

# A comprehensive approach to the prevention of central venous catheter complications: results of 10-year prospective surveillance in pediatric hematology-oncology patients

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**Abstract** We report our decennial experience with 1161 newly-placed long-term central venous catheters inserted in 919 hematology-oncology patients for a total of 413,901 CVC-days of observation. Most of the CVCs were partially-implanted, open-ended, Broviac-Hickman type of CVC (95 %). One thousand and twenty-four complications were recorded equal to 2.47 per 1000 CVC-days. The frequency of complications per CVC, the rate of episodes per 1000 CVC-days, and removal rate were malfunction/occlusion 42 %, 1.18/1000, and 2.3 %; mechanical (dislodgement/rupture/kinking) 18.3 %, 0.51/1000, and 77.4 %; bacteremia 14.8 %, 0.42/1000, and 18.6 %; exit-site/tunnel infection 11.5 %, 0.32/1000, and 9.7 %; thrombosis 0.86 %, 0.02/1000, and 30 %; pneumothorax 0.52 %, 0.01/1000, and 0. In multivariate analysis, the risk factors were for mechanical complications, a younger age <6.1 years at CVC insertion (HR 1.8,  $p=0.0006$ ); for bacteremia, a double lumen CVC (HR 3.1,  $p<0.0001$ ) and the surgical modality of CVC insertion (HR 1.5,  $p=0.03$ ); for exit-site/tunnel infection, a double lumen CVC (HR 2.1,  $p=0.0003$ ) and a diagnosis of leukemia or lymphoma (HR 1.8,  $p=0.01$ ); for malfunction/occlusion, an age <6.1 years (HR 1.6,  $p=0.0003$ ), the diagnosis of leukemia or lymphoma (HR 1.9,  $p<0.0001$ ) and double lumen

CVC (HR 1.33,  $p=0.023$ ). The cumulative incidence of premature CVC removal was 29.2 % and the risk factors associated with this event were the surgical modality of CVC insertion (HR 1.4,  $p=0.0153$ ) and an age at CVC positioning less than 6.1 years (HR 1.6,  $p=0.0025$ ). We conclude that a best-practice set of rules resulted in reduced CVC complications.

**Keywords** Central venous catheter · Pediatric malignancy · Complication · Infection · Occlusion · Malfunction

## Introduction

The introduction of long-term central venous catheters (CVCs) several decades ago represented one of the major advances in the quality of care of oncology patients, in particular for pediatric patients [1, 2]. The use of partially or totally implanted devices permits the safe administration of chemotherapy schedules requiring continuous infusion or high doses of drugs, hyperhydration, hyperosmolar solutions for parenteral nutrition, and intensive supportive care or blood testing [3]. Partially implanted CVCs are often preferred by the pediatric hematologist-oncologist because this CVC is more suitable for complex oncological and supportive treatment than a totally implanted CVC, especially in the youngest patients, and their use does not require skin puncture at every new access [4–6].

Despite the fact that the adoption of a CVC to deliver intravenous therapies is nowadays considered the standard of care in an oncology setting, its use exposes the patient to complications that can cause hospitalization or be life-threatening requiring its early removal [7, 8]. Mechanical and infection complications such as occlusion, dislodgment, rupture, bacteremia, and tunnel exit-site infection are the main causes of hospitalization for patient treatment and/or for premature removal of the CVC [4, 9]. In order to prevent CVC

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complications, every team involved in CVC management must define the standard procedures to adopt during CVC life and periodically re-assess them to evaluate their efficacy and the need for modification [10].

Our center adopted written procedures and set up educational programs to improve CVC standard care more than 10 years ago and, thereafter, decided to monitor their efficacy by a prospective recording of complication episodes year by year. We present here the results of this 10-year data collection that is the largest pediatric series so far reported on the incidence and type of complication of a partially implanted CVC and on the frequency of premature loss of the CVC due to complications.

## Patients and methods

The study included prospectively all the pediatric and adolescent patients, aged 0 to 18 years, affected by malignant or non-malignant hematology or oncology diseases who needed the positioning of long-term, partially or totally implantable, tunneled, open-ended, CVCs for chemotherapy or hematopoietic stem cell transplantation (HSCT) purposes. The study period was from January 1st 2000 to December 31st 2009 whereas the follow-up data are as at December 31st 2011.

