Central venous catheter-related complications in children with oncological/hematological diseases: an observational study of 418 devices

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Background: The use of indwelling central venous catheters (CVCs) has become commonplace in the management of children undergoing anticancer treatment. Several types of CVC are available, while information on complications observed in children is scarce. We describe the experience of two tertiary care centers in Italy that prospectively followed up three types of CVC used at both institutions over a 30-month period.

Patients and methods: Between January 2000 and May 2002, double-lumen (DL) or single-lumen (SL) Hickman–Broviac (HB) catheters, and single-lumen pressure-activated safety valve (PASV) catheters were used and prospectively evaluated. Four types of possible complication were defined a priori: mechanical, thrombotic, malfunctioning and infectious.

Results: Four hundred and eighteen CVCs (180 SL-HB, 162 DL-HB and 76 PASV) were inserted in 368 children, for a total of 107 012 catheter days at risk of complication. At least one complication occurred while using 169 of the devices (40%): 46% of the DL-HB, 46% of the PASV and 33% of the SL-HB ($P = 0.02$) catheters. Subjects with hematological malignancies or non-malignant diseases had significantly more complications than those with solid tumors ($P < 0.0001$). Overall, 234 complications were documented: 93 infectious [complication rate per 1000 catheter days at risk (CR) = 0.87], 84 malfunctioning (CR = 0.78), 48 mechanical (CR = 0.45) and nine thrombotic (CR = 0.08). SL-HB had statistically fewer infectious complications, while PASV had more mechanical complications. In a multivariate regression model, the most significant risk factors for having a CVC complication were hematological disease [relative risk (RR) = 3.0; 95% confidence interval (CI) 1.8–4.8] and age <6 years at CVC insertion (RR = 2.5; 95% CI 1.5–4.1). As for the type of CVC, compared with SL-HB, the DL-HB catheter had a statistically significant two-fold increased risk of any complication (RR = 2.1; 95% CI 1.2–3.6), while the PASV catheter had a borderline RR of 1.8 (95% CI 1.0–3.6). Analysis by tumor type showed a higher risk of any kind of complication in patients with solid malignancies who had received a DL-HB catheter as compared with an SL-HB catheter (RR = 7.2; 95% CI 2.8–18.7).

Conclusions: CVCs may cause complications in up to 40% of patients, with type of CVC, underlying disease and patient age being the three main factors that affect the incidence of CVC-related complications. SL-HB catheters have the best performance.

Key words: central venous catheters, infections, surgical complications, thrombosis

Introduction

Indwelling central venous catheters (CVCs) guarantee a reliable vascular access, and are essential for the management of children undergoing anticancer chemotherapy or bone marrow transplantation [1]. However, they might present disadvantages [2], such as the risk of mechanical accidents [3, 4], thromboses [5] or infections [6], which may interfere with the course of treatment.

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The most frequently used CVCs in children with cancer are usually partially implantable, tunneled devices that may be either valved or not valved. The group of valved CVCs comprises those with a valved tip (Groshong) and those with a pressure-activated safety valve (PASV), which acts as an automatic clamp built into the hub of the catheter. The classical Hickman–Broviac (HB) catheter is an open-ended (non-valved), partially implanted device that may be either single (SL-HB) or double lumen (DL-HB).

To our knowledge, most of the literature on CVC-related complications refers to studies performed on adults [1, 7], and the literature that specifically focuses on children usually refers to studies with <200 devices [3, 4, 8–15].

In order to quantify the real impact upon the everyday practice of CVC-related complications observed in pediatric centers, we decided to evaluate prospectively the number and type of complications occurring in partially implanted, indwelling central venous catheters inserted over a 28-month period in a large cohort of children with onco/hematological diseases at two pediatric hospitals in Italy.

Patients and methods

All the CVCs consecutively inserted between January 2000 and May 2002 at the G. Gaslini (Genoa) and Regina Margherita (Turin) Children’s Hospitals, for the management of patients <18 years of age with hematological or oncological malignancies, or with other diseases requiring allogeic stem cell transplantation, were considered eligible for this study.

