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Infectious complications of percutaneous central venous catheterization in pediatric patients

A Spanish multicenter study

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Abstract *Objective:* Analysis of infectious complications and risk factors in percutaneous central venous catheters. *Design:* One-year observational, prospective, multicenter study (1998–1999). *Setting:* Twenty Spanish pediatric intensive care units. *Patients:* Eight hundred thirty-two children aged 0–14 years. *Intervention:* None. *Measurements and main results:* One thousand ninety-two catheters were analyzed. Seventy-four (6.81%) catheter-related bloodstream infections (CRBSI) were found. The CRBSI rate was 6.4 per 1,000 CVC days (95% CI 5.0–8.0). Risk factors for CRBSI were weight under 8 kg ($p < 0.001$), cardiac failure (RR 2.69; 95% CI 1.95–4.38; $p < 0.001$), cancer (RR 1.66; 95% CI 0.97–2.78; $p = 0.05$), silicone catheters (RR 2.82; 95% CI 1.49–5.35; $p = 0.006$), guidewire exchange catheterization ($p = 0.002$), obstructed catheters (RR 2.67; 95% CI 1.63–4.39; $p < 0.001$), and more than 12 days' indwelling time (RR

5.9; 95% CI 3.63–9.41; $p < 0.001$). Multivariate Cox regression identified lower patient weight (HR 2.4; 95% CI 1.11–5.19; $p = 0.002$), guidewire exchange catheterization (HR 2.2; 95% CI 1.07–4.54; $p = 0.049$) and more than 12 days' indwelling time (HR 1.97; 95% CI 0.89–4.36; $p = 0.089$) as significant independent predictors of CRBSI. Factors which protected against infection were the use of povidone-iodine on hubs (HR 0.42; 95% CI 0.19–0.96; $p = 0.025$) and porous versus impermeable dressing (HR 0.41; 95% CI 0.23–0.74; $p = 0.004$). Two children (0.24%) died from endocarditis following catheter-related sepsis due to *Stenotrophomonas maltophilia* in one case and *P. aeruginosa* in the other. *Conclusions:* Catheter-related sepsis is associated with lower patient weight and more than 12 days' indwelling time, but not with the insertion site. Cleaning hubs with povidone-iodine protects from infection.

Keywords Catheter-related infection · Children · Multicenter study · Multivariate

Introduction

Central venous catheters (CVC) are widely used in pediatric intensive care units (PICUs). Although their insertion is relatively simple, they are not risk-free, and associated complications, especially infection, increase morbidity, mortality, hospital stay and healthcare costs [1, 2, 3]. The most frequent cause of nosocomial infection in American PICUs is sepsis, which, in 90% of cases, is related to intravascular devices [4]. A recent bibliographical review [5] and several published studies [6, 7, 8, 9, 10, 11, 12, 13, 14] analyze the complications of CVC in pediatric patients. The objective of our study was to analyze the infectious complications of percutaneous insertion of CVC, and the risk factors associated with infection. Our investigation, the only pediatric, multicenter, observational study covering a large number of patients, may help solve problems associated with CVC.

Methods

Ours was a one-year multicenter, prospective and observational study carried out in Spanish PICUs from April 1998 to March 1999. All PICUs in Spain were invited to participate. The study was approved by the ethics committee of each center and included patients aged 0–14 years.

CVC were inserted with the informed consent of child and/or tutors. Catheterization was performed in the PICU by a ward physician, fellow-in-training or both, using the Seldinger technique [15], under aseptic conditions (except in emergency situations). Heparin-bonded, antibiotic-impregnated, tunneled and umbilical catheters were excluded. The insertion site varied depending on the reason for catheterization, availability of vascular access, and physician preference. It was agreed that catheter care would be carried out according to the individual protocol of each PICU.

When catheter-related infection was suspected, the recommendation was to obtain both CVC and peripheral blood samples for culture; however, there was no standard procedure for location or number. Blood was cultured by qualitative technique using the Bactec pediatric system and germ-specific culture media. There were no standard recommendations on blood sample volume; this depended on culture media (aerobes 1–3 ml, anaerobes and fungi 3 ml, according to the manufacturer's recommendations) and patient weight.

