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Incidence, severity and outcome of central line related complications in pediatric oncology patients; A single center study

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ABSTRACT

Background: Central venous access device (CVAD)-related complications are associated with high morbidity rates. This study was performed to underline the importance of CVAD-complication prevention and treatment.
Methods: An audit of practice of CVAD-related complications in pediatric oncology patients receiving a CVAD between January 2015 and June 2017 was performed. CVADs included were totally implantable venous access ports (TIVAPs), Hickman–Broviac® (HB), nontunneled, and peripherally inserted CVADs.
Results: A total of 201 children, with 307 CVADs, were analyzed. The incidence rates per 1000 CVAD-days for the most common complications were 1.66 for malfunctions, and 1.51 for central line-associated bloodstream infections (CLABSIs). Of all CVADs inserted, 37.1% were removed owing to complications, of which 45.6% were owing to CLABSIs. In 42% of the CLABSIs, the CLABSI could be successfully cured with systemic antibiotic treatment only. Of all included patients, 5.0% were admitted to the intensive care unit owing to CLABSI. The HB-CVAD compared to the TIVAP was a risk factor for CVAD-related complications, CLABSIs and dislocations in particular.
Conclusions: The incidence of CVAD-related complications is high. Research on the prevention and treatment of CVAD-related complications in pediatric oncology patients should be a high priority for all health care professionals.
Type of study: Prognosis study (retrospective).
Level of evidence: Level II.

Central venous access devices (CVADs) are essential in pediatric oncology. Most commonly used CVADs in pediatric oncology are totally implantable venous access ports (TIVAPs), and Hickman–Broviac® (HB) CVADs [1–3]. CVAD-related complications are commonly seen in this patient group and often result in removal of the CVAD, prolonged hospital stays, intensive care unit admission, and death [1–22]. Especially, infections of the CVAD are known to have a high morbidity rate and can result in early removal of the CVAD [1–22]. Previous studies performed on the incidence of CVAD-related complications described little about the severity of CVAD-related complications, the influence of disease severity of the underlying malignancy during the observed central line associated bloodstream infections (CLABSIs), the occurrence of relapses and reinfections after treatment for CLABSIs, and did not exclude mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBIs) [4–22]. The aim of this study was to observe the

Abbreviations: CVAD, Central Venous Access Device; TIVAP, Totally Implantable Venous Access Device; HB, Hickman–Broviac; CLABSI, Central Line Associated Bloodstream Infection; MBI-LCBI, Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection; UMCU, University Medical Center Utrecht; PICC, Peripherally Inserted Central Catheter; SAT, Systemic Antibiotic Treatment; BSI, Bloodstream Infection; CDC, Centers for Disease Control and Prevention; NT, Nontunneled; ICU, Intensive Care Unit; TPN, Total Parenteral Nutrition; CRBSI, Central line Related Bloodstream Infection.

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incidence, severity, and outcome of early and late CVAD-related complications in order to identify risk factors for CVAD-related complications, and to evaluate what the focal points in CVAD-related complication prevention and treatment should be. By focusing on these aspects, preventative and treatment strategies for CVAD-related complications in pediatric oncology patients can be developed.

1. Material and methods

1.1. Patients and study design

A review of published literature on CVAD-related complications and an audit of practice of all patients, 18 years or younger, who received a CVAD at the Princess Máxima Center for Pediatric Oncology (Utrecht, The Netherlands), from January 2015 up to June 2017, were performed. The electronic patient files of these patients were evaluated, and the outcome measurements described below were scored. Exclusion criteria were: age older than 18 years, patients with a primary immunological disorder, and CVADs inserted in any other hospital than the Princess Máxima Center. Patient/CVAD characteristics scored were age at insertion, gender, diagnosis, CVAD-type, access vein, surgical introduction, CVAD lumen number/diameter, number of CVAD-days, and CVADs per person. The medical ethics committee of the University Medical Center Utrecht (UMCU) declared that official approval by the medical ethics committee was not required.