For the purposes of this study, four groups of possible complications were defined a priori: (i) mechanical; (ii) symptomatic thrombosis; (iii) malfunctioning; and (iv) infectious. In particular, a mechanical complication was defined as a CVC dislocation due to malpositioning of the catheter tip, or cuff migration, CVC rupture or accidental self-removal by the patient [4]. If right atrial thrombosis, pulmonary embolism, or deep venous thrombosis occurred, they were recorded as thrombotic complications. A malfunctioning event was defined as a difficulty in withdrawing blood and/or infusing fluids through the catheter that could not be solved by postural changes or by heparinized saline solution flushes in the absence of documented thrombosis [16]. Finally, infectious complications included CVC-related bacteremias, and tunnel or exit-site infections as defined by internationally accepted definitions [6, 17].

During the study period, three different types of right atrial, indwelling, partially implanted, tunneled silicone rubber catheters were inserted at the two hospitals in a non-randomized fashion. In general, subjects scheduled for stem cell transplantation received DL-HB, while single-lumen catheters (either SL-HB or PASV) were inserted in all other patients. Besides the specific medical indication of stem cell transplantation, the choice regarding the type of device to insert was based on the surgeon’s opinion and the availability of the catheter.

Catheter insertion into the upper venous system was always performed either by surgical venous cut-down or by the percutaneous technique. In case of venous cut-down, catheter insertion was accessed by surgical preparation of the external or internal jugular vein. Percutaneous CVC insertion was done using either the subclavian vein by the infracavicular approach, or the internal jugular vein. During placement, the correct position of the distal tip of the catheter (at the superior vena cava–right atrium junction) was checked by fluoroscopy, and a standard chest radiograph with the patient in the upright position was always obtained immediately afterwards [18, 19]. Maintenance procedures were always performed according to international recommendations [20], and employing a protocol approved by the Italian Association of Pediatric Hematology and Oncology (AIEOP). In particular, when not in use HB catheters were flushed three times a week with a heparinized solution, while PASV catheters were flushed with normal saline once a week. In any case, no antibiotic prophylaxis was performed with the flushing. The catheter exit-site dressing was changed once a week for all devices. Maintenance procedures were performed by trained pediatric nurses when the patient was in hospital and by parents when at home. Parents received specific training during the first weeks after CVC insertion, and were allowed to perform maintenance procedures only after having reached an adequate level of skill. Periodic re-evaluations were conducted.

With regard to each single catheter, data were recorded on type, date of positioning, age and underlying disease of the patient, date and type of any complication, date of the last examination, and cause of catheter removal, if applicable.

Statistical analysis

For each catheter, the total number of catheter days at risk (cdr) was calculated as the total number of days from insertion to last observation (last examination, removal or patient’s death, whichever occurred first). The observation period was censored on 31 May 2002. The complication rate (CR) per 1000 days was calculated as 1000 times the number of complications divided by the total number of cdr.

Univariate analysis was carried out to determine significant differences in frequency and type of complications among the three different CVC types and by the various risk factors that were taken into consideration. Age at CVC insertion was considered as a dichotomous variable, with 6 years (school age) being the cut-off between the two strata. A separate analysis has also been performed using age at CVC insertion as a continuous variable. Differences for categorical variables were tested using the Pearson χ² statistical test, while the Kruskal–Wallis test was used for continuous variables [21]. The number of complications for each catheter type was regarded as a Poisson variable and in a multivariate analysis, results were obtained using the Poisson regression model allowing for overdispersion and adjusting for age at CVC insertion and underlying disease [22]. The reasons why underlying disease was considered a risk factor and stratified accordingly were that treatment protocols for the three categories considered (i.e. solid tumor, hematological malignancies and non-malignant diseases) have, in general, different schedules and intensities, thus requiring different frequencies of catheter manipulation. In this analysis, the group of children with inborn errors and the group with hematological malignancies were pooled due to the small number of cdr and of events in the former group. Interaction between type of CVC and underlying disease was also assessed within the same model.

All parameters were estimated by the maximum likelihood method, and confidence intervals (CI) were calculated at the 95% level [23]. All statistical tests were two-tailed and the tests were considered significant when P <0.05.