When catheter was removed, the recommendation was to culture, if possible; the decision about when to remove an infected catheter was left to the clinician's judgment. Two culture techniques were used, depending on the hospital; if available, Maki's semiquantitative method [16] was used. Once the catheter was removed, the last 5 cm of it was rolled on a blood–agar plate and the number of colony-forming units (CFU) was counted after 48 h incubation. If

that was not available, qualitative culture of the catheter segment was made by placing it in enrichment broth (thioglycolate) for 24–48 h before resowing it in blood–agar.

The data collection sheet was prepared and approved by a team of physicians composed of representatives of each PICU. All case-report forms were reviewed by the coordinating center. The following data were collected:

1. Patient data (age, weight, sex, underlying condition); indication for catheterization; reason for withdrawal; catheter (size, lumen, brand, material); person who inserted catheter; number of attempts, defined as number of punctures per line inserted; route of access; circumstances [emergency, scheduled, recatheterization (guidewire exchange), mechanical ventilation, sedoanalgesia]; complications during insertion; obstruction (partial: solution could be infused but no blood aspirated; total: impossible infusion and aspiration); presence of central venous thrombosis (CVT), diagnosed by clinical signs, contrast venography and/or ultrasound, whereby routine ultrasound evaluation was not performed. There were no standard recommendations for obstructed catheters.

2. Infectious complications arising from catheter maintenance:

- a) Catheter care [use and type of stopcock and hub protection, number of three-way stopcocks, dressing (porous, impermeable), frequency of dressing change]; location of culture (tip, hub, skin, blood); type of microorganism cultured; culture technique; date of infection; therapy administered; outcome.

- b) Type of infection, classified according to the guidelines of consensus of experts recently published [17], listed in Table 1.

3. Death of patient due to a catheter complication was recorded.

Statistical analysis

Qualitative variables are presented with their frequency distribution. Quantitative variables are summarized as the mean and standard deviation (SD) and/or median and interquartile range (IQR; P25–P75).

Association between qualitative variables was evaluated using the χ^2 test, or Fisher's exact test if 25% or more cells had an expected count less than 5. Behavior of quantitative variables was analyzed by each of the response variables using the Student *t*-test.

Cox regression models were adjusted to identify and evaluate the relationship between the set of explicative variables and occurrence of an event. Models included independent variables whose significance (*p*) in the univariate analysis was below 0.10. Event-free survival was estimated using a Kaplan–Meier analysis.

Existence of interactions was evaluated by entering the multiplicative independent variables with statistical significance tests, and the model maintained the statistically

Table 1 Clinical definitions for intravascular catheter infections

I. Catheter colonization

Significant growth of a microorganism by semiquantitative (≥ 15 cfu) or quantitative (≥ 1000 cfu) culture of the catheter tip.

II. Exit site infection

Erythema or induration within 2 cm of the catheter exit site, in the absence of concomitant BSI and without concomitant purulence.

III. Systemic infection

A. Definite catheter-related BSI

One of the following should be present in addition to at least one peripheral positive blood culture:

1. A positive semiquantitative (≥ 15 cfu) or quantitative (≥ 1000 cfu) catheter tip culture, whereby the same microorganism (species and antibiogram) is isolated from the catheter tip and peripheral blood.
2. Simultaneous quantitative blood cultures with a $> 5:1$ ratio CVC vs peripheral.
3. Differential time to positivity of > 2 h between peripheral and CVC blood culture positivity.
4. Pus from the catheter exit site, growing the same microorganism as peripheral blood.

B. Probable catheter-related BSI

Either 1 or 2 should be met:

1. Clinical catheter-related sepsis: Positive (semi-)quantitative catheter tip in a patient with clinical sepsis and no other apparent source than the catheter that resolves within 48 h of catheter removal in the absence of new antibiotic therapy.
2. Bacteriemia/fungemia: At least two positive blood cultures (including one peripheral) with a common skin commensal (e.g., diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci or micrococci) in a patient with an intravascular catheter and clinical manifestations of infection (i.e., fever, chills, and/or hypotension; in children aged under 1 year: fever, hypothermia, apnea, bradycardia, lethargy), in the absence of catheter segment culture and no apparent source for the BSI except the catheter.