Signed informed consent was obtained by the parents both for CVC insertion and the anonymous use of patient demographic and clinical data for research purposes in accordance with Italian privacy policy. The study was approved by the local ethics committee. This comprehensive analysis also included data on 129 and 203 CVCs previously reported in two different reports [6, 9]. The study was part of an internal program of implementation of the policies for daily CVC maintenance care, and for prevention and treatment of CVC complications. The study was preceded by the preparation of common written center policies for CVC management by a multidisciplinary committee composed of nurses, pediatric hematologist, pediatric surgeon, anesthetist, and infectivologist. The methodology used to define CVC policies was based on three steps: (1) review of literature available as of 2000, (2) revision by discussion of internal procedures already existing, and (3) writing the revised policies and presentation to all components of the team. The prospective collection of data regarding type and number of CVCs and their complications was adopted as an internal method of monitoring the efficacy of interventions. The tools used for this purpose were (a) a form recording the characteristics of any CVC inserted (type, vessel incannulated, body site, CVC French, number of lumens, early complications) with the essential patient demographic and clinical information (age, sex, diagnosis, indication for CVC, phase of therapy); this form was completed by a trained nurse in the first week after CVC positioning and transferred to a database by a data manager; (b) common

written policies regarding medication of the CVC exit-site, CVC maintenance flushing, and modality to check the CVC functioning at every use; these instructions were adopted by all of the nursing team working in the stem cell transplant unit, hematology and oncology inpatient and outpatient clinics, and also illustrated and distributed to doctors and nurses of referral network hospitals that cooperate in treating the patients; (c) a form recording complications by type (infection, thrombosis, malfunctioning) filled in by nurses or physicians who first made the diagnosis.

## CVC insertion and maintenance care

The CVC was inserted in the operating theater by an experienced pediatric anesthetist or surgeon who used a percutaneous or open cutdown approach according to standard procedures [9, 11]. The open cut was preferred to the percutaneous approach in patients at major risk of bleeding complications or pneumothorax such as (a) those requiring daily platelet transfusion to maintain a count  $>50 \times 10^9/L$ , (b) a second or third insertion, or, (c) in case of failure of vein cannulation by percutaneous technique. From January 2005, both techniques were modified by introducing the Sri Paran method to improve the fixation of the CVC to the chest wall [12] while the blind percutaneous venipuncture (landmark venipuncture) was substituted by ultrasound-guided venipuncture from 2007 [13]. No perioperative antimicrobial prophylaxis was adopted for CVC implantation.

CVC maintenance care was handled by trained pediatric nurses and consisted of flushing the CVC with 3 mL of normal solution and heparin 200 IU/mL twice a week by using a standard CVC cap. This procedure differed only in 101 patients who constituted the experimental arm of a randomized study on two different modalities of flushing CVCs performed at our center from January 2003 to January 2005. That study compared flushing with normal saline at least weekly (experimental arm), by using a positive-pressure CVC valve cap device (CLC 2000, ICU Medical Inc), versus flushing with normal saline and heparin (control arm) at least two times a week [9]. The skin care at CVC exit remained constant for the whole study period and consisted of weekly cleansing of the CVC exit-site with a 10 % povidone-iodine solution followed by covering with a sterile gauze dressing. Moreover, strict aseptic techniques and scrupulous hand hygiene were observed always in positioning and handling the CVC. Table 1 shows the main rules put into practice by our procedures.

After CVC insertion, the parents and/or patients received a diary in which every flushing, exit-site medication, and complication of the CVC was dated, described, and signed by the health personnel, i.e., nurse or physician who performed the assessment, made the diagnosis of the complication, performed the intervention, or prescribed the treatment. This diary and, for completeness of data, the clinical charts were

**Table 1** Main rules adopted for central venous catheter maintenance

1. Assessment of line functionality and dressing site daily if inpatient or, if outpatient, every 2–3 days
2. Hand washing, sterile gloves and aseptic technique for all catheter entries
3. Cap scrubbed with 10 % povidone-iodine solution for each entry
4. Sterile gloves and mask worn by provider/assistant
5. Cap connection site scrubbed with 10 % povidone-iodine solution
6. Dressing/needle site scrubbed with 10 % povidone-iodine solution
7. Change gauze dressings every 7 days or before in case of soiled, dampened, loosened
8. Use of prepackaged dressing change kit
9. Replace administration sets, including add-on devices at 96 h, unless soiled or suspected to be infected
10. Replace tubing used to administer blood, blood products, or lipids at 24 h interval.
11. Change caps at 72 h (or 7 days if pressure-positive device used)
12. Use of prepackaged cap change kit

reviewed by a trained nurse on each admission to, or discharge from, the ward or outpatient clinic to check that any CVC complications were captured. Data on CVC complications, i.e., date, type of CVC, type of complication, treatment, and outcome were recorded on a specific form and were signed by the trained nurse. All CVC complication forms were reviewed by the data managers for completeness and consistency before storage into the database and analysis of the results.