The cumulative probability of CVC remaining in place with no complications was calculated using the Kaplan–Meier method, and comparisons among the three CVC types were carried out using the log-rank test. For this analysis, only the first complication, if any, was calculated as an event. With regards to calculation of the overall CVC survival, only removals due to complications were considered events. All the other removals, such as those carried out because of other medical decisions (end of therapy, death of the subject, other), were censored at the date of removal. Stata and Statistica software packages were used for the analyses.
Results

During the study period, 418 indwelling central venous catheters (180 SL-HB, 162 DL-HB and 76 PASV) were consecutively inserted in 368 children (212 males, 156 females) with hematoo-oncological diseases; 51 had more than one CVC inserted. Among them, 190 had solid tumors, 162 had acute leukemia or lymphoma, and 16 had non-malignant disease requiring stem cell transplantation. Patients’ age at CVC insertion ranged between 21 days and 17 years, with a mean age of 7.3 years (95% CI 6.8–7.8); 203 CVC (49%) were inserted in children <6 years of age. The overall length of observation ranged between 3 and 868 days for a total of 107 012 catheter days. Table 1 reports on the number, type of CVC and length of observation, by underlying disease, of patients enrolled into the study.

Overall, 234 complications were observed in 169 devices (40% of all devices) with a maximum of six complications in two CVCs. The overall complication rate was 2.2 (95% CI 1.92–2.48): it was 0.87 (n = 93) for infectious complications; 0.78 (n = 84) for malfunctioning; 0.45 (n = 48) for mechanical complications; and 0.08 (n = 9) for thrombotic complications (Table 2).

Differences existed among the three types of CVC with regard to the frequency of the various complications observed (Table 2). In fact, infections were most frequently reported among DL-HB catheters (56 of 114; 49% of all complications in this type of CVC), while malfunctioning was more frequent among SL-HB (35 of 75; 47%) and mechanical complications occurred more frequently in PASV catheters (16 of 45; 36%) (P = 0.0074). Thrombotic complications were rare (only nine events overall), with no differences in incidence among the three types of CVC that were taken into consideration. The cause-specific complication rates were also different among the three types of CVC (Table 2). In fact, infections were less frequent among SL-HB catheters (infection rate = 0.46), with a statistically significant difference only as compared with DL-HB ones (infection rate = 1.40) (P < 0.001). The CR for mechanical complications was higher among SL-HB catheters (0.96), with a statistically significant difference only as compared with SL-HB ones (0.28) (P < 0.001). No differences among the three CVC types were observed for rates of

- Infectious complications: 49% (95% CI 42.6–56.5) for DL-HB, 67% (95% CI 57.0–76.6) for SL-HB, and 35% (95% CI 25.1–47.0) for PASV
- Malfunctioning complications: 67% (95% CI 56.6–78.0) for DL-HB, 43% (95% CI 32.7–55.0) for SL-HB, and 77% (95% CI 65.6–89.0) for PASV
- Mechanical complications: 35% (95% CI 25.1–47.0) for DL-HB, 18% (95% CI 9.5–32.7) for SL-HB, and 50% (95% CI 33.8–67.1) for PASV
- Thrombotic complications: 9% (95% CI 4.5–15.5) for DL-HB, 4% (95% CI 0.9–8.7) for SL-HB, and 18% (95% CI 10.4–31.0) for PASV

Table 1. Number and type of CVC inserted in 368 children with hematological or oncological malignancies, or undergoing allogeneic bone marrow transplant (some children may have had more than one CVC inserted)

<table>
<thead>
<tr>
<th>Type of CVC</th>
<th>DL-HB [n (%)]</th>
<th>SL-HB [n (%)]</th>
<th>PASV [n (%)]</th>
<th>Total [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumors</td>
<td>66 (30.9)</td>
<td>113 (53.1)</td>
<td>34 (16.0)</td>
<td>213 (100)</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>80 (43.0)</td>
<td>65 (35.0)</td>
<td>41 (22.0)</td>
<td>186 (100)</td>
</tr>
<tr>
<td>Non-malignant diseases</td>
<td>16 (84.2)</td>
<td>2 (10.5)</td>
<td>1 (5.3)</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>162 (38.8)</td>
<td>180 (43.1)</td>
<td>76 (18.1)</td>
<td>418 (100)</td>
</tr>
<tr>
<td>Mean length of observation</td>
<td>247 (217–276)</td>
<td>279 (248–311)</td>
<td>219 (173–266)</td>
<td>256 (236–276)</td>
</tr>
<tr>
<td>Catheter days at risk</td>
<td>39 986</td>
<td>50 342</td>
<td>16 684</td>
<td>107 012</td>
</tr>
</tbody>
</table>