C. Possible catheter-related BSI

Either 1 or 2 should be met:

1. Clinical catheter-related sepsis: Positive (semi-) quantitative catheter tip in a patient with clinical sepsis and no other apparent source than the catheter that resolves after catheter removal and initiation of antibiotic therapy.
2. Bacteriemia/fungemia: At least one positive blood culture, either through the catheter or peripheral, with a common skin commensal (e.g., diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci or micrococci) in a patient with an intravascular catheter and clinical manifestations of infection (i.e., fever, chills, and/or hypotension), in the absence of catheter segment culture and no apparent source for the BSI except the catheter.

Contamination of the catheter was considered to be present when there was no significant growth of a microorganism by semiquantitative (< 15 cfu) or quantitative (< 1000 cfu) culture of the catheter tip.

cfu, colony-forming units; BSI, bloodstream infection; CVC, central venous catheter.

Adapted from reference [17]

significant terms of interaction. Adjusted relative risks (adjRR) are presented together with their 95% confidence intervals (CI). In all cases, distribution of variable was checked against the theoretical models and the variance homogeneity hypothesis was contrasted. In all hypothesis contrasts, null hypothesis was rejected with a type 1 error or α error below 0.05.

Data were processed using the SPSS database, version 12.

Results

During the study period, we collected 1092 catheters consecutively inserted in 835 pediatric patients whose ages ranged from 0 to 14 years (mean 3.85 ± 3.95 , median 2, IQR 0.74–6 years); 27 children (3.2%) were less than 1 month old. There were 459 boys (55%) and 376 girls

(45%). Patient weight ranged from 1 to 80 kg (mean 17.09 ± 13.51 , median 12.5, IQR 7.5–22.5 kg).

Twenty PICUs from throughout Spain participated in the study.

Underlying diseases and indications leading to line insertion are shown in Table 2.

A total of 1041 catheters were made of polyurethane (95%) and 51 (5%) of silicone. The most common route of access was the femoral vein (54%) (Fig. 1). Insertion was carried out by a ward physician (49%), fellow-in-training (41%) or both (10%). Catheterization was scheduled in most cases (53%), an emergency procedure in 39.5% and guidewire exchanged in 6.2%. During the procedure, 531 patients (48.6%) were receiving mechanical ventilation. Systemic sedoanalgesia (85.7% of cases), local sedoanalgesia (17.3%) or both (91.5%) were used. There were 10 episodes of central venous thrombosis (1%) and 117 catheters were obstructed (10.7%), 82 partially and 35 totally.

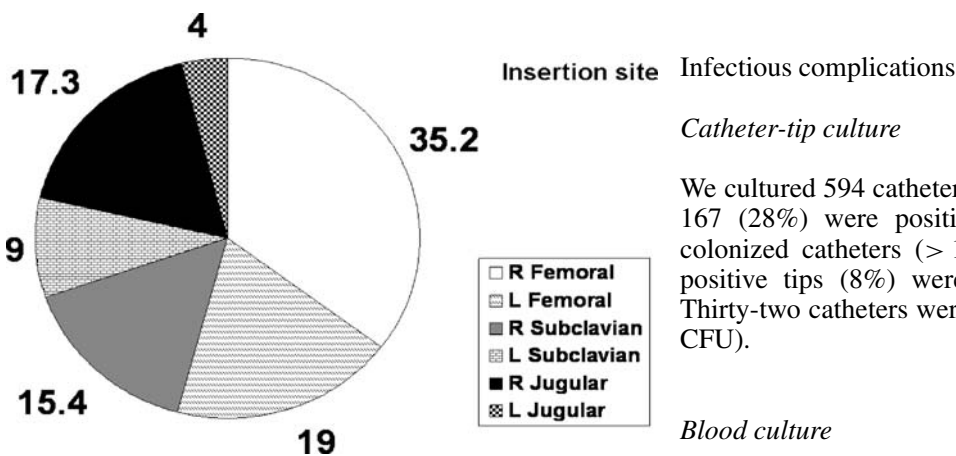
Table 2 Underlying diseases and indications for insertion of a central venous catheter

