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A prospective 7-year survey on central venous catheter-related complications at a single pediatric hospital

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Abstract The aims of this study were to assess the incidence and risk factors of major central venous catheter (CVC)-related complications in a large cohort of children affected by oncological, hematological, or immunological diseases in a 7-year prospective observational study at a single center. Nine hundred fifteen CVCs were inserted in 748 children for a total period of 307,846 CVC-days. Overall, 298 complications were documented with a complication rate of 0.97/1,000 CVC-days: 105 mechanical complications (dislocations 0.30/1,000 CVC-days, ruptures 0.04/1,000 CVC-days), 174 infections (bloodstream infections 0.46/1,000 CVC-days, tunnel infections 0.10/1,000 CVC-days), and 19 thrombosis (0.06/1,000 CVC-days). Significant risk factors were: diagnosis of acute lymphoblastic leukemia (ALL) and age ≤3 years for dislocations; nonmalignant disease for ruptures; ALL for thrombosis; double-lumen and partially implanted CVCs for bloodstream infections; age ≤3 years for tunnel infections. In conclusion, the rate of CVC-related complications in children was lower than that usually reported.

Keywords Central venous catheter complications · Children · Mechanical complications · CVC-related infections · CVC-related thrombosis

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Introduction

A central venous catheter (CVC) is an essential device for the management of children affected by oncological, hematological, or immunological diseases. Indeed, it provides them with a consistent and atraumatic access for blood sampling, drugs infusion, blood products, or support therapy as parenteral nutrition. However, it may have some disadvantages, such as mechanical accidents, infections, and thrombosis. These adverse events may be life-threatening, prolong hospital stay, increase hospitalization costs, and require premature CVC removal [3, 12, 30, 36]. In infants and children, CVC replacement is often problematic because another venous access may not be easily available. Prevention and treatment of CVC-related complications thus play a pivotal role, and specific surveillance programs are crucial both to monitor the risk factors for CVC complications and to improve their management.

Although an extensive body of literature illustrates benefits and adverse effects of CVC in adults [4, 10, 13, 23, 26, 27, 31], there are few prospective studies in children, mostly based on small samples [6, 14–17, 22, 36]. The aims of this study were to assess the incidence and risk factors of major long-term CVC-related complications in a large cohort of children affected by oncological, hematological, or immunological diseases in a 7-year prospective observational study at a single center.

Materials and methods

All the CVCs consecutively inserted from 1 January 2001 through 31 December 2007 at the Regina Margherita Children's Hospital (Turin, Italy), for the management of patients <20 years of age affected by oncological, hemato-

logical, or immunological diseases, were considered eligible for this study.

The CVC insertion procedures were performed in an operating room using general anesthesia or, in some teenagers, local anesthesia according to the common sterile barrier precautions. The choice regarding the type of device (partially or totally implantable) was based on the patient's age and body constitution, underlying disease, and type of treatment. The surgical technique (percutaneous or surgical approach) was chosen by the surgeon on the basis of the patient's condition, underlying disease, and type of cannulated vein. During placement, the correct position of the catheter distal tip was checked by fluoroscopy followed by a standard chest X-ray. Teicoplanin (10 mg/kg/dose, 30 min before and 12 and 24 h after the surgical intervention) was routinely given as a prophylaxis.

Standard CVC care was handled by trained pediatricians and nurses according to the Italian Association of Paediatric Hematology and Oncology guidelines [20]. In case of CVC removal, a CVC tip qualitative culture was routinely performed.

CVC-related complications were classified as follows:

1) Complications occurring during surgical or percutaneous insertion, such as pneumotorax, vessel perforation, hematoma, bleeding, and hydrothorax. We only documented major events requiring a surgical intervention.

2) Mechanical complications, such as catheter dislocations and ruptures. These were diagnosed using standard chest X-ray, color Doppler ultrasound, or magnetic resonance imaging (MRI).

3) CVC-related thrombosis: symptomatic thrombosis was defined as the presence of clinical symptoms or signs (pain, headache, swelling of neck or arms, upper arm erythema, superior vena cava syndrome). It was detected by appropriate imaging procedures: color Doppler ultrasound of neck vessels, chest X-ray, echocardiography, and/or angiography–computed tomography. Occlusions not responding to urokinase instillation and requiring CVC removal were also included.