- DL-HB: double-lumen Hickman–Broviac
- SL-HB: single-lumen Hickman–Broviac
- PASV: pressure-activated safety valve

Table 2. Distribution and complication rates of CVC-related complications among different types of CVC

<table>
<thead>
<tr>
<th>CVC Type</th>
<th>Infectious [n (%)]</th>
<th>Malfunctioning [n (%)]</th>
<th>Mechanical [n (%)]</th>
<th>Thrombotic [n (%)]</th>
<th>Total [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL-HB</td>
<td>56 (49)</td>
<td>36 (32)</td>
<td>18 (16)</td>
<td>4 (3)</td>
<td>114</td>
</tr>
<tr>
<td>SL-HB</td>
<td>23 (31)</td>
<td>35 (47)</td>
<td>14 (19)</td>
<td>3 (4)</td>
<td>75</td>
</tr>
<tr>
<td>PASV</td>
<td>14 (31)</td>
<td>13 (29)</td>
<td>16 (35)</td>
<td>2 (4)</td>
<td>45</td>
</tr>
<tr>
<td>Overall</td>
<td>93 (40)</td>
<td>84 (36)</td>
<td>48 (20)</td>
<td>9 (4)</td>
<td>234</td>
</tr>
</tbody>
</table>

- RR in comparison to DL-HB catheters (P < 0.0001).
- RR in comparison to SL-HB catheters (P < 0.05).

CVC, central venous catheter; DL-HB, double-lumen Hickman–Broviac; SL-HB, single-lumen Hickman–Broviac; PASV, pressure-activated safety valve; cdr, catheter days at risk; RR, relative risk.
The overall catheter-specific CR was 2.85 for DL-HB, 2.70 for PASV, and 1.49 for SL-HB. The difference among the three types of CVC was statistically significant for SL-HB compared both with DL-HB ($P<0.001$) and with PASV ($P=0.002$). If the type of underlying disease was taken into consideration, the complication rate was 3.6 (95% CI 3.02–4.19) among children with hematological malignancies ($n=143$), 2.0 (95% CI 1.01–3.60) among those with non-malignant disease ($n=80$) ($P<0.001$) (likelihood ratio test). In a Poisson’s multivariate regression model that took into consideration the type of CVC, age at CVC insertion, and the underlying disease of the subject (Table 3), the most significant risk factors for CVC complications were having a hematological disease [relative risk (RR) 3.0] and being <6 years of age at CVC insertion (RR=2.6). In a separate analysis, for which age was treated as a continuous variable, the results did not change substantially and the risk of complications decreased by 7% with each extra year of age (data not shown). Regarding the CVC type, as compared with SL-HB, the DL-HB catheter had a statistically significant two-fold increased risk of any complication (RR=2.1; 95% CI 1.2–3.6), while PASV had a borderline RR of 1.8 (95% CI 1.0–3.6). This observational study was not randomized, and as it occurs in clinical practice, some types of catheters (e.g. DL-HB) were inserted more frequently under particular conditions (e.g. stem cell transplantation recipients). Therefore, further analysis was performed to evaluate any possible interaction between the type of underlying disease and type of CVC in the risk of developing any complications, using age at insertion as a confounder. A statistically significant interaction was observed between CVC type and tumor type ($P=0.0003$, likelihood ratio test). Thus the same analysis was performed, stratifying by type of underlying disease (Table 3), and a significant effect was observed ($P<0.001$, likelihood ratio test) in DL-HB catheters inserted in children with solid tumors, with a seven-fold increased risk compared with SL-HB catheters (RR=7.2; 95% CI 2.8–18.7).

The complication could not be resolved in 72 (31%) episodes, thus leading to catheter removal. In particular, it was required in 52% (25 of 48) of the mechanical complications, in 44% (41 of 93) of the infections, in 44% (four of nine) of thrombotic complications, and in 2% (two of 84) of malfunctioning. At the end of the present study, besides the 72 CVCs that had been removed due to complications, 164 further devices were no longer in place: 97 because of end of treatment, 51 because of death of the subject and 16 because of replacement with another type of CVC due to other medical indications. It should be noted that even though CVC abduction after death is not routinely performed in our centers, no death certificates referred to any CVC-related complication as the cause of death. Figure 1 reports the overall probability of survival of the CVC. In this analysis, only removals that were needed due to irresolvable complications were considered events. Overall, CVC survival after >800 days was estimated at 74.9% for SL-HB, 53.2% for PASV and 52.4% for DL-HB catheters. The difference among the three types of CVC was significant only with regard to the comparison between DL-HB and SL-HB ($P=0.01$), while there was no significant difference between PASV and SL-HB ($P=0.06$), or between PASV and DL-HB ($P=0.9$).