1.2. CVAD insertion and maintenance

The appropriate CVADs were chosen by health care professionals depending on the risks, frequency of use, quality of the veins, and duration/type of treatment [1–3]. Peripherally inserted central catheters (PICCs), nontunneled (NT) CVADs, HB-CVADs and TIVAPs were inserted. The HB-CVAD and TIVAP were inserted most commonly since they provide long-term central venous access. Either a specialized PICC-team, pediatric anesthesiologist or surgeon inserted the CVADs. The mode of introduction differed between a (non) ultrasound-guided percutaneous, open, or rewiring introduction. The maintenance of the CVAD was managed by experienced pediatric oncologic nurses. The maintenance of all CVADs consisted of disinfection of the surrounding skin (chlorhexidine 0.5% in ethanol 70%). The CVAD was flushed with 10 mL sodium chloride (NaCl) (0.9%) before every use and locked with heparin 100 IU/ml after every use and once every four weeks if the CVAD was not used. If the CVAD was disconnected for less than one hour, the CVAD was locked with NaCl 10 mL (0.9%). TIVAPs were filled with 5 mL and all other CVADs were filled with 3 mL heparin or NaCl. Needle-free collectors were used for the collection of blood samples. In case of persistent malfunction, the inability to aspirate or flush the CVAD, alteplase 2 mL (1 mg/mL) was instilled in the CVAD. When there was a suspicion of a CLABSI, at least one blood culture per lumen was collected from the CVAD. Often, empirical systemic antibiotic treatment (SAT) was started. A switch to directed SAT was performed once a pathogen was cultured. If a *Staphylococcus aureus, Pseudomonas aeruginosa,* or *Candida* spp. was cultured, the CVAD was removed immediately, following the protocol of our institution based on the Infectious Diseases Society of America 2009 guideline [23]. In all other cases, treatment response was evaluated after 48 h of SAT. If there was no significant response after 48 h (e.g. persistence of fever, chills, hypotension, or persisting positive blood cultures), removal was indicated. If the patient responded well, SAT was continued for one to two weeks, depending on the pathogen.

1.3. Definitions and outcome measurements

The primary outcome of this study was the incidence of CVAD-related complications defined per 1000 CVAD days. The mean CVAD days until complication, the incidence of severe neutropenia during CLABSI, the incidence of intensive care unit admission, the severity of the postoperative complications defined by the Clavien–Dindo classification (Table 1) and, when indicated, the reasons for removal were described [24]. Complications scored owing to the surgical procedure were a pneumothorax or hemothorax, confirmed by a chest X-ray. Surgical complications defined as "other" included: failure of puncturing the vein, puncturing an artery, cardiac arrhythmias, hematomas detected by ultrasound, malfunction and dislocation immediately after insertion. Complications scored after the surgical procedure were hematomas, infections (local infections and CLABSIs), malfunctions, thromboses, and mechanical complications (dislocation, breakage/rupture and detachment). Hematomas were scored if the hematoma was detected by visual inspection within 2 cm of the CVAD track or exit-site. Local infections such as phlebitis, exit-site or tunnel-infections were diagnosed by a positive exit-site culture, or erythema, purulent drainage and tenderness within 2 cm of the CVAD track and exit-site [23]. Patients with a bacteremia were classified into patients with a bloodstream infection (BSI), CLABSI, and MBI-LCBI. A BSI was scored in patients with a bacteremia that did not meet the CLABSI or MBI-LCBI criteria. CLABSI and MBI-LCBI were defined using the U.S. Centers for Disease Control and Prevention (CDC) criteria (January 2017) [25]. CLABSI was scored if the patient met one of the following: (1) the patient had a recognized pathogen cultured from ≥1 blood cultures, or (2) the patient had at least one of the following signs: fever (> 38°C), chills, or hypotension, and the same matching potential contaminant microorganism had to be cultured from ≥2 blood cultures drawn on separate occasions. A CLABSI could only be scored if the CVAD was in place for >48 h on the date of the event, if no CLABSI with the same microorganism was scored in the past two weeks (infection relapse time frame), and if the pathogen cultured was not related to an infection at another site [25]. The MBI-LCBI criteria of the CDC (January 2017) were used to exclude bacteremias that were more likely caused by the weakened mucosal barrier of the gut in immunocompromised patients than by CLABSI [25–27]. Malfunction of the CVAD was defined as difficult aspiration of blood, or inadequate flushing of the CVAD lumen [12]. A thrombosis around the CVAD-tip was diagnosed by ultrasound. Mechanical complications were defined as the detachment of CVAD parts, dislocation of the CVAD diagnosed by an X-thorax or a visible cuff, and rupture of the CVAD parts causing a leakage. Furthermore, the outcomes after CLABSI treatment were analyzed, e.g. the incidence of successful SAT, relapses and reinfections. Successful SAT was defined as treatment of CLABSI with SAT only, without further reinfections. A relapse was scored if