4) CVC-related infections: these were divided into (a) local (subcutaneous tunnel infections) and (b) systemic infections according to the following criteria. Tunnel infection was defined as tenderness, erythema, and induration extending more than 2 cm beyond the CVC exit site along the subcutaneous tract of a tunneled catheter, irrespective of a concomitant bloodstream infection or microbiological confirmation. CVC-related bloodstream infection (CRBI) was defined as signs of systemic infection if no other source of infection was identified and if at least one of the following conditions was found: (a) CVC tip positive culture with clinical manifestations of infection; (b) differential time to positivity (i.e., a positive culture from CVC 2 h earlier than from peripheral blood); (c) positive qualitative culture from CVC with negative peripheral blood culture; (d) isolation of the same pathogen from blood and from the catheter tip; (e) isolation of the same pathogen from blood and from purulent material draining from the catheter exit site or from the subcutaneous tunnel; (f) temporal relationship (maximum of 2 h) between CVC manipulation and the onset of shivering and fever with positive culture from CVC or peripheral blood.

Data were recorded using a specifically designed software. Information was collected on the patient's age and underlying disease, catheter type, date of positioning, date, and cause of removal. In patients with the CVC still in place at the end of the study, the observation period was censored at that date. Any complication occurring during the follow-up was registered in terms of date of appearance, type of event, diagnostic criteria (see above), therapeutic measures, outcome, and CVC removal.

The hospital's ethical committee approved the study. An informed consent form for the scientific use of the collected data was signed either by parents or a legal representative.

Statistical analysis

The incidence of complications was calculated per CVC and per 1,000 CVC-days. For each catheter, the total number of catheter days at risk (cdr) was calculated as the total number of days from insertion to the last observation (the end of examination period, the day of removal, or the day of patient's death). The complication rate per 1,000 days was calculated as 1,000 times the number of complications divided by the total number of cdr.

The association between CVC type, number of lumens, place of catheter insertion, underlying disease, tumor type, and age of patients and the risk of developing CVC-related complications was explored using Fisher exact test or χ^2 method.

All statistical tests were two-tailed and considered significant with a p value <0.05. Confidence intervals (CI) were calculated at the 95% level. The SPSS 15 software package was used for the analysis.

Results

During the study period, 915 indwelling central venous catheters were consecutively inserted in 748 children (419 males, 329 females) with oncological/hematological or immunological diseases, for a total period of 307,846

CVC-days. The mean number of inserted CVCs was 1.22 for each patient. The baseline characteristics of patients and CVCs are shown in Table 1.

We calculated the ratio between CVC diameter (in French) and the patient's weight (in kilograms) only in the last 2 years of the study period because patients' weight at CVC insertion was registered only from 2006. The choice of the insertion site changed over the study period. Surgical catheter insertion in the external or the internal jugular vein was the access of choice by our surgeons until 2002. Percutaneous access in the subclavian vein was subsequently preferred because our preliminary results had shown few acute complications during CVC insertion (data not shown).

CVCs remained in situ for a median period of 291 days (range=0–1,923 days). At the end of the study, 738 CVCs (81%) had been removed, while 177 (19%) were still in place. Besides the 163 CVCs (22%) being removed due to complications, 378 (51%) were removed for end of treatment and 145 (20%) for the patient's death.

Overall, 298 complications were observed. During CVC insertion, no major complications were documented. The overall complication rate was 0.97/1,000 CVC-days. It was 0.57/1,000 CVC-days for infectious complications (n=174), 0.34/1,000 CVC-days for mechanical complications (n=105), and 0.06/1,000 CVC-days for thrombotic complications (n=19). Data for each complication are summarized in Table 2.

The risk factors for all CVC-related events are shown in Table 3. The most significant risk factors for having a dislocation were a diagnosis of acute lymphoblastic leukemia (ALL) (OR=2.37; 95%CI=1.51–3.73) and an age ≤3 years (OR=2.03; 95%CI=1.30–3.15).

Oncological patients had a lower risk of rupture compared to patients with immunological or hematological nonmalignant disease (OR=0.12; 95%CI=0.04–0.38).