### Definition and management of CVC-related complications

A standard approach to the diagnosis and treatment of a CVC-related infection was adopted.

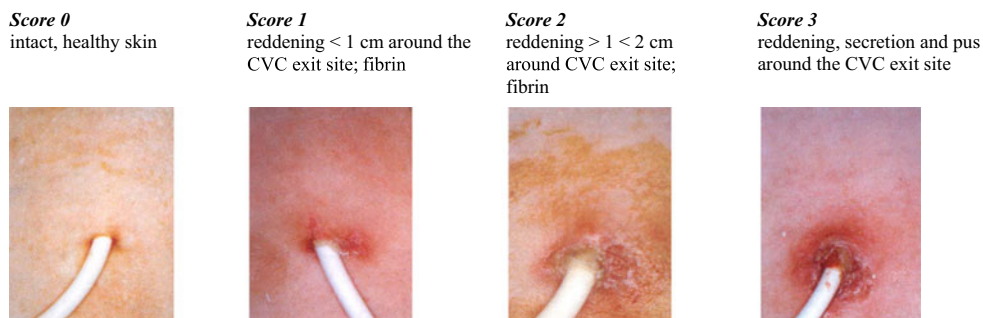
**CVC exit-site infection** We set up a visual score to define the severity of CVC exit-site infection and to guide the intervention. The score comprised four steps of severity, from 0 to 3, as indicated in Fig. 1. CVC exit-site infection was managed according to the algorithm showed in Fig. 2. Any CVC exit-site infection was treated more frequently, i.e., every 1 to 2 days, by cleansing the CVC exit-site with povidone-iodine solution

and changing the sterile dressing. Topical antibiotic treatment was performed, if needed, according to the results of the skin swab culture. The exit-site infection was monitored visually and microbiologically, if the swab was positive initially, until resolution or for at least 7 days, before a decision to remove the CVC was made.

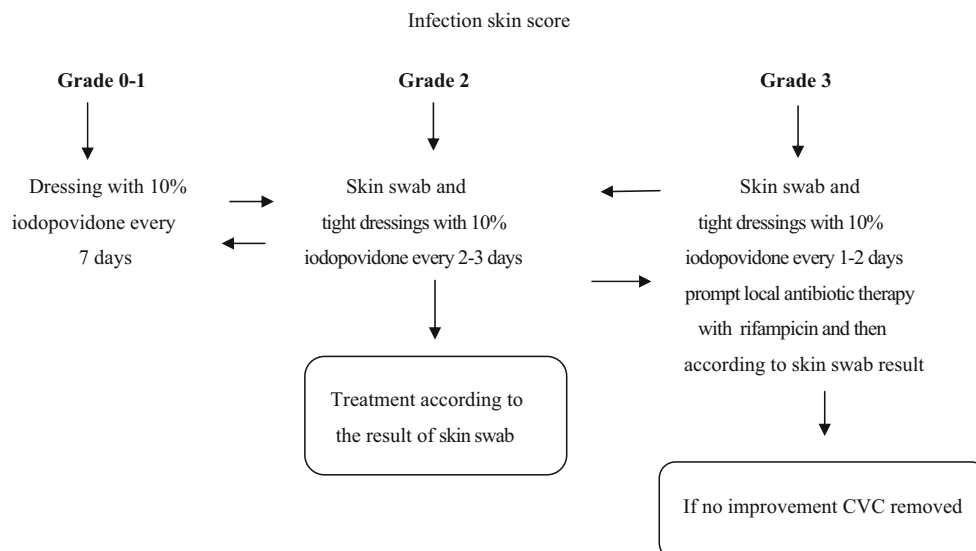
**Tunnel infection** This included any inflammation that extended more than 2 cm beyond the CVC exit-site or along the CVC subcutaneous tunnel. Diagnostic procedures included taking a skin swab and CVC-blood cultures. This complication required prompt empiric antibiotic treatment that was continued for at least 3 days before deciding whether or not to remove the CVC or until resolution.

**CVC-associated bacteremia or fungemia** This was defined as one or more blood cultures positive for bacteria or fungus obtained through a CVC in patients with fever ( $>38\text{ }^{\circ}\text{C}$ ) or other signs of infection, i.e., chills or hypotension. According to our standard practice, all febrile patients were investigated with one set of blood cultures obtained from each CVC lumen and peripheral vein; in case of inability to access a peripheral vein (severe hypotension or shock, infant baby, obesity), two sets of blood cultures were drawn from the CVC after a time interval of 15–30 min. Subsequently, they were treated promptly with empiric antibiotics, i.e., the combination of teicoplanin and a third-generation cephalosporin (mainly ceftazidime or cefipime); amikacin was added in the case of severe neutropenia (polymorphonuclear [PMN] cells  $<0.5 \times 10^9/\text{L}$ ) [8]. Adjustments were made, if necessary, according to the sensitivity testing on the organisms isolated from the blood culture. The treatment was continued until resolution of the infection or for at least 3 days before deciding whether or not to remove the CVC, or immediately in case of CVC-related septic shock.