Table 1
Clavien–Dindo [24] classification per CVAD.

Grade	Definitions	CVADs, *n* (%)
No complications	No complications during the postoperative course	98 (31.9)
Grade I	Any deviation from the regular postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regiments are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.	25 (8.1)
Grade II	Pharmacological treatment required for the treatment of a CVAD-related complication with drugs other than such allowed for grade I complications.	63 (20.5)
Grade III	Surgical, endoscopic, or radiological interventions required for the treatment of a CVAD-related complication.	111 (36.2)
Grade IV	Life-threatening complication requiring intensive care unit admission owing to a CVAD-related complication.	10 (3.3)
Grade V	Death of the patient owing to a CVAD-related complication.	0 (0.0)

CVAD, central venous access device.

the same microorganism was cultured within 14 days, with the same CVAD still in situ. A reinfection was scored if (1) a positive blood culture was found with another microorganism during treatment of the initial CLABSI (MBI-LCBI/another infection site excluded), or (2) a CLABSI with the same microorganism was found after 14 days of treatment, and if the blood cultures in the period of 14 days of treatment were negative or not obtained. Additionally, the cultured microorganisms during CVAD-infections, and the risk factors for CVAD-related complications were retrieved. The risk factor analysis was focused on patient- (age at insertion, and diagnosis) and CVAD-characteristics (surgical introduction, site, access vein, CVAD-type, lumen diameter, and lumen number). We chose for an age threshold of two years, since younger patients are more at risk for CVAD-infections [1]. We hypothesized that patients less than two years of age, in our hospital, might be more at risk of CVAD-related complications, owing to a higher risk of self-removal and more intense chemotherapy (i.e. longer periods of deep aplasia, and more frequent CVAD manipulation) compared to older patients. Surgical introduction, site and access vein were excluded in the multivariant analyses since less than five events were observed in the subgroups. Since lumen diameter and number corresponded with the CVAD-type, these were also excluded in the multivariate analyses. Disease severity of the underlying malignancy and the associated longer neutropenia episodes have been associated with the incidence of, and removal owing to CLABSI [16,22,28]. Disease severity was therefore investigated by scoring the presence of severe neutropenia, a neutrophil granulocyte count of less than 100×106 /L, during CLABSI in the HB-CVAD group compared to the TIVAP group.

1.4. Statistical analysis

To study the association between possible risk factors for CVAD-related complications in general and CLABSIs in particular, univariate and two multivariable logistic regression models were estimated. Odds ratios (ORs) along with their 95% confidence interval (CI) are provided. IBM SPSS (version 21) was used to perform the statistical analyses.

2. Results

2.1. Clinical characteristics

Over a study period of 30 months, 201 patients (52.2% males, 47.8% females) with a median age at insertion of four years (0-≤18) were included. In this patient group, 129 (64.2%) patients were diagnosed with solid tumors, 61 (30.3%) with hematooncologic malignancies, 9 (4.5%) with neurologic malignancies, and 2 (1.0%) with bone marrow failure. In these patients, a total number of 307 CVADs were inserted, 136 (67.7%) patients received one, and 65 (32.3%) patients received more than one CVAD. The CVADs were in situ for a total of 68,010 CVAD-days, with a median of 181 (range: 0–827) CVAD-days per CVAD. Peripherally inserted central catheters (PICCs) were inserted for a median (minimum–maximum) of 19 days (0–386), nontunneled (NT) catheters for 13 days (2–285), HB catheters for 111 days (0–698) and TIVAPs for 266 days (5–827). More characteristics of the CVADs are presented in Table 2.