Underlying disease ^a	No.	%	Indication for a central line ^a	No.	%*
Sepsis	191	22.8	Hemodynamic monitoring	614	56.2
Post-surgical status	150	18	Medication	303	27.7
Neurologic	141	13	Parenteral feeding	282	25.8
Respiratory failure	130	15.6	Absence of peripheral line	228	20.9
Shock	114	13.7	High-flow exchange techniques	102	9.3
Cancer	101	12.1	Cardiopulmonary resuscitation	20	1.8
Cardiac failure	85	10.2	Other ^c	50	4.6
Immunodepression	46	5.5			
Renal failure	43	5.1			
Coagulopathy	37	4.4			
Trauma	36	4.3			
Gastrointestinal	34	4.1			
Cardiorespiratory arrest	16	1.9			
Other ^b	121	14.5			

No., number of cases; % percentage values in relation to total patient number; %* percentage values in relation to total number of catheters
^a The illnesses and indications are not exclusive; therefore, their total is greater than the total numbers of patients and catheters.

^b The most common illnesses in this section are other infections, 22 (2.6%); metabolic diseases, 21 (2.5%); burns, 16 (1.9%); and liver transplant, 12 (1.4%).

^c The most frequent indications in this section are bone marrow transplant, 16 (1.4%); blood sampling, 11 (1%); diagnostic techniques, 7 (0.6%); and transfusion of blood derivatives, 7 (0.6%).

**Fig. 1** Route of access. R right; L left

Indwelling time ranged from 0.1 to 145 days (mean 10.81 ± 12.27 SD, median 7, IQR 4–12 days) and varied significantly according to the insertion site: 38% of subclavian lines remained in place for > 12 days compared with 17% of jugular lines and 24% of femoral lines ($p < 0.001$).

The catheter was withdrawn due to end of therapy in 637 cases (58.3%), complications in 154 (14.1%), death in 106 (9.7%), accidental removal in 91 (8.3%) and other causes in 90 cases (8.2%). This information was not recorded for 14 catheters as the patients were transferred to another center.

Insertion site Infectious complications

Catheter-tip culture

We cultured 594 catheter tips (54% of the total), of which 167 (28%) were positive. Of these, 116 (20%) were colonized catheters (> 15 CFU) without sepsis and 51 positive tips (8%) were related to systemic infection. Thirty-two catheters were considered contaminated (< 15 CFU).

Blood culture

Blood cultures were obtained in 211 cases on at least one occasion. A blood culture was taken from the catheter in 206 cases (88 were positive), and in 95 the culture was peripheral (47 were positive); both blood cultures were taken in 90 cases.

Microorganisms found in catheter tips and in blood cultures are shown in Table 3.

Catheter-related bloodstream infections

Seventy-four CRBSIs (6.8% of the catheters, 8.8% of the patients) were found. The rate was 6.4 per 1,000 CVC days (95% CI 5–8). Definite CRBSI was present in 26 cases (2.4%), probable CRBSI in 10 (0.9%), and there

Table 3 Pathogens causing catheter-related bloodstream infection (definite, probable and possible) isolated from catheter tips and from peripheral or catheter blood

Pathogen	Catheter-related bloodstream infections						Total	Positive catheter tip		Positive blood culture				
	Definite		Probable		Possible			No.	%	Catheter		Peripheral		
	No	%	No	%	No	%	No	%	No.	%	No.	%	No.	%
Coagulase-negative staphylococci	14	53.8	7	70	27	71	48	64.8	113	67.6	56	63.6	25	53.2
<i>Pseudomonas</i>	2	7.7	0	0	5	13.1	7	9.4	16	9.6	7	7.9	4	8.5
<i>S. aureus</i>	2	7.7	1	10	3	7.9	6	8.1	13	7.8	8	9	4	8.5
<i>Candida</i> spp.	5	19.2	2	20	1	2.6	8	10.8	10	6	12	13.6	10	21.2
<i>Enterococcus</i>	1	3.8	1	10	2	5.2	4	5.4	12	7.2	4	4.5	2	4.2
<i>E. coli</i>	0	0	1	10	2	5.2	3	4	4	2.4	4	4.5	1	2.1
Other	2 ^a	7.7	1 ^b	10	4 ^c	10.5	7	9.4	16 ^d	9.6	9 ^e	10	4 ^f	8.5
Total	26		13		45		83		184		100		50	

Contaminated catheters (< 15 cfu) are not included.

No., number of cases; % percentage values of infections per pathogen.

The percentage totals are greater than 100%; the No. total can be greater than the number of CRBSIs (definite 26, probable 10, possible 38, total 74), than the number of positive catheter tips (167), and than the number of positive blood cultures (from the catheter 88, peripheral 47) because in some cases infections were polymicrobial.