**Mechanical complications** These included dislocation of the CVC tip or external migration of the cuff, fracture, or accidental CVC self-removal by the patient. The diagnostic evaluation was based on the visual and manual assessment of the position of the Dacron cuff and a chest X-ray or line contrast

**Fig. 1** CVC exit-site skin infection score

**Fig. 2** Algorithm for the management of central venous catheter exit-site infection



study with enhancement medium to rule out CVC dislodgement, breakage, or leakage. A fracture of the external part of the CVC was repaired whenever possible; otherwise, the CVC was removed if it was a fracture of the internal portion of the CVC.

**Malfunction** This diagnosis was based on difficulty, i.e., partial occlusion or complete occlusion resulting in inability to withdraw blood and/or infuse liquids through the CVC despite postural changes and in the absence of thrombosis or other mechanical complications. Treatment was based on one or two administration(s) of 10,000 IU of urokinase left in the CVC lumen for 2 h [9, 14, 15]. Sudden onset of CVC malfunction during or immediately after the infusion of drugs, blood components, or parenteral nutrition was considered a result of the precipitation of crystals or the formation of microaggregates among the infused components. In these cases, alcohol or hydrochloric acid was used, as reported elsewhere [16]. If urokinase and/or alcohol or hydrochloric acid failed to restore CVC patency, the CVC was removed.

**CVC-related thrombosis** When suggested by clinical symptoms, i.e., swelling, pain, or pulmonary embolism, color-Doppler ultrasound, computed tomography, or magnetic resonance imaging was used for the noninvasive diagnosis of CVC-related thrombosis. Treatment was based on published guidelines for antithrombotic therapy in cancer patients [17].

### Statistical analysis

Descriptive statistics were reported for the main demographic and clinical characteristics of patients as well as type of CVC and CVC complications. Median and range were used in case of continuous data, frequency, and percentage in case of discrete variables.

Cumulative incidence of mechanical complications, malfunction, exit-site and tunnel infection, CVC-associated bacteremia, CVC-related thrombosis, and pneumothorax was calculated only for the first CVC and estimated from the date of CVC insertion to the date of complication or to the date of latest follow-up. CVC survival was also calculated considering the time elapsed from CVC insertion to CVC premature removal due to complication or the date of the last follow-up.

The Kaplan-Meier method was used and differences between groups were compared by log-rank test. Impact of the main host- or CVC-related characteristics (gender, age at insertion, type of diagnosis, type of vessel accessed, body side of CVC access, modality of insertion, and number of lumen) on the different types of complications and on premature removal of the CVC was analyzed. After verifying the assumption of proportional hazards, univariate and multivariate Cox regression models were estimated taking into account the first event. If several recurrent complication episodes occur, an extension of the Cox proportional hazards model for recurrent events (the PWP Gap-time model) was applied [18]. Hazard rate (HR), 95 % CI, and two-sided *p* values were calculated. The level of significance was set at  $\alpha < 0.05$ .

### Results

Over a 10-year period, 919 patients (57.3 % males and 42.7 % females) were included in the study: 538 patients (58.5 %) were affected by leukemia or lymphoma, while 381 patients (41.5 %) were affected by solid tumor or non-malignant disease. A total of 1161 newly placed long-term CVCs were inserted for a total of 413,901 CVC-days of observation. The vast majority of CVCs were partially implanted, open-ended, Broviac-Hickman type CVC (95 %). Table 2 lists main patient and CVC characteristics.

**Table 2** The main characteristics based on type of CVC, modality of insertion, and incannulated vessel are shown

Number of CVCs	Total (N= 1161) N (%)
Age at positioning (years)	
<median (6.1y)	591 (50.9)
≥median (6.1y)	570 (49.1)
Modality of insertion	
Percutaneous	726 (62.5)
Surgical	365 (31.4)
Percutaneous/surgical	70 (6.0)
Type of CVC	
Broviac-Hickman	1114 (96)
Port	46 (4.0)
Other	1 (0.1)
Lumen no.	
Single	649 (55.9)
Double	512 (44.1)
French diameter	
<7	612 (52.7)
≥7	547 (47.1)
Missing	2 (0.2)
Type of vessel accessed	
Jugular	975 (84.0)
Subclavian	136 (11.7)
Other	9 (0.8)
Missing	41 (3.5)
Body side of CVC access	
Right	1016 (87.5)
Left	102 (8.8)
Missing	43 (3.7)
CVC insertion operator	
Surgeon	406 (35.0)
Anesthetist	755 (65.0)