Of the 307 CVADs inserted, 209 (68.1%) obtained one or more CVAD-related complications. During the study period, a total of 391 CVAD-related complications occurred. Of all CVADs inserted, none obtained Clavien–Dindo grade V after surgery, 10 (3.3%) CVADs eventually obtained grade IV owing to CLABSI-related intensive care unit (ICU) admission, 111 (36.2%) CVADs obtained grade III, 63 (20.5%) grade II, 25 (8.1%) grade I, and 98 (31.9%) never obtained any postoperative complications (Table 1) [24]. Eventually, 114 (37.1%) of the inserted CVADs were removed early owing to complications, 11 (3.6%) owing to switch of treatment, 74 (24.1%) owing to end of treatment, 10 (3.3%) owing to death of the patient, 96 (31.3%) were still in place at the end of this study, and two (0.7%) reasons for removal are missing.

Table 2
Baseline characteristics of TIVAP, HB, NT, and PICC CVADs.

CVAD	Total ($n = 307$), n (%)
Introduction	
Percutaneous	20 (6.5)
Percutaneous + Ultrasound	216 (70.4)
Open	9 (2.9)
Rewired	8 (2.6)
Missing	54 (17.6)
Type of CVAD	
PICC	10 (3.3)
NT	8 (2.6)
HB	123 (40.1)
TIVAP	166 (54.1)
Single or Double lumen	
Single	184 (59.9)
Double	123 (40.1)
Lumen diameter (French)	
<4	7 (2.3)
≥4–<6	17 (5.5)
≥6–<7	154 (50.2)
≥7–<8	111 (36.2)
≥8	8 (2.6)
Missing	10 (3.3)
Type of vein	
Jugular	258 (84.0)
Subclavian	35 (11.4)
Brachial	2 (0.7)
Basilic	6 (2.0)
Cephalic	3 (1.0)
Femoral	2 (0.7)
Missing	1 (0.3)
Side of access	
Right	257 (83.7)
Left	48 (15.6)
Missing	2 (0.7)

NT, nontunneled catheter; PICC, peripherally inserted central catheter; HB, Hickman–Broviac catheter; TIVAP, totally implantable venous access port; CVAD, central venous access device.

2.2. Noninfectious CVAD-related complications

The incidence of each CVAD-related complication, their occurrence per 1000 CVAD days, the mean days until complication and the reasons for removal are summarized in Table 3. Malfunction was the most common CVAD-related complication with an incidence rate of 1.66/1000 CVAD days and appeared after a median of 62 days. Five CVADs were removed owing to malfunction.

2.3. Infectious CVAD-related complications

Local infections had an incidence rate of 0.59/1000 CVAD days and caused seven early removals of the CVAD. A total of 195 episodes of bacteremia were analyzed, of which 103 (52.8%) were scored as CLABSI, 7 (3.6%) as MBI-LCBI, and 85 (43.6%) as BSI. CLABSI was the second most common CVAD-related complication, with an incidence rate of 1.51/1000 CVAD-days. CLABSIs appeared after a median of 60 CVAD days. Of all CVADs inserted, 52 (16.9%) were removed owing to CLABSIs, 20 (6.5%) owing to BSIs, and one (0.3%) owing to an MBI-LCBI. In total 10 (5.0%) out of 201 patients were admitted to the ICU owing to CLABSI. Microorganisms commonly cultured during CLABSI episodes were: 51 (32.9%) coagulase-negative staphylococci (CoNS), and 22 (14.2%) enterococci. The prevalence of all microorganisms causing CLABSI episodes and local infections is shown in Table 4. The treatment outcomes of all initial CLABSIs are described in a flowchart (Fig. 1). From the 103 CLABSIs (87 initial CLABSIs, and 16 reinfections) that occurred, 43 (41.7%) were treated successfully with SAT only.

Table 3
Description of CVAD related complications.