Children suffering from ALL had a significantly increased risk of thrombosis compared to patients affected by other tumors (OR=2.84; 95%CI=1.13–7.14). Subclavian access was associated with a lower risk of thrombosis than jugular insertion (OR=0.19; 95%CI=0.07–0.50).

Single-lumen CVCs were associated with a lower risk of CRBIs compared to double-lumen CVCs (OR=0.20; 95% CI=0.13–0.29), while partially implanted CVCs had a significantly increased risk of CRBIs versus totally implanted ports (OR=4.78; 95%CI=1.15–19.87). Subclavian access was associated with a lower risk of CRBIs than jugular insertion (OR=0.57; 95%CI=0.39–0.82).

Age ≤3 years was a significant risk factor for tunnel infections (OR=2.30; 95%CI=1.12–4.74).

Infectious agents of CRBIs were gram-positive cocci (n=92; 64%), gram-negative bacteria (n=39; 27%), and fungi (n=7; 5%), while polymicrobical infections were observed in five (4%) CRBIs. In 19 (61%) tunnel infections, the diagnosis was microbiological, while in 12 (39%), it was based on clinical elements. Gram-positive bacteria were found in 17 (90%) infections, gram-negative bacteria in the remaining two (10%). Table 4 shows the isolated microorganisms in all CVC-related infections.

Discussion

This prospective, observational study is one of the largest with the most prolonged follow-up in a pediatric population. In our series, the overall complication rate of adverse events was 0.97/1,000 CVC-days. Other similar studies in Italy, based on a smaller size sample and a shorter follow-up, found a complication rate ranging between 2.2/1,000 and 6.2/1,000 CVC-days [6, 17]. This gap is probably due to the type of CVC-related complications taken into consideration rather than to differences in study populations and CVC management. In fact, we did not consider minor CVC-related complications.

In our study, CVC-related infections were the most frequent complication, with a lower rate than values reported in other studies in which exit-site infections were also evaluated [6, 17]. According to the National Nosocomial Infection Surveillance, the incidence of CRBIs ranges from 3% to 6%, with a rate of 1.7–2.4/1,000 CVC-days, depending on the type of device, the patient's age, and the underlying disease [26]. Our low complication rate may be due to the good CVC management by specifically trained staff and parents. Moreover, a prospective single-center study allowed a better analysis of CVC-related adverse events than multicenter studies and a reduced bias between the results.

In our series, the most significant risk factor for developing CRBIs was having a double-lumen CVC. Catheters with multiple lumens have been associated with a higher rate of infections because they are usually inserted in patients with high-intensity treatment who require a great number of catheter manipulations for prolonged periods [5, 34]. A recent meta-analysis found that multilumen CVCs had a greater risk of CRBIs than single-lumen CVCs, although this difference was not statistically significant when only high-quality studies were considered [11]. Our finding of a higher complication rate gives evidence that these devices should be used restrictively or removed as early as possible. Several studies compared infectious complications between externalized CVCs and totally implantable ports, reporting a significantly lower rate of infections in the latter because they need fewer maintenance procedures when not in use [1, 2, 8, 19]. Despite the unbalanced distribution of CVC type, our findings are consistent with previous reports. The increase in infectious