Overall, 1024 complications were recorded, which was equivalent to 2.47 per 1000 CVC-days. Table 3 lists the types

of complication, their incidence, and the removal rate. The incidence of complications ranged from 0.5 % for pneumothorax to 42 % for malfunction/occlusion, respectively. The malfunction/occlusion episodes were 488 and occurred at a median time of 75 days from insertion of CVC, range 0–1303. They were classified as malfunction for the difficulty to withdraw blood or infuse solutions through the CVC in 292 episodes (60 %) and as complete CVC occlusion in 192 episodes (39 %). In four cases, the type of malfunction was not reported. Despite their high frequency, malfunction/occlusion complications were managed successfully in most cases and, therefore, were associated with a very low rate of CVC removal (2.3 %). Conversely, mechanical complications, affecting 18.3 % of CVCs, were associated with the highest premature removal rate (77.4 %) and represented 74 % of all CVCs removed due to complications (164 of 223). Mechanical complications, classified as dislocation (80 %), fracture (16 %), kinking (4 %), occurred at a median time of 61 days, range 0–818 from insertion. In six cases (3 %), these episodes happened early, by 48 h from insertion.

Bacteremia affected 14.8 % of CVCs and caused a CVC removal rate of 18.6 %. Among the 172 episodes, 107 (62 %) were caused by Gram positive, 49 (28 %) were caused by Gram negative, two (1 %) were polymicrobial Gram positive/Gram negative and twelve (7 %) were fungemias, unknown in two cases. These episodes occurred at a median time of 98 days, range 0–1297, from insertion of CVC. Among the Gram positive bacteria, the most frequent strain was *Staphylococcus epidermidis* and among the Gram negative bacteria, the most frequent strain was *Escherichia coli*. The list of all bacteria cultured from the blood is shown in Table 4.

Exit-site/tunnel infection affected 11.5 % of CVCs and resulted in a removal rate of 9.7 %. There were 134 episodes of exit-site infection which were diagnosed at a median time from CVC insertion of 62 days, range 2–640. According to our score, they were classified as grade 1 in 38 episodes, grade 2 in 69 episodes, grade 3 in 18 episodes, whereas the score was not known in 9 episodes. The CVC removal rate was

**Table 3** Incidence frequency of complications expressed as absolute number, percentage of number of CVCs, rate per 1000 CVC-days of utilization, and percentage of CVCs removed

Type of CVC complication	Absolute number (N)	N/100 CVC <sup>a</sup>	N/1000 CVC-days <sup>b</sup>	CVC removal N (%)
Malfunction/occlusion	488	42.0	1.179	11 (2.3)
Dislodgement/rupture/kinking	212	18.3	0.512	164 (77.4)
Bacteremia	172	14.8	0.416	32 (18.6)
Exit-site/tunnel infection	134	11.5	0.324	13 (9.7)
Thrombosis	10	0.86	0.024	3 (30.0)
Pneumothorax	6	0.52	0.014	0 (0.0)

CVC central venous catheter

<sup>a</sup> Total number of CVCs inserted = 1161

<sup>b</sup> Cumulative number of CVC-days of observation = 413,901

**Table 4** Type of germs isolated for each episode of CVC infection

Germs	Total (N= 172) Number of episodes
<b>Gram positive</b>	
<i>Coagulase-negative staphylococci</i>	78
<i>Staphylococcus aureus</i>	9
Gram positive rods <sup>a</sup>	8
<i>Streptococcus</i> spp.	7
<i>Enterococcus</i> spp.	5
Total	107
<b>Gram negative</b>	
<i>E. coli</i>	12
<i>Pseudomonas</i> spp.	15
<i>Enterobacter</i> spp.	13
Non-fermentative gram negative <sup>b</sup>	9
Total	49
<b>Fungemias</b>	
<i>Candida albicans</i>	2
<i>Candida non-albicans</i> <sup>c</sup>	6
<i>Fusarium</i> spp.	2
Other yeasts <sup>d</sup>	2
Total	12
<b>Gram positive and Gram negative</b>	
<i>Enterococcus faecalis</i> and <i>Pseudomonas</i> spp.	1
<i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Enterococcus fecalis</i>	1
Germ not specified	2

<sup>a</sup> This group included *Corynebacterium* spp. 3, *Corynebacterium jeikeium* 1, *Bacillus* spp. 2, *Lactobacillus* 1, *Nocardia* spp. 1

