need total parenteral nutrition (TPN) or chemotherapy [6]. However, no advantage regarding the prevention of CLABSI has been observed in hospitalised and critically ill adult patients [7, 8]. There is a lack of studies regarding the role of PICCs in reducing the risk of CLABSI compared to CVCs in paediatric critical care settings. The objective of our study was to evaluate whether PICCs were associated with a protective effect for CLABSI when compared to CVCs in children admitted to four PICUs in Brazil.

Methods

Patients and devices

We performed a retrospective multicentre study in four PICUs (total 56 beds) at four non-teaching private hospitals in São Paulo, Brazil. The four PICUs were embedded in a network, had a closed model of organisation and staff, and were under central administration. All PICUs received clinical (including oncological, neurological and cardiological patients) and surgical patients, aged 0–14 years. We included patients admitted to any of the 4 PICUs who received a CVC or PICC during their PICU stay from January 2013 to December 2015. We excluded patients under the age of 30 days at the time of catheter insertion, catheters removed on the same day as placement, long-term use catheters and those whose catheters were inserted by dissection, because these catheters have specific characteristics and risk factors associated with CLABSI. There were no haemodialysis catheters as we only have peritoneal dialysis in our units.

The data were extracted from the Epimed Monitor System[®] and electronic medical records. The Epimed Monitor System[®] (Epimed Solution[®], Rio de Janeiro,

Brazil), is a commercial cloud-based registry for quality improvement, performance evaluation, and benchmarking purposes. Data were entered in the Epimed Monitor System by registered nurses trained in case-management of critically ill patients [9, 10]. We retrieved data for age, gender, weight, main reason for admission, type of admission (i.e. medical/surgical), underlying diseases, PIM and PRISM scores, and organ support during PICU stay. We also extracted details of the site of catheter insertion, placement and removal dates and daily use of parenteral nutrition during the entire PICU stay.

Our exposure was defined as the type of catheter: PICC and CVC. The use of PICC or CVC was at the discretion of the attending physician. Our units have standard operating procedures (SOPs) for device placements, and the PICC and CVC placement technique was standardised across the 4 units and audited by a trained nurse with a checklist. CVCs were placed either by a paediatric intensive care physician or a paediatric surgeon, and PICCs were placed by a specially trained nurse. Both CVC and PICC were placed using maximal sterile barrier precautions and alcoholic chlorhexidine for skin asepsis. All PICUs have infection control policies based on Institute of Healthcare Improvement bundles for CLABSI. This bundle has five main pillars: hand hygiene; maximal barrier precautions; chlorhexidine skin asepsis; optimal catheter site selection; and daily review of line necessity [11]. The staff had continuing training on aseptic precautions during device placement and maintenance. All catheter dressings were audited daily by a trained nurse, and devices were evaluated daily in a multidisciplinary round and removed as soon as possible. All four hospitals have a centrally coordinated hospital infection committee; healthcare-associated infection rates are analysed monthly by the committee and every positive case is discussed, promoting educational feedback and identifying improvement action [10].

Our primary endpoint was CLABSI up to 30 days after catheter placement. We defined CLABSI based on the Center for Disease Control and Prevention's National Healthcare Safety Networks (NHSN) 2015 surveillance definitions [12]. We measured the primary endpoint as the CLABSI rate, defined as the number of CLABSI occurrences divided by the total days of catheter use, multiplied by 1000. The Hospital Infection Surveillance Committee from each hospital prospectively tracked all blood cultures (Vitek[®] XL and Vitek[®] MS; bioMérieux, France) collected in the respective hospital. For patients with positive blood cultures, CLABSI was defined if the criteria from the NHSN 2015 definition were fulfilled [12]. CLABSI cases were prospectively entered in the hospital-acquired infections module of the Epimed

Table 1 Demographic and clinical characteristics of the 1255 children admitted to the PICUs