^a *Streptococcus* 1, *Enterobacter* 1

^b *Micrococcus* 1

^c *Acinetobacter* 1, *Proteus* 1, *Stenotrophomonas maltophilia* 1, *Enterobacter* 1

^d *Proteus* 3, *Enterobacter* 2, *Klebsiella pneumoniae* 1, *Corynebacterium* 1, *Acinetobacter* 1, *Streptococcus* 1, *Stenotrophomonas maltophilia* 1, not specified 6

^e *Enterobacter* 3, *Stenotrophomonas maltophilia* 2, *Acinetobacter* 1, *Streptococcus morbilliforme* 1, *Klebsiella pneumoniae* 1, *Micrococcus* 1

^f *Streptococcus* 1, *Enterobacter* 1, *Klebsiella pneumoniae* 1, *Micrococcus* 1

Table 4 Risk of catheter-related infection

	Incidence %	No.	RR	95% CI	p
Weight					<0.001
< 8 kg	10.5	305			
8–14 kg	2.6	269			
14–25 kg	8.7	277			
> 25 kg	4.6	240			
Cardiac failure, yes/no	15.3/5.7	124/968	2.69	1.95–4.38	<0.001
Oncology, yes/no	10.2/6.2	166/926	1.66	0.99–2.78	0.05
Trauma, yes/no	0/7.1	46/1046	1.07	1.05–1.09	0.068
Mechanical ventilation, yes/no	7.7/5.9	531/561	1.31	0.84–2.04	0.22
Material			2.82	1.49–5.35	0.006
Silicone	17.6	51			
Polyurethane	6.3	1040			
Access site					0.1
Subclavian	9.8	265			
Femoral	5.8	587			
Jugular	6	232			
Emergency	6.5	431			
Scheduled	5.7	577			
Recatheterization	18.8	69			0.002
Povidone iodine on hub and stopcocks, yes/no	2.5/8.1	284/689	0.3	0.14–0.65	0.001
Three-way stopcocks, yes/no	7.7/1.1	906/90	7.95	0.97–49.46	0.02
Dressing at entrance site, porous/impermeable	5.5/11.6	804/224	0.47	0.34–0.87	0.001
Central venous thrombosis, yes/no	20/6.7	10/1082	3	0.88–10.59	0.14
Catheter obstruction, yes/no	15.4/5.7	117/975	2.67	1.63–4.39	<0.001
Indwelling time > 12 days yes/no	17.9/3	280/793	5.9	3.69–9.41	<0.001

No. number of cases; RR relative risk; CI confidence interval

Table 5 Cox regression model: independent variables associated with catheter-related bloodstream infection

Variable		Hazard ratio	95% CI	<i>p</i>
Weight	< 8 kg	2.40	1.11–5.19	0.002
	8–14 kg	0.47	0.15–1.54	
	4–25 kg	1.63	0.75–3.56	
	> 25 kg	1		
Indwelling time	> 12 days	1.97	0.89–4.36	0.089
	≤ 12 days	1		
Insertion type	Recatheterization	2.2	1.07–4.54	0.049
	Emergency or scheduled	1		
Povidone–iodine on hub and stopcocks	Yes	0.42	0.19–0.96	0.025
	No	1		
Dressing	Porous	0.41	0.23–0.74	0.004
	Impermeable	1		

was a possible CRBSI in 38 (3.5%). The causal agents of sepsis are shown in Table 3. Infection time ranged from 1 to 63 days (mean 16.77 ± 13.91 SD, median 14, IQR 7–20 days).

The results of univariate and multivariate analysis are shown in Tables 4 and 5 respectively. Figure 2 shows the cumulative survival rate of catheters that remained free of CRBSI for each of days 1–60.