<sup>b</sup> This group included *Klebsiella* spp. 4, *Stenotrophomonas maltophilia* 2, *Alcaligenes xylosoxidans* 2, *Acinetobacter* spp. 1, *Capnocytophaga* spp. 1, *Chryseobacterium meningosept* 1, *Flavimonas oryzihabitans* 1, *Flavobacterium* spp., *Neisseria sicca* 1, *Salmonella enteridis* 1, *Salmonella typhimurium* 1

<sup>c</sup> This group included *Candida parapsilosis* 4, *Candida krusei* 1, *Candida sake* 1

<sup>d</sup> This group included *Geotrichum capitatum* 1, *Trichoderma longibrachiatum* 1

higher in grade 3 exit-site/tunnel infection (28 %) vs. episodes with grade 1 or 2 (3 %),  $p=0.001$ .

CVC thrombosis and post-insertion pneumothorax were the least frequent complications, 0.86 % and 0.52 % respectively, but thrombosis, although rare, was associated with the highest CVC removal rate of 30 %.

### Incidence and risk factor analysis

The cumulative incidence of mechanical complications was 24.5 % (95 % CI 20.7, 28.8). A younger age <6.1 years at CVC insertion was the only risk factor for the occurrence of mechanical complications: HR 1.8 (CI 1.3–2.4),  $p=0.0006$ .

Second or further events occurred in only 16 of the total episodes (8 %); thus, no recurrent event analysis has been performed.

The cumulative incidence of CVC-associated bacteremia was 17.1 % (CI 13.9, 20.8). In multivariate analysis, a double lumen CVC and the surgical modality of CVC insertion were the factors significantly associated with this complication, as follows: double lumen CVC: HR 3.1, CI 2.1–4.6,  $p<0.0001$ ; surgical modality of CVC insertion: HR 1.5, CI 1.0–2.2,  $p=0.03$ ). Due to the low number of recurrent events, only the first episode was considered for this analysis.

The cumulative incidence of exit-site/tunnel infection was 13.3 % (CI 10.6, 16.5). In multivariate analysis, the risk factors for this type of complication were a double lumen CVC (HR 2.1, CI 1.4–3.2,  $p=0.0003$ ) and a diagnosis of leukemia or lymphoma (HR 1.8, CI 1.1–2.8,  $p=0.01$ ).

The cumulative incidence of malfunction/occlusion was 36.0 % (CI 31.9, 40.4). In multivariate analysis, the factor significantly associated with this complication was an age at positioning less than 6.1 years (HR 1.6, CI 1.2–2.0,  $p=0.0003$ ), the diagnosis of leukemia or lymphoma (HR 1.9, CI 1.4–2.4,  $p<0.0001$ ) and double lumen CVC (HR 1.33, CI 1.04–1.7,  $p=0.023$ ). A high number of recurrent malfunctions have been observed, but no significant associations were found among the variables analyzed.

Overall, premature removal was performed in 189 cases of 919 first CVCs, with a cumulative incidence of 29.2 % (CI 25.1, 33.8). The factors associated with this event were the surgical modality of CVC insertion (HR 1.4, CI 1.1–1.9,  $p=0.0153$ ) and an age at CVC positioning less than 6.1 years (HR 1.6, CI 1.2–2.1,  $p=0.0025$ ). Table 5 summarizes the results of the analysis of risk factors.

### Discussion

The CVC is an essential tool to safely administer intravenous therapy in hematology and oncology patients who undergo chemotherapy or hematopoietic stem cell transplantation. However, CVC life can be affected by complications that may require its premature removal, or necessitate hospitalization, increasing health costs for patient treatment and/or presenting a life-threatening risk. Several authors have demonstrated that CVC-related morbidity can be reduced, especially that due to infectious complications, by adopting best-practice procedures and checking their implementation over time among the team members involved in the CVC maintenance [7, 10, 19]. Since 2000 our center established a protocol for insertion, maintenance care, diagnosis and treatment of CVC complications by a multidisciplinary working group. Most of the current set of rules recommended to prevent infection were part of the adopted protocol of CVC handling and care [10, 20]. The main difference was the absence from our procedures of chlorhexidine solution for skin antisepsis and the use of