	CVC (n = 540)	PICC (n = 715)	p value
Age, months			0.28
Mean (SD)	39.0 (46)	45.6 (49)	
Median (IQR)	16.1 (7.2–57.3)	23.5 (5.5–73.9)	
Age categories			0.063
01–12 months	221 (40.9%)	260 (36.4%)	
12–36 months	135 (25.0%)	153 (21.4%)	
36–72 months	72 (13.3%)	117 (16.4%)	
72–120 months	65 (12.0%)	102 (14.3%)	
>120 months	47 (8.7%)	83 (11.6%)	
Sex (male)	271 (50.6%)	385 (54.1%)	0.219
Weight (kg)			0.33
Mean (SD)	14.7 (13)	15.8 (14)	
Median (IQR)	9.7 (6.4–20.0)	11.7 (5.9–21.0)	
Baseline disease			
Oncologic	47 (8.7%)	58 (8.1%)	0.71
Immunosuppression	14 (2.6%)	27 (3.8%)	0.243
Cardiomyopathy or myocarditis	52 (9.6%)	32 (4.5%)	<0.001
Bronchiolitis and/or asthma	75 (13.9%)	149 (20.8%)	0.001
Chronic neurological diseases	11 (2.00%)	3 (0.4%)	0.007
Severity at admission			
PRISM (points)			<0.001
Mean (SD)	9.7 (7)	8.1 (6)	
Median (IQR)	9 (5–13)	7 (4–11)	
PRISM, probability death			<0.001
Mean (SD)	7.4 (14)	4.6 (9)	
Median (IQR)	2.6 (1.2–6.9)	2.2 (1.0–4.1)	
PIM2, probability death			<0.001
Mean (SD)	8.4 (15)	4.3 (9)	
Median (IQR)	2.6 (1.0–7.6)	1.4 (0.9–4.1)	
Readmission	58 (10.7%)	85 (11.9%)	0.53
Type of admission			
Medical	309 (57.3%)	580 (81.2%)	<0.001
Main reason of admission			<0.001
Infection	123 (22.8%)	234 (32.7%)	
Respiratory	129 (23.9%)	222 (31.1%)	
Neurologic	85 (15.7%)	78 (10.9%)	
Cardiovascular	101 (18.7%)	30 (4.2%)	
Gastro-intestinal	49 (9.1%)	69 (9.7%)	
Onco-haematological	16 (3.0%)	24 (3.4%)	
Other	37 (6.9%)	58 (8.1%)	
First day of ICU			
Cardiac arrest before ICU admission or d1	35 (6.5%)	23 (3.2%)	0.006
Invasive mechanical ventilation	276 (51.1%)	218 (30.5%)	<0.001
Vasoactive drugs	139 (25.7%)	70 (9.8%)	<0.001
Upon central line placement			
Parenteral nutrition	11 (2.0%)	20 (2.8%)	0.39

Table 1 continued

	CVC (n = 540)	PICC (n = 715)	p value
Invasive mechanical ventilation	321 (59.4%)	235 (32.9%)	<0.001
During ICU stay			
Parenteral nutrition	46 (8.5%)	56 (7.8%)	0.66
Invasive mechanical ventilation	367 (68.0%)	348 (48.7%)	<0.001
Vasoactive drugs	203 (37.7%)	150 (21.0%)	<0.001
Renal support	15 (2.8%)	11 (1.5%)	0.127
Blood products	210 (38.9%)	200 (28.0%)	<0.001
Cardiorespiratory resuscitation	48 (8.9%)	35 (4.9%)	0.005
Tracheostomy	33 (6.1%)	31 (4.3%)	0.156

Only the first central line device were used for the population characterisation

Monitor System[®]. For this study, we revised the electronic medical records of all previously defined CLABSI cases to check if all NHSN criteria were fulfilled. The reviewing process was blinded as to whether the patients had received a PICC or CVC.

Statistical analysis

Continuous data are presented as means (standard deviation) or as medians and interquartile range (IQR), as appropriate. Categorical variables are shown as percentages. For comparison of categorical variables, Fisher's exact test or a Chi square test were used; for continuous variables, an unpaired *t* test or the Mann–Whitney *U* test was used, as appropriate.

As the choice between PICC and CVC was not randomised, we used a propensity score strategy to correct for potential confounding factors, indication, and unbalanced variables upon device insertion [13–15]. We used the covariate-balancing propensity score (CBPS) method, which concurrently maximises the covariate balance and the treatment assignment prediction. CBPS is a new and robust method which outperformed other propensity score methods in simulations and empirical data [16, 17]. We defined a priori the variables listed in Table 1 to include in the CBPS model, allowing for a non-parsimonious model and aiming for an optimal covariate balance, as recommended by the propensity score literature [13, 18]. To avoid selection- and immortal-time bias, we included only variables from ICU admission up to the day of device insertion. The dependent variable for the CBPS model was every catheter used for a patient, and we accounted for clustering at the unit and patient levels [15, 19]. To evaluate the association between our exposure (device type) and the occurrence of CLABSI, we fitted Cox proportional hazards regression models. First, we ran a model only with the exposure. Second, we

applied the optimal weights from the CBPS and fitted the Cox model in the weighted population [15, 20]. Additionally, we fitted the same Cox model in the weighted population, adjusting for place of insertion and total parenteral nutrition as a time-dependent variable. In a sensitivity analysis, we re-estimated the propensity score model and fitted the previously Cox models after exclusion of patients with bronchiolitis/asthma as baseline comorbidities, because of the potential different reasons for central venous line indication in these patients. The assumption of proportionality was verified with an interaction term in the model and graphically by a log–log plot. The models accounted for multiple catheters per patient using a robust variance estimator [15, 21]. To evaluate the covariate balance, we assessed the absolute standardised difference before and after weighting.