Table 1 Baseline characteristics of CVCs and patients

Year	2001	2002	2003	2004	2005	2006	2007	Total
CVCs inserted	133	129	116	135	125	125	152	915
Catheter days at risk	46,018	50,645	47,299	48,275	45,696	26,488	43,425	307,846
Age at CVC insertion (years)	8 (0.3–19)	8 (0.7–19)	7 (0.04–19)	6 (0.16–18)	7 (0.07–18)	8.9 (0.1–19.7)	7.8 (0.2–19.4)	7.3 (0.04–19.7)
Underlying disease								
Oncological disease, n (%)	126 (95)	114 (88)	107 (92)	126 (93)	107 (86)	118 (94)	142 (93)	840 (92)
ALL, n (%)	36 (27)	42 (33)	32 (28)	46 (34)	36 (29)	40 (32)	47 (31)	279 (31)
Other tumors[a], n (%)	90 (68)	72 (56)	75 (65)	80 (59)	71 (57)	78 (62)	95 (63)	561 (61)
Nonmalignant diseases[b], n (%)	7 (5)	15 (12)	9 (8)	9 (7)	18 (14)	7 (6)	10 (7)	75 (8)
CVC type								
Partially implanted, n (%)	125 (94)	123 (95)	112 (97)	130 (96)	120 (96)	114 (91)	140 (92)	864 (94)
Single-lumen, n (%)	57 (43)	56 (43)	74 (64)	99 (73)	80 (64)	52 (42)	78 (51)	496 (54)
Double-lumen, n (%)	68 (51)	67 (52)	38 (33)	31 (23)	40 (32)	62 (50)	62 (41)	368 (43)
Totally implanted, n (%)	8 (6)	6 (5)	4 (3)	5 (4)	5 (4)	11 (9)	12 (8)	51 (6)
Access vein								
Jugular vein, n (%)	98 (74)	73 (57)	49 (42)	21 (16)	17 (13)	7 (6)	8 (5)	273 (30)
Subclavian vein, n (%)	35 (26)	56 (43)	67 (58)	114 (84)	108 (87)	118 (94)	144 (95)	642 (70)
CVC lumen size								
≤4 Fr, n (%)	5 (4)	3 (2)	14 (12)	10 (7)	13 (10)	14 (11)	16 (11)	75 (8)
4–9 Fr, n (%)	48 (36)	60 (47)	74 (64)	90 (67)	70 (56)	63 (51)	82 (54)	487 (53)
≥9 Fr, n (%)	80 (60)	66 (51)	28 (24)	35 (26)	42 (34)	48 (38)	54 (35)	353 (39)
CVC diameter (Fr)/weight (kg)[c]	–	–	–	–	–	0.35	0.34	0.35

Continuous variables: median (range); categorical variables: number (%)

ALL acute lymphoblastic leukemia

[a] Other tumors: acute myeloid leukemia (44), lymphomas (101), brain tumors (132), neuroblastoma (60), other solid tumors (224)

[b] Nonmalignant diseases: hematological nonmalignant diseases (60), primary immunodeficiencies/AIDS (15)

[c] CVC diameter (in French)/weight (in kilograms) ratio was calculated only in the last 2 years of the study period because patients' weight at CVC insertion was evaluated only from 2006

Table 2 Complication rates, number of CVCs and patients involved, and number of CVC removed for CVC-related complications

Complications	Events, n (%)	CR	CVCs[a], n (%)	Patients[b], n (%)	CVC removals[c], n (%)
Mechanical complications					
Dislocations	93 (31)	0.30	89 (10)	82 (11)	58 (8)
Ruptures	12 (4)	0.04	12 (1)	12 (2)	11 (2)
All	105 (35)	0.34	101 (11)	94 (13)	69 (9)
CVC-related thrombosis	19 (6)[d]	0.06	19 (2)	19 (3)	12 (2)
CVC-related infections					
Tunnel infections	31 (10)	0.10	28 (3)	28 (4)	17 (2)
CRBIs	143 (48)	0.46	113 (12)	106 (14)	65 (9)
All	174 (58)	0.57	141 (15)	134 (18)	82 (11)
Total	298	0.97	261 (29)	247 (33)	163 (22)

CR complication rate per 1,000 CVC-days (cdr=307,846)

[a] Percentage of all CVCs (915)

[b] Percentage of all patients (748)

[c] Percentage of all CVCs removed (738)

[d] Thrombosis: deep venous thrombosis (17), right atrium thrombosis (one), pulmonary embolism (one)