### CVCs with at least one complication

As mentioned before, the 234 complications were observed in 169 CVCs. Considering the catheter type, 45 of 162 (46%) DL-HB catheters, 35 of 76 (46%) PASV catheters, and 59 of 180 (33%) SL-HB catheters had at least one complication ($P=0.02$). If the underlying disease was taken into consideration, at least one complication was observed in 95 of 168 (51%) CVCs inserted in patients with hematological malignancies, in nine of 19 (47%) of those inserted in children with...
non-malignant diseases, and in 65 of 213 (30%) of those inserted in patients with solid tumors ($P<0.001$). Finally, 94 of the 203 CVCs inserted in children <6 years of age (46%) had at least one complication, compared with only 75 of the 215 inserted in patients ≥6 years (34%; $P=0.017$).

The interval between insertion and the first complication ranged between 0 and 724 days (median 52 days). Considering the three different CVC types, the median interval was 31 days (range 1–724) for PASV, 77 days (range 0–665) for DL-HB, and 62 days (range 1–565) for SL-HB; there were significant differences among them. The estimated probability of CVC survival without any complications after >800 days following CVC positioning was 55.8% for SL-HB, 36.6% for DL-HB and 32.6% for PASV catheters (Figure 2). The difference among the three CVC types was statistically significant ($P=0.004$). In particular the SL-HB catheter performed significantly better compared with the PASV ($P=0.012$) and DL-HB catheters ($P=0.006$), while no differences in the probability of developing a complication were observed between the SL-HB and PASV catheters.

Finally, 44 CVCs (11%) had more than one complication [24 DL-HB (15%), 12 SL-HB (7%), eight PASV (11%)], and in 20 the same type of complication occurred at least twice. In particular, 16 CVCs had more than one episode of malfunctioning or thrombosis for a total of 18 extra episodes, and eight CVCs had more than one infection, for a total of 11 extra infectious episodes. Among the 51 patients with more than one CVC inserted, only two had both CVCs with more than two identical complications (both infections).

**Discussion**

In this prospective, observational study of 418 partially implanted CVCs, for a total of >100 000 days of observation, we demonstrated that even by adopting internationally approved procedures for CVC management, complications occur in 40% of devices inserted in children with oncohemato-logic diseases, with an overall CR of 2.2. SL-HB catheters perform best (33% of complications, overall CR = 1.49), and catheters inserted in children with solid tumors and of school age (≥6 years) have the fewest complications.

Infections represent the most frequently reported complication, showing a rate of 0.87, which is lower than the mean 1.2 and 3.9 values reported in two literature reviews [24, 25].

The fact that DL-HB catheters had the highest rate of infectious complications is not unexpected, since these devices require a greater number of CVC manipulations, which has been shown to be strictly related to the risk of infections [26]. However, the rate of 1.4 for infectious complications that we observed among DL-HB catheters is lower than that reported in two retrospective studies on adults for this type of CVC [27, 28], which describe an infection rate up to 2.02. We believe that these satisfactory results may be, at least in part, due to the routine use of internationally approved standards for CVC maintenance, and to continuous surveillance of the hospital and home care of the devices. However, we cannot rule out that different study designs and populations may have had some influence on the results.

Catheter removal for complete resolution of the infection was required in 44% of the episodes. This percentage of removal is between the 29% and 67% reported in two other retrospective studies in children with cancer [29, 30]. These differences might in fact reflect different policies with respect to the definition and management of catheter-related infections. However, it should be emphasized that in our institutions we adopted the guidelines for the diagnosis and management of CVC-related infections implemented by the Infectious Disease Society of America [6]. Therefore, it is reasonable to assume that the percentage of CVC removals due to infection that we observed represents what would be expected under these conditions.