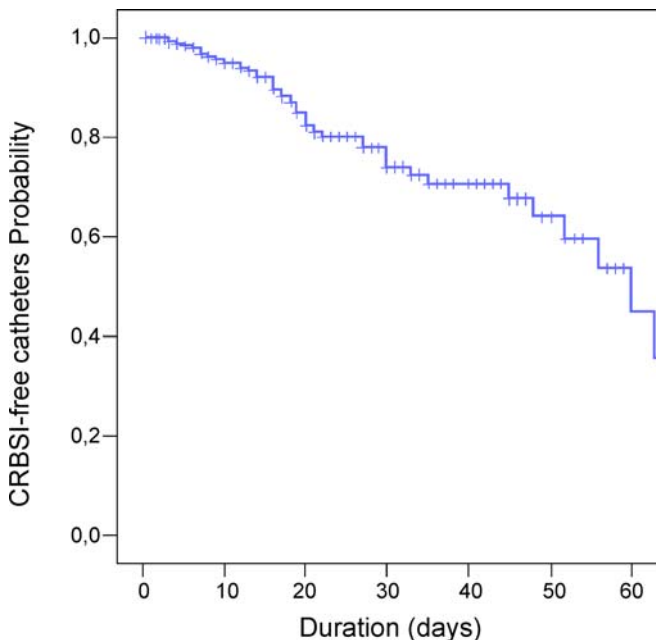


Fig. 2 Cumulative survival analysis of catheter duration. The probability of a catheter remaining free of catheter-related bloodstream infection decreases with time. At 4, 7 and 12 days after insertion (corresponding to p25, median and p75, respectively), 98.77%, 96.7% and 93.9% of catheters were infection-free, respectively. The median duration of CRBSI-free catheter survival was 60 days

Infection, obstruction and CVT

Infection was more frequent in obstructed catheters (15.4% vs 5.7%, $p < 0.001$; Table 4), but this was not confirmed in the multivariate analysis. CVT was more common in obstructed catheters (1.8% vs 0.8%), but the difference was not significant ($p = 0.29$).

Treatment, outcome and catheter-related deaths

Table 6 shows the outcome of infections in terms of catheter removal and etiological agent. The catheter was removed or changed in 58 cases: as soon as infection was suspected in 28, after 1–3 days in 17, and after more than 3 days in 13 cases. Three cases of CRBSI were treated by removing the catheter only, without antibiotic therapy; the remaining 71 (96%) received antibiotics (39 received one, 33 two or more). Four children (0.48%) presented endocarditis after CRBSI, three of them were diagnosed with heart disease.

Two children (0.24%), 4 and 19 months old, died from catheter-related complications. Both had undergone cardiac surgery, both developed endocarditis as a result of catheter-related sepsis, and one had superior cava thrombosis. The causal pathogens were *Staphylococcus epidermidis* and *Stenotrophomonas maltophilia* in one case and *Pseudomonas aeruginosa* in the other.

Discussion

We analyzed the infectious complications of 1092 CVC in 835 patients aged 0–14 years. Ours is one of the widest studies with these characteristics.

Mortality directly related to the catheter was 2.4/1,000 patients, but we did not analyze how complications affected mortality indirectly as this was not our objective.

Table 6 Treatment and outcome of CRBSI. Relation between catheter management and infection outcome, depending on etiological pathogen

		Pathogens	Removal No.	Catheter management Guidewire exchange No.	No removal No.		
Infection Outcome	Recovery	Coagulase-negative staphylococci	22	6	9		
		<i>Staph. aureus</i>	3		1		
		<i>Enterococcus</i>	1				
		<i>Pseudomonas</i>	1				
		<i>Candida</i> spp.	4				
		Other	3 ^a			1 ^b	
		Two pathogens	3 ^c	3 ^d		1 ^e	
		Subtotal		37	9	12	58
	Persistence	<i>Candida</i> sp			2	1 ^{***}	
		<i>Pseudomonas</i>			1		
		<i>E. coli</i>			1		
		Subtotal			4	1	5
	Endocarditis	Coagulase-negative staphylococci		2 (1 ^{*#})	1 ^{*#}		
		<i>Staph. aureus</i>		1			
		<i>Pseudomonas</i>		1 [*]			
		<i>Stenotrophomonas</i>			1 ^{*#}		
		Subtotal		4	2		6
	Other	Coagulase-negative staphylococci + <i>Pseudomonas</i>		1 ^{**}			
		<i>E. coli</i> + <i>Enterococcus</i>				1 (thrombosis)	
		Subtotal		1		1	2
	Not available	Coagulase-negative staphylococci			1	2	3
		Total		42 (56.7%)	16 (21.6%)	16 (21.6%)	74