Table 3 Risk factors for CVC-related complications

CVC-related complications	CVC type		Number of lumens		Site of CVC insertion		Underlying disease		Tumor type		Age at CVC insertion	
	Partially implanted n (%)	Totally implanted n (%)	Single-lumen n (%)	Double-lumen n (%)	Subclavian vein n (%)	Jugular vein n (%)	Oncological n (%)	Nononcological n (%)	ALL n (%)	Other n (%)	≤3years n (%)	>3years n (%)
Dislocations	–	–	56 (11)	37 (10)	63 (10)	30 (11)	85 (10)	8 (11)	44 (16)	41 (7)	38 (15)	55 (8)
OR (95%CI)	–	–	1.14 (0.73–1.77)	1 (ref)	0.88 (0.56–1.40)	1 (ref)	0.94 (0.44–2.03)	1 (ref)	2.37 (1.51–3.73)	1 (ref)	2.03 (1.30–3.15)	1 (ref)
p	–	–	0.581		0.633		1		0.0001ᵃ		0.002ᵃ	
Ruptures	–	–	5 (1)	7 (2)	6 (1)	6 (2)	7 (1)	5 (7)	4 (1)	3 (1)	5 (2)	7 (1)
OR (95%CI)	–	–	0.53 (0.17–1.67)	1 (ref)	0.42 (0.13–1.31)	1 (ref)	0.12 (0.04–0.38)	1 (ref)	2.71 (0.60–12.17)	1 (ref)	1.95 (0.61–6.21)	1 (ref)
p	–	–	0.379		0.199		0.002ᵃ		0.229		0.323	
Thrombosis	19 (2)	0 (0)	9 (2)	10 (3)	6 (1)	13 (5)	19 (2)	0 (0)	11 (4)	8 (1)	7 (3)	12 (2)
OR (95%CI)	Not calculable	1 (ref)	0.66 (0.27–1.65)	1 (ref)	0.19 (0.07–0.50)	1 (ref)	Not calculable	1 (ref)	2.84 (1.13–7.14)	1 (ref)	1.59 (0.62–4.10)	1 (ref)
p	0.622		0.483		0.0005ᵃ		0.256		0.027ᵃ		0.432	
CRBIs	141 (16)	2 (4)	36 (7)	105 (29)	85 (13)	58 (21)	133 (16)	10 (13)	46 (16)	87 (16)	42 (17)	101 (15)
OR (95%CI)	4.78 (1.15–19.87)	1 (ref)	0.20 (0.13–0.29)	1 (ref)	0.57 (0.39–0.82)	1 (ref)	1.22 (0.61–2.44)	1 (ref)	1.08 (0.73–1.59)	1 (ref)	1.15 (0.78–1.71)	1 (ref)
p	0.027ᵃ		<0.0001ᵃ		0.003ᵃ		0.624		0.763		0.538	
Tunnel infections	–	–	14 (3)	17 (5)	24 (4)	7 (3)	26 (3)	5 (7)	11 (4)	15 (3)	14 (6)	17 (3)
OR (95%CI)	–	–	0.60 (0.29–1.23)	1 (ref)	1.48 (0.63–3.47)	1 (ref)	0.45 (0.17–1.20)	1 (ref)	1.49 (0.68–3.30)	1 (ref)	2.30 (1.12–4.74)	1 (ref)
p	–	–	0.195		0.430		0.169		0.397		0.025ᵃ	

ᵃ Significant risk factor

Table 4 Isolated microorganisms in CVC-related infections

Isolated microorganisms	Number of cases, n (%)	
	CRBIs	Tunnel infections
Staphylococcus epidermidis	46 (30)	4 (21)
Staphylococcus aureus	13 (9)	11 (58)
Staphylococcus warneri	9 (6)	1 (5)
Staphylococcus haemoliticus	5 (3)	1 (5)
Other coagulase-negative cocci	8 (5)	0
Other gram-positive bacteria[a]	16 (11)	0
Escherichia coli	11 (7)	0
Pseudomonas spp.[b]	4 (3)	2 (11)
Burkholderia cepacia	4 (3)	0
Klebsiella spp.	4 (3)	0
Acinetobacter spp.	6 (4)	0
Aeromonas hydrophila	3 (2)	0
Other gram-negative bacteria	13 (9)	0
Candida albicans	2 (1)	0
Candida parapsilosis	5 (3)	0
Candida tropicalis	2 (1)	0
Candida incospicua	1 (1)	0
Total	152	19

[a] Micrococci, enterococci, alpha-haemolytic streptococci, beta-haemolytic streptococci

[b] *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Rhizobium radiobacter*

risk when using externalized CVCs is probably offset by their atraumatic access, thereby justifying the continued use of this CVC type in all Italian pediatric cancer centers. In our study, the underlying disease was not a significant determinant of risk, in contrast with other studies which reported a higher risk of infection in children with acute leukemia [5, 28].