Malfunctioning events were the second most frequently reported complication, with no significant differences among the three types of CVC evaluated. This type of complication, however, has little impact on CVC life since it was solved in 98% of cases by the salvage protocols that employ urokinase, as previously reported [16], thereby leading to only 2% of CVC removals. Symptomatic thrombotic complications were rare, occurring in 2% of CVCs (nine of 418 events). This result confirms another of our previous retrospective studies [16]. Pooled together, thrombotic or malfunctioning events were recorded in 22% of CVCs (93 complications in 418 CVCs); this value is lower than the 25%–40% reported in the literature [31, 32].

We acknowledge that our definition of thrombotic complication is more restrictive than that used in other reports since it is based on clinical criteria alone. However, our strategy, which promptly calls for urokinase in malfunctioning catheters [16], likely prevented clot progression from becoming symptomatic. Therefore, we believe that the prompt use of urokinase in the management of a malfunctioning CVC that is refractory to postural changes and heparin flushes, is a safe and cost-effective approach which may have prevented the progression
of an undetectable thrombosis [33], and which also avoids the widespread use of more invasive diagnostic approaches in children [34, 35].

Mechanical complications represented 20% of all the events we observed, with a complication rate of 0.45, but in 52% of cases the catheter had to be removed. PASV catheters performed the worst in this respect, as shown by the sharp decline in CVC survival shortly after insertion (Figure 2). A possible explanation for this finding is that the size of the cuff in this type of catheter does not favor adhesion to the subcutaneous tissue. After this problem was first observed, the manufacturer provided a silicone device to place around the CVC to suture to the skin as an anchorage, but this did not prove to be as effective as expected (data not shown). Recently, Cesaro et al. reported mechanical complications to be the main cause of premature loss of CVC, especially in younger children [14]. In our experience, young age at CVC insertion has also been associated with a higher incidence of any complication. The observation that the younger the patient with the CVC, the greater the probability of a complication, could be at least partially due to a higher incidence of malfunctioning events linked to the small size of the CVC and to the increased risk of self-removal.

This study has also documented different complication rates between children with solid tumors and those with hematological diseases. This observation is not surprising since, at least with regard to infections, patients with acute leukemia have a higher incidence of CVC-related infections as compared with patients with solid tumors because they require a greater number of CVC manipulations for the treatment and management of chemotherapy-induced side-effects [36, 37]. As this prospective, non-randomized observational study allowed us to collect a sizable number of catheters and days of observation, we used multivariate analysis to study the role and interaction of some possible risk factors in the development of CVC-related complications. This analysis confirms that the most significant risk factors for developing any type of CVC-related complication include having a hematological disease, being <6 years of age at CVC insertion and having a DL-HB catheter inserted. However, since there are interactions between CVC type and the underlying disease of the patients, the stratified analysis by tumor and catheter type showed a significant, increased risk of any complications among DL-HB catheters inserted in children with solid tumors. This fact is probably due to our previous policy of inserting DL-HB catheters, even for the management of children with solid tumors scheduled for autologous stem cell transplantation. Since supportive care following this procedure is much less intensive compared with that required after allogeneic transplant, after the preliminary analysis of this study we decided not to routinely implant DL-HB catheters in children scheduled for autologous stem cell transplantation.

We agree that totally implanted devices have an overall lower risk of complications. In particular, the risk of self-removal in toddlers is absent, and infections are by far lower because of the need for fewer maintenance procedures when not in use. However, we believe that the psychological reasons (fear of needles) that drive all Italian pediatric cancer centers to use partially implanted CVCs allow acceptance of this increased risk.

Caution should be taken considering these results when dealing with smaller and less experienced institutions than those that contributed to this study. We believe that continuous medical education should also consider the management of possible CVC-related complications.

Finally, the design of this study was catheter-oriented and not patient-oriented. We acknowledge that the repeated complications occurring in some CVCs, or in different CVCs inserted in the same child, could be at least partially due to the patient’s predispositions (e.g. hypercoagulability, immunodeficit, low socio-economic status). However, we believe that in order to analyze the role of these variables, the study should have been planned differently, in particular acquiring data on the presence of possible ‘genetic’ risk factors at diagnosis, and on the occurrence of other risk factors (e.g. type of drugs administered, course of the underlying disease) throughout the course of therapy. Such a study might in fact yield valuable additional information, but should be designed specifically.

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