No., number of CRBSI

^a *S. pneumoniae*, *Acinetobacter*, *Proteus*^b *Enterobacter*^c 1 Coagulase-negative staphylococci + *Micrococcus*, 1 *S. aureus* + *Enterococcus*, 1 *Pseudomonas* + *Enterococcus*^d 1 Coagulase-negative staphylococci + *Candida* spp., 2 coagulase-negative staphylococci + *Pseudomonas*^e 1 *E. coli* + *Enterobacter*

* Death; ** death by hypoxemia 2 days after diagnosis of infection; *** death by non-catheter-related factors 4 days after diagnosis of infection

The same patient

The infection rate (definite, probable and possible CRBSI) in our series (6.4/1,000 catheter-days; 6.8%) is similar to that found by the National Nosocomial Infection Surveillance System from 1990 to 1999 [18] and from 1992 to 2003 [19], which, in 67 and 74 PICUs, respectively, found an infection rate of 7.9 and 7.6/1,000, respectively. Nevertheless, infection rates in adult ICU patients vary widely (from 2.9 to 9.7/1,000) according to the type of ICU [19]. The widely differing definitions of infection and culture methods in different studies mean that it is often difficult to compare infection rates [20]. Recently, an expert committee published the clinical definitions of definite, probable or possible CRBSI in infants and

children, for the purpose of identifying infections for epidemiologic and surveillance reasons. They also recommended that only those patients fulfilling definite CRBSI criteria should be enrolled in clinical trials involving sepsis [17]. Our study classified CRBSI according to these new criteria, which facilitates the interpretation of our findings and their comparison with other data on CRBSI.

We cultured slightly over half the catheters because the design of the study involved culturing as many catheters as possible. However, a recent meta-analysis recommended culture only in the case of clinically suspected CRBSI [21]. The yield of different diagnostic techniques varies from one study to another; the above-mentioned meta-analysis

(which included 51 selected papers) found that paired quantitative blood cultures of central and peripheral lines had the greatest specificity, followed by qualitative blood culture obtained from the catheter and the acridine orange stain test. The most accurate diagnostic methods involving withdrawal of the catheter were quantitative culture of the tip followed by semi-quantitative culture; qualitative culture of the tip had the highest sensitivity but very low specificity. Nevertheless, these results may vary in pediatric patients [17], as peripheral blood cultures are often difficult to obtain and catheters are not withdrawn for diagnostic purposes, due to the difficulty in inserting another. Therefore, techniques such as calculating the time differential of qualitative blood culture positivity between both lumina, or paired quantitative blood cultures of both lumina, or using a cut-off point of > 100 CFU/ml for the blood culture of a single lumen, could be useful in these patients [17]. Nevertheless, few hospitals routinely use quantitative blood culture techniques.

Some of the risk factors associated with CRBSI found in our study have been described elsewhere. These include an extended indwelling period, which is associated with a greater risk of infection [12, 14]. In our study, more than 12 catheter days meant a greater incidence of infection. Stenzel et al. [10] found no association between infection and indwelling time.

Routine changing of CVC does not reduce the rate of infection [22], and some studies have even shown that the number of infections increases when the change is made by guidewire [20, 22]. Current AAP guidelines on the prevention of CRBSI and a meta-analysis [23] recommend not changing catheters on a routine basis in order to prevent infection. If it is necessary to change the line and catheter-related infection is suspected, a new insertion site should be chosen, except in patients with very limited vascular access sites (e.g. small children), in whom change should be accompanied by antibiotherapy. When no infection is suspected, change may be performed using a guidewire. The results of our study support this recommendation, since CRBSI are more frequent in catheters changed by guidewire. However, the reason for changing our catheters (infection or other) was unknown, as these data were not collected in the protocol. Prophylactic change by guidewire or at a new site is common practice in burn patients [8], an exception which is not considered in the current AAP guidelines for prevention of CRBSI [20].

According to the literature [24], the most frequent path of infection for short-term CVC is the extraluminal route (45%), due to migration of cutaneous flora across the skin surrounding the catheter. Endoluminal colonization is produced by the entry of pathogens via the external hubs during frequent handling or via the infusion of contaminated liquids (26%), this being more serious in long-term catheters [24]. We found fewer infections in catheters whose hubs and three-way stopcocks were protected

by povidone–iodine when they are handled. This fact indirectly demonstrates the importance of endoluminal contamination in our catheters, whose mean indwelling period was 10.8 days with a median of 7 days. Several studies in adults show a significant decrease in CRBSI, cost and time required for care when the hub is protected with povidone–iodine by different methods [25, 26, 27, 28].