**Table 5** Risk factor analysis of central venous catheter complications

Type of complications	Gender M vs. F (95 % CI)	Age at insertion <6.1 years vs. ≥ (95 % CI)	Diagnosis leukemia/ lymphoma vs. solid tumor/other (95 % CI)	Vessel incannulated Jugular vs. subclavian/other (95 % CI)	CVC body side Left vs. right (95 % CI)	Insertion technique Percutaneous vs. surgical (95 % CI)	Number of lumens Double vs. single (95 % CI)
Mechanical complications	n.s.	<i>p</i> 0.0004 Multivariate HR 1.75 (1.27–2.41), <i>p</i> 0.0006	n.s.	n.s.	n.s.	n.s.	n.s.
Exit-site/tunnel infection	n.s.	n.s.	<i>P</i> 0.0140 Multivariate HR 1.77 (1.12–2.79), <i>p</i> 0.0137	n.s.	<i>P</i> 0.0438	<i>P</i> 0.05	<i>P</i> 0.0005 Multivariate HR 2.14 (1.42, 3.24), <i>P</i> 0.0003
CVC-associated bacteremia	n.s.	n.s.	<i>P</i> 0.0654	n.s.	n.s.	<i>p</i> 0.01 Multivariate HR 1.51 (1.04, 2.19), <i>p</i> 0.0301	<i>p</i> < 0.0001 Multivariate HR 3.13 (2.11, 4.65), <0.0001
Malfunction/occlusion	n.s.	<i>p</i> 0.0049 Multivariate HR 1.58 (1.23, 2.04), <i>p</i> 0.0003	<i>p</i> < 0.0001 Multivariate HR 1.85 (1.42, 2.42), <i>p</i> < 0.0001	n.s.	n.s.	n.s.	<i>p</i> 0.0839 Multivariate HR 1.33 (1.04, 1.70), <i>p</i> 0.023
Premature CVC removal	n.s.	<i>p</i> 0.0019 Multivariate HR 1.58 (1.18, 2.13), <i>p</i> 0.0025	n.s.	n.s.	n.s.	<i>p</i> 0.0109 Multivariate HR 1.43 (1.07, 1.90), <i>p</i> 0.0153	n.s.

n.s not significant

10 % povidone-iodine solution. This is explained by the fact that at the beginning of the study, the superiority of chlorhexidine solution over 10 % povidone-iodine solution was not yet clear and, importantly in the following years, the delayed adoption of chlorhexidine solution in our hospital. In fact, povidone-iodine solution has been associated with difficulty or delay in visually determining the signs of local inflammation and with inactivation by a protein-rich exudate. A meta-analysis on eight randomized studies involving 4143 central lines showed that chlorhexidine gluconate reduced the risk for CVC-associated bacteremia over povidone-iodine by 49 % [21], but most of the evidence derived from studies with short- or medium-term or peripheral CVCs while this superiority with tunneled long-term CVCs is not yet clear. In a recent prospective study, Yamamoto et al. found that in adult patients with long-term CVCs, the use of 1 % chlorhexidine-gluconate ethanol versus 10 % povidone-iodine for skin antisepsis of the CVC exit-site was associated with CVC-associated blood stream infections of 0.75 vs. 3.62 per 1000 CVC-days, respectively [22]. Interestingly, the use of povidone-iodine solution in our study was associated with a bacteremia rate of 0.4/1000 CVC-days that is even lower than that reported with chlorhexidine gluconate solution in the Yamamoto study. A recent randomized study performed in French intensive care units showed that skin antisepsis with

chlorhexidine-alcohol versus povidone iodine-alcohol significantly reduced the rate of intravascular catheter-related infection but this effect was not evident for CVCs [23].

Although infections are usually believed to be the principal cause of CVC morbidity, mechanical complications and malfunctioning were in fact the most frequent complications accounting for 1.7 complications/1000 CVC-days. Overall, CVC malfunctioning did not have severe consequences for the patient because the protocol adopted to restore the patency of the CVC, based on urokinase administration, was successful in most cases and CVC removal was needed in only 2.3 % of episodes. Despite the limited prospective data available, the use of urokinase to restore the patency of a CVC is considered the most effective treatment together with alteplase with the advantage of a lower cost [24]. The risk factors for malfunction/occlusion complications, i.e., age range <6 years, diagnosis of leukemia/lymphoma, double lumen CVC, are consistent with the fact that all three situations require a high number of CVC accesses per day and/or expose the patient to procoagulant drugs, such as prednisone, dexamethasone or L-asparaginase, which can favor the formation of fibrin inside the CVC or fibrin cap on the tip of the CVC [4, 5, 9]. Considering the very low rate of CVC-related thrombosis, i.e., 0.86 % of CVCs and 0.024 episodes/1000 CVC-days, and the fact that malfunction and occlusion can be managed with urokinase

treatment, our findings agree with the current recommendation that anticoagulation with low molecular weight heparin or vitamin K antagonists is not needed for prophylaxis of CVC-related thrombosis and occlusions [25]. However, mechanical complications were rarely repairable, comprising 77.4 % of episodes of premature loss of the CVC. An age younger than 6 years was the only risk factor for this complication because in the infant, or in young babies, it is difficult to prevent sudden traction of the CVC or to monitor movements or positions that could pull out the CVC. According to these findings, the age range group of 0–6 years could benefit from the adoption of a sutured secure device provided that it is tolerated by the patient [13]. However, we highlight that the evidence of efficacy of this type of device (prolongation of dwell time, reduction of dislodgments, and reduction of infections) is limited to non-tunneled peripheral CVCs [26].