Statistical analysis was performed using Stata 13.1 (StataCorp, Texas) and R statistical software (R Foundation for Statistical Computing, Vienna), packages *cbps* and *cobalt*.

The study was reviewed and approved by the Ethics Committee of every hospital and informed consent was waived.

Results

Patients

From January 2013 to December 2015, we identified 1786 catheters placed in 1316 children. We excluded 23 long-term use catheters, 56 catheters inserted by dissection and 47 catheters removed on the same day as placement, resulting in a total of 1660 catheters implanted in 1255 children (eFig. 1).

The demographic and clinical characteristics of the population are described in Table 1. There were similar distributions of demographic variables in the CVC and PICC groups but there was a shift for using PICCs in older children ($p = 0.063$). We observed higher prevalence of cardiologic (CVC 9.6% \times PICC 4.5%, $p < 0.001$) and chronic neurological diseases (CVC 2.0% \times PICC 0.4%, $p = 0.007$) in the CVC group but lower prevalence of acute respiratory diseases (bronchiolitis and asthma) (CVC 13.9% \times PICC 20.8%, $p = 0.001$). We also observed more frequent use of CVCs in more severe patients, measured by the prognostic scores (PRISM and PIM), use of mechanical ventilation and vasoactive drugs, and history of cardiac arrest, both in admission and during PICU stay. The main reasons for PICU admission were similar in both groups, with infection and respiratory diseases being the most common. The crude ICU mortality was higher in the CVC group (CVC 9.4% \times PICC 6.3%; $p = 0.038$); however no difference was observed for crude in-hospital mortality (CVC 9.8% \times PICC 7.2%; $p = 0.089$). Median ICU LOS [CVC 10 (4–20) \times PICC 9

(5–17) days; $p = 0.83$] and median hospital LOS [CVC 18 (9–39) \times PICC 19 (10–37) days; $p = 0.37$] were similar in both the CVC and PICC groups.

Catheter characteristics

A total of 1660 devices were included in the study, 738 (44.5%) CVCs and 922 (55.5%) PICCs. The distribution of number of catheters per patient during the ICU stay was as follows: 977 (77.8%) children had only 1 central line catheter, 198 (15.8%) had 2, 51 (4.0%) had 3, 17 (1.4%) had 4, 7 (0.6%) had 5, 4 (0.3%) had 6 and 1 (0.1%) had 7. The catheter characteristics are shown in Table 2. Overall, the median time from ICU admission to catheter insertion was comparable between devices. PICCs and CVCs were mainly implanted in supra-diaphragmatic sites (PICC ~97% \times CVC ~80%), with superior limbs and jugular accesses as the preferred sites of insertion for PICCs and CVCs, respectively. The median catheter duration was comparable between devices.

CLABSI incidence

We observed 44 CLABSIs in 1660 catheters (2.6%), and higher incidence in the CVC group (CVC 4.2% \times PICC 1.4%; $p < 0.001$). There was no difference in median time between catheter placement and infectious event [CVC 9 (6–16) \times PICC 10 (6–15) days; $p = 0.95$]. The pathogens

Table 2 Comparison of CVC and PICC characteristics accordingly to time and place of insertion, duration, infection and time to infection

	All catheters		
	CVC (n = 738)	PICC (n = 922)	p value
Time to insertion from ICU admission			0.001
Mean (SD)	6.6 (19)	5.9 (17)	
Median (IQR)	1 (0–4)	1 (0–4)	
Place of insertion (original)			
Jugular	413 (56.0%)	–	
Sub-clavian	152 (20.6%)	–	
Femoral	173 (23.4%)	–	
Cervico-cephalic	–	349 (37.9%)	
Superior limbs	–	546 (59.2%)	
Inferior limbs	–	27 (2.9%)	
Place of insertion (categorised)			<0.001
Supra-diaphragm	565 (76.6%)	895 (97.1%)	
Infra-diaphragm	173 (23.4%)	27 (2.9%)	
Total catheter duration			0.82
Mean (SD)	12.3 (10)	13.6 (14)	
Median (IQR)	10 (5–17)	10 (5–16)	

CVC central venous line, PICC peripherally inserted central catheter, CLABSI central line-associated bloodstream infection

isolated in all infectious events are presented in eTable 1. More than half of the CLABSIs (56.8%) were caused by Gram-negative bacteria, with *Klebsiella pneumoniae* as the main agent. The second most isolated agent was fungus (27.3%), especially *Candida parapsilosis*, followed by Gram-positive bacteria (15.9%).