	All CVADs[a] ($n=307$)						HB-CVAD ($n=123$)				TIVAP ($n=166$)			
	Events ($n=391$)	CVADs ($n=307$)	Patients ($n=201$)	Events per 1000 CVAD days	Days until complication	Removal reason	Events ($n=190$)	Events per CVAD	Events per 1000 CVAD days	Removal reason	Events ($n=185$)	Events per CVAD	Events per 1000 CVAD days	Removal reason
Complications	*n* (%)	*n* (%)	*n* (%)	/1000[b]	Median (min–max)	*n* (%[c])	*n* (%)	Mean	n/1000[b]	*n* (%[c])	*n* (%)	Mean	/1000[b]	*n* (%[c])
Surgical complications:														
▪ Pneumothorax	1 (0.3)	1 (0.3)	1 (0.5)	-	-	0 (0.0)	1 (0.5)	0.01	-	0 (0.0)	0 (0.0)	0.00	-	0 (0.0)
▪ Hemothorax	0 (0.0)	0 (0.0)	0 (0.0)	-	-	0 (0.0)	0 (0.0)	0.00	-	0 (0.0)	0 (0.0)	0.00	-	0 (0.0)
▪ Other[d]	23 (5.9)	21 (6.8)	20 (10.0)	-	-	2 (0.7)	11 (5.8)	0.09	-	1 (0.8)	7 (3.8)	0.04	-	0 (0.0)
Hematoma	32 (8.2)	31 (10.1)	30 (14.9)	0.47	10 (0-409)	0 (0.0)	12 (6.3)	0.10	0.73	0 (0.0)	19 (10.3)	0.11	0.38	0 (0.0)
CLABSI	103 (26.3)	81 (26.4)	60 (29.9)	1.51	60 (1-406)	52 (16.9)	64 (33.7)	0.52	3.91	34 (27.6)	35 (18.9)	0.21	0.70	17 (10.2)
Local Infection	40 (10.2)	39 (12.7)	34 (16.9)	0.59	55 (5-460)	7 (2.3)	27 (14.2)	0.22	1.65	4 (3.3)	12 (6.5)	0.07	0.24	3 (1.8)
Malfunction	113 (28.9)	74 (24.1)	63 (31.3)	1.66	62 (0-547)	5 (1.6)	37 (19.5)	0.30	2.26	2 (1.6)	75 (40.5)	0.45	1.49	3 (1.8)
Thrombosis	9 (2.3)	9 (2.9)	9 (4.5)	0.13	58 (13-440)	4 (1.3)	5 (2.6)	0.04	0.31	2 (1.6)	3 (1.6)	0.02	0.06	2 (1.2)
Mechanical complications:														
▪ Dislocation	23 (5.9)	23 (7.5)	21 (10.4)	0.34	20 (0-412)	16 (5.2)	13 (6.8)	0.11	0.79	11 (8.9)	7 (3.8)	0.04	0.14	3 (1.8)
▪ Breakage/rupture	14 (3.6)	14 (4.6)	14 (7.0)	0.21	75 (2-320)	4 (1.3)	10 (5.3)	0.08	0.61	3 (2.4)	4 (2.2)	0.02	0.08	1 (0.6)
▪ Detachment	33 (8.4)	29 (9.4)	28 (13.9)	0.49	41 (0-231)	3 (1.0)	10 (5.3)	0.08	0.61	1 (0.8)	23 (12.4)	0.14	0.46	2 (1.2)

CVAD, central venous access device; CLABSI, central line associated blood stream infection; HB, Hickman–Broviac®; TIVAP, totally implantable venous access port.

[a] Including: TIVAP, HB, NT, and PICC CVADs.

[b] Complication rate per 1000 CVAD days: total CVAD days = 68,010, total HB-days = 16,384, total TIVAP-days = 50,336.

[c] Percentage of all CVADs inserted: total $n=307$, HB-CVAD $n=123$, TIVAP $n=166$.

[d] Other surgical complications: failure of puncturing the vein, accidentally puncturing an artery, cardiac arrhythmias, a bleeding or hematoma, dislocation of the catheter-tip (detected by radiology) and negative blood return after insertion.

Table 4
Prevalence of cultured microorganism episodes in CLABSI (polymicrobial $n=38$) and local infections (polymicrobial $n=1$).

Microorganisms	Cultured during CLABSI, n (%)	