Systemic and exit-site/tunnel infections represented the third- and the fourth-ranked causes of CVC complications and the second- and third-ranked causes of CVC premature removal, respectively. Indeed, in this study, one out of five CVCs and one out of ten CVCs with bacteremia or exit-site/tunnel infection were removed, respectively. In particular, CVC-associated bacteremia may be life-threatening for the patient, and it is always associated with a cost increase for the health system and with a prolongation of the length of patient hospital stay [27]. Although still debated among experts, our internal policy to draw blood cultures both from CVC and peripheral vein at the onset of fever is supported by the demonstration that up to 12 % of true bloodstream infections may have the germ isolated only from peripheral vein [28]. Moreover, the use of a double set of blood cultures makes it possible to define a CVC-associated bacteremia without removing the CVC by recording, if available, the different times of positivization of cultures. Several strategies have been experimented with over the years to keep the incidence of CVC BSI as low as possible, ranging from the use of antibiotic/antibacteric-coated CVCs to flushing or locking the CVC with urokinase or antibiotic solutions [29, 30]. Despite these interventions resulting in a reduction of the incidence of CVC-related infections compared to controls, we and other pediatric groups reported an incidence rate of CVC-related infections comparable to that reported in the experimental arms simply by establishing a precise best-practice set of rules to prevent CVC infection from the daily handling for blood sampling or therapy administration [4, 5, 9]. The incidence of 0.4/1000 CVC-days for CVC-associated bacteremia found in this study is even better than that reported recently in a pediatric prospective study in which CVC-related blood stream infections decreased from 2.29 to 0.56/1000 CVC-days within 2 years through the implementation of a set of measures including the use of chlorhexidine gluconate [10]. Our better results may depend on the fact that we report the complications as events per 1000 utilization days whereas other authors

report the events per 1000 inpatient days [10, 31]. In multivariate analysis, surgical insertion by cutdown technique and dual lumen CVC were the risk factors for CVC-associated bacteremia. In our experience, both characteristics were typical of patients at higher risk of infectious complications because a dual lumen CVC was used in patients eligible for high dose chemotherapy or stem cell transplant whereas surgical positioning of CVC was reserved for patients at major risk of bleeding because of the status of the underlying disease.

In this study, we paid special attention to the management of the minor infectious complications, such as the exit-site/tunnel infections, by establishing “a priori” a protocol of intervention based on a visual score of severity. This type of complication is usually under-investigated, compared with CVC-associated bacteremia, despite the fact that it can result, though more rarely, in the loss of the CVC. We found an overall incidence of 0.3 episodes of exit-site/tunnel infection/1000 CVC-days that compared favorably with the figure of 2.59 episodes/1000 CVC-days reported by other authors in the past [31]. Notably, this complication was recently reported as high as 3.74 episodes/1000 CVC-days in pediatric patients with a tunneled CVC for chronic hemodialysis, when routine skin medication was performed with iodine-povidone [32]. The factors predicting a high risk of occurrence of this type of infectious complication were an underlying diagnosis of leukemia/lymphoma and the need for a dual lumen CVC. Both factors are usually present in patients who develop a prolonged, severe leukopenia and a high grade of immunosuppression due to chemotherapy.

The risk factors for premature removal of CVC, i.e., younger age and the surgical technique of insertion, reflect the most important complications for the survival of CVCs, which are the mechanical complication and CVC-related bacteremia. This suggests that a better fixation of the CVC could increase the probability of a longer CVC-life at least in younger patients, while the poorer outcome of CVCs inserted by the cutdown technique reflects the worst underlying clinical conditions and the higher bleeding risk of this group of patients.

In conclusion, we found that using a best-practice set of rules for a decade resulted in us keeping low the number of complications that may affect the CVC or the patient’s life without introducing into the practice flushing with antibiotics or using an antibiotic-coated CVC. Future prospective studies are needed to assess whether the benefit found in non-tunneled CVCs in using skin antisepsis with chlorhexidine solutions or sutured secure device is applicable also to long-term tunneled CVCs.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.



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