The overall rate of CLABSI was 2.28 (95% CI 1.70–3.07) per 1000 catheter-days (44 events in 19,278 catheter-days). The rate for CVCs was 3.72 (95% CI 2.61–5.29) compared with 1.19 (95% CI 0.69–2.05) per 1000 catheter-days for PICCs. The unadjusted analysis showed a higher risk of CLABSI in the CVC group compared with PICC (HR 3.13, 95% CI 1.64–5.98; $p < 0.001$) (Table 3). The distributions of the propensity scores and the standardised differences before and after weighting are shown in eFigs. 2 and 3. After weighting, we observed an important reduction on the standardised differences for all covariates, remaining below 0.10 as recommended (eFig. 4). The positive association between CVC and CLABSI remained significant in the weighted population

(adjHR 2.20, 95% CI 1.05–4.61; $p = 0.037$; Fig. 1; eFig. 5). This association was also observed after adding place of insertion and use of parenteral nutrition into the model (Table 3).

In the sensitivity analysis, we analysed 1389 catheters from 1031 children. The positive association between CVC and CLABSI remained significant (adjHR 2.25, 95% CI 1.01–5.03; $p = 0.047$; eTable 2, propensity score and model diagnosis: eFigs. 6, 7, 8 and 9), after adjusting for the inverse probability of treatment weighting (IPTW), place of insertion and use of parenteral nutrition.

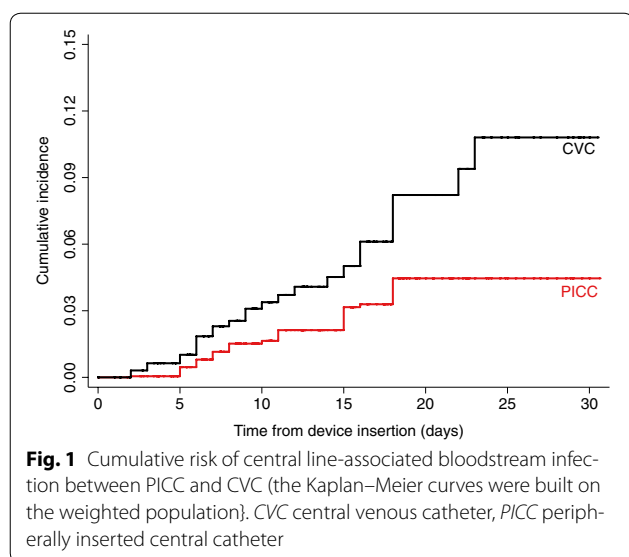
Discussion

This is the first multicentre study to compare the incidence of CLABSI in PICCs and CVCs in the paediatric critical care setting. We observed that PICCs have been used for a large proportion of critically ill children (around 56%) in our study, and that the use of CVCs, compared to PICCs, increased the risk for CLABSI after adjusting for several potential confounding factors.

Table 3 Crude and adjusted association between type of catheter and CLABSI within the first 30 days

All devices	HR (95% CI)	p value
Crude		
Device type		
PICC	Reference	
CVC	3.13 (1.64–5.98)	0.001
	Adjusted HR (95% CI)	p value
Adjusted for propensity score (IPTW)		
Device type		
PICC	Reference	
CVC	2.20 (1.05–4.61)	0.037
Adjusted for propensity score (IPTW) + place of insertion		
Device type		
PICC	Reference	
CVC	2.24 (1.04–4.80)	0.039
Place of insertion		
Supra-diaphragmatic	Reference	
Infra-diaphragmatic	0.93 (0.42–2.03)	0.85
Adjusted for propensity score (IPTW) + place of insertion + parenteral nutrition as time-dependent variable		
Device type		
PICC	Reference	
CVC	2.18 (1.02–4.64)	0.044
Place of insertion		
Supra-diaphragmatic	Reference	
Infra-diaphragmatic	0.84 (0.39–1.83)	0.66
Parenteral nutrition (time-dependent)		
No	Reference	
Yes	3.76 (1.44–9.84)	0.007