To date, few studies have evaluated the rate of local CVC-related infections. Our rate of tunnel infections was similar to the value reported in adults [18]. Younger children had a higher risk of tunnel infections, probably due to age-related differences in skin defense barrier. Moreover, maintenance procedures are generally performed with more difficulty in younger patients.

The principal source of CVC-related infections is the contamination of the catheter hub or the port bell through the hands during catheter manipulations. For this reason, the most common microorganisms in our series and elsewhere [4, 13, 27, 33] were coagulase-negative staphylococci and *Staphylococcus aureus*. Fungi (especially *Candida* spp.) can also colonize the hands of the staff, infusions containing glucose, or parenteral nutrition. In our series, fungi were isolated in a lower percentage than values reported in other studies [13, 27].

Mechanical complications were the second most frequent events. Our rate was lower than the value reported in another study [17].

Dislocations may originate from accidental self-removal by the patient, nonoptimal size of the Dacron cuff or its incomplete cicatrization and adhesion to the subcutaneous tunnel tissues. A younger age at CVC insertion was associated with a higher risk of dislocations, probably due to the increased risk of accidental self-removal by younger children [9, 31]. The higher rate of dislocations in patients with ALL may be explained by the common use of corticosteroids in their therapeutic protocols, which notably impair the cicatrization process.

Catheter ruptures were rare complications. We did not find published studies to compare our data. Ruptures were generally late events almost always requiring CVC removal, probably because they involve CVCs worn by frequent and prolonged use. Notably, children with nononcological diseases had a higher risk of ruptures. CVC management might be performed less carefully in these patients because of their more favorable prognosis.

CVC is the most frequent cause of thrombosis in children [21, 22]. In our study, clinically relevant thromboembolic events were rare, but with a great impact on the CVC remaining in place. Our rate was similar to values reported in two reviews [10, 23]. This finding is presumably underestimated because such episodes are usually asymptomatic in children [21, 22]. It must be underlined that the rate of CVC-related thrombosis was higher when a Doppler ultrasound scan or a venography were performed at some time after CVC placement irrespective of symptoms [10, 23, 35], whereas we performed specific investigations only in case of repeated CVC malfunctions or clinical clues of thromboembolic complications. The higher rate of thrombosis in patients with ALL may be explained by the disease itself (hypercoagulable status initially induced by blastic cells) and treatment with L-asparaginase, causing a depletion of antithrombin [10, 23]. This risk was highest during induction therapy, which includes concomitant administration of L-asparaginase and steroids, acting as procoagulant activators [14]. Screening investigations and various heparinization schedules are suggested in this group of patients to prevent thrombosis. Large lumen size CVCs have been associated with a higher rate of CVC-related thrombosis because they cause irritation against the inner lining of the vein [14]. Children with median values of CVC diameter (in French)/weight (in kilograms) ratio ≥0.4 have been shown to have a significantly increased risk of thrombosis [14]. The 0.35 and 0.34 values found in the last 2 years were lower than the above-reported value, suggesting that CVC size had been tailored to the size of the single patient.

Subclavian access was reported as being associated with a lower risk of CRBIs [7, 29, 32, 34] and a higher rate of

thrombosis [24, 25]. Conversely, we found that it was protective for both CRBIs and thrombosis development. However, results about the site of catheter insertion were not discussed because of the radical change in the choice of the access vein during the study period. We, therefore, acknowledge that any considerations derived from that might have a low strenght of recommendation.

In conclusion, results suggest that the use of double-lumen CVCs should be restricted as far as possible to reduce infections, despite their advantages in patients who need numerous infusions and blood samples. Double-lumen CVCs should be inserted only in patients requiring intensive supportive care as children scheduled for allogenic stem cell transplantation. Insertion of CVCs adapted to the size of each patient should be encouraged to avoid placing large catheters in the relatively small vessels of young children, with a consequent development of thrombotic events. Dedicated surveillance programs are of paramount importance especially in younger patients who are at risk of dislocations and tunnel infections and in children suffering from ALL who are at risk of dislocations and thrombotic events. Finally, the low complication rate of adverse events in our patients may derive from the correct CVC management both in the hospital and at home due to the good compliance with the specific protocol and the routine use of internationally approved standards for CVC maintenance.

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