It is well known that the risk of infection can be reduced by the use of antiseptic at the insertion site [29, 30, 31, 32, 33] before catheterization and during dressing change. Maki et al. [29] and the AAP guidelines [20] prefer 2% chlorhexidine to other antiseptics, although this is still a matter for debate [32, 33]. Other recommendations include minimal handling, heparin-bonded catheters [34], antiseptic-antibiotic-coated catheters when the indwelling time is expected to be more than 7 days [35, 36], tunneled catheters or chlorhexidine dressings. Nevertheless, continuous training of physicians and nursing staff in CVC maintenance is still the most effective way of reducing CRBSI [37, 38, 39].

In our study, lower patient weight (< 8 kg) was an independent factor with a greater risk for catheter-related infection. This may be because of young age and/or malnourishment, both of which are associated with immunodepression. In the published studies we reviewed, we found that lower weight was a risk factor for infection in premature neonates [13, 18, 19], and Damen et al. found greater colonization of CVC in children under 1 year of age [40].

Our study found more infections in subclavian lines than in femoral or jugular lines in the univariate analysis, although this was not significant ($p=0.1$). Multivariate analysis showed that insertion site was not a risk factor for infection. There is no increased risk of infection with femoral insertion in infants and children compared with non-femoral insertion [5, 6, 7, 8, 41]. The 1997 meta-analysis by Vekataraman [7] reviews 23 publications about CVC in children and concludes that femoral insertion is safe, with high success rate and no more infections than other access routes. Our results and those reported in the literature recommend femoral insertion over other sites in pediatric patients.

Nevertheless, the experience in adults is different [26, 42, 43, 44, 45]. Thus, Goetz et al. [42] report a greater risk of catheter contamination with femoral insertion, although the rate of CRBSI is not greater. Safdar et al. [24] recommend using subclavian rather than jugular insertion, and jugular rather than femoral insertion to prevent CRBSI in adults.

The type of dressing used to protect the catheter may affect the risk of infection, but published results are contradictory. Some studies claim that impermeable polyurethane reduces the risk of infection, as it avoids exposure to nearby flora (from tracheostomy secretions, saliva, feces or urine), whereas other investigations,

including one meta-analysis [46], argue that impermeable dressings macerate the catheter entry and lead to infection by saprophytes. Several studies found no differences. The results of our study support the second hypothesis, thereby maintaining the controversy. Given that both hypotheses are coherent, experts recommend selecting the dressing on an individual basis [5].

No relationship between infection, obstruction and thrombosis has been established in our study, unlike other studies [47]; even though the risk of infection is higher in children with obstruction (univariate analysis $p < 0.001$), it was not predictive in the multivariate model. The number of thromboses detected in our series was small, probably because they can be asymptomatic and routine ultrasound and X-ray examinations with contrast medium were not performed; furthermore, mere obstruction was not considered a clinical sign of CVT.

As far as catheter management (removal or not) in the presence of infection is concerned, our results on the outcome of infection support the recommendations of other authors [48]: patients not affected by heart disease with coagulase-negative staphylococcus infection can receive antibiotics if catheter removal proves problematic (limited vascular access sites, potential complications related to reinsertion); however, the catheter must be removed in infections caused by *Candida* spp., *Staphylococcus aureus*, Gram-negative organisms and in patients suffering from heart disease.

Our study is limited in that it does not analyze the influence of CRBSI on morbidity, duration of admission, or cost, which are extremely important both for the patient and for health service.

Another limitation is that there was no standard procedure for catheter care, only the procedures of the individual protocols of each PICU. Therefore, results on povidone and dressings are based on a non-randomized design.

To conclude, central venous catheterization, a frequent procedure, is not exempt from morbidity and mortality. Catheter-related sepsis is associated with lower

patient weight, more than 12 days' indwelling time and recatheterization, but not with the insertion site.

Many studies, especially pediatric studies, are necessary to ascertain the diagnostic capacity and yield of different culture techniques (classic or novel) for diagnosis of CRBSI in pediatric patients.

Appendix

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