CI confidence interval, CVC central venous line, HR hazard ratio, IPTW inverse probability of treatment weighting, PICC peripherally inserted central catheter, CLABSI central line-associated bloodstream infection



We observed an overall incidence of 2.28 CLABSIs per 1000 catheter-days, similar to incidences currently reported in PICUs in high-income countries (from 0.3 to 5.2 infections per 1000 catheter-days) [1, 22–25]. In contrast, middle- and low-income countries reported higher incidences, ranging from 1.6 to 44.6 events per 1000 catheter-days [26–28]; in Brazil, specifically, the incidence reported in PICUs was 8.46 [26]. In recent decades, there have been efforts to improve practice in ICUs regarding the prevention of CLABSI, but it remains one of the most important infectious complications during hospital, and especially ICU, stay [29–32]. Importantly, the reduction in CLABSI incidence associated with these measures seems to have reached a plateau, so additional actions are needed to further reduce the rate of CLABSI [25, 33].

Two systematic reviews and meta-analyses in adult patients showed controversial results regarding the role of PICCs in CLABSI prevention. Maki et al. found a slightly lower risk of CLABSI in PICCs when compared to CVCs [6], while Chopra et al. observed this protective effect only in outpatients [8]. In the paediatric population, three studies showed a protective [34] or no effect [35, 36] of PICC on the incidence of CLABSI in non-intensive care patients. Our study contributes in a singular way to the literature showing that, in a large sample of critically ill children, PICC use was associated with lower risk of CLABSI after adjusting for several potential confounders in a setting with a low incidence of CLABSI. Some possible reasons for this result can be highlighted. First, the choice of catheter insertion site is usually inherited in the choice between a PICC or a CVC. Because one of the pathogenesis pathways of CLABSI is the extra luminal migration of bacteria from

the skin [37], the longer length of the PICC, and the lower density of bacteria in extremities [7], it is expected that PICCs may lead to a lower incidence of CLABSI. Second, the number of lumens, a risk factor for CLABSI [38, 39], is also intrinsic to the catheter type, because in a paediatric population CVCs are usually double-lumen and PICCs single-lumen [5]. Finally, gauge is another physical characteristic that could contribute to our results. In younger children, PICCs have a reduced gauge, which leads to less manipulation of the device because it is virtually impossible to take blood samples and transfuse blood products due to the increased resistance.

Our data have strengths that should be mentioned. The use of PICCs has been increasing recently, thus it is worth noting that more than half the children in our study received only a PICC, placed soon after PICU admission. Therefore, our multicentre study with a large sample can provide information with a potential clinical application in the paediatric population. Second, we used a robust method to adjust for confounders, such as the covariate-balancing propensity score, also accounting for the number of devices used. Additionally, we adjusted for the use of parenteral nutrition through each device on a daily basis, one of the most important risk factors for CLABSI [40].

However, our study has limitations. First, this is a retrospective observational study and the device choice was not randomised. Thus, although we use a robust method to adjust for confounding, there is still the risk of residual confounding. Second, we had no individual data regarding the compliance to the CLABSI prevention bundle. However, the four units were centrally coordinated and received similar training, material supply and routinely audit and feedback about the unit compliance to the prevention measures. Thereby, it would be unexpected that PICC and CVC were unequally exposed to the recommended prevention measures. Third, we retrieved data about blood transfusion for all patients, but were not able to identify if the transfusion occurred after device insertion, thus, to avoid bias, we did not use this variable in our analysis. Fourth, we could not retrieve information about the number of lumens of all catheters placed, a risk factor already described in the literature [38, 39]. Fifth, we did not study the incidence of thrombosis, an important complication commonly associated with PICCs, nor other mechanical complications associated with the use of central lines devices and did not apply a cost-effectiveness analysis. Finally, we included PICUs with low incidence of CLABSI and located in private/non-teaching centrally coordinated hospitals in Brazil. Because local practices and resources availability could be different in other PICUs, other studies should be conducted to assess the generalisability our findings.

Conclusion

CLABSI is an important infectious complication in PICU patients. The role of PICC use in the prevention of CLABSI is unknown in paediatric critical care patients. Our study confirms the hypothesis that PICCs have a protective role in CLABSI prevention when compared to CVCs, in PICUs with low incidence of CLABSI, and their use should be considered instead of CVCs, whenever possible, in the paediatric intensive care setting.

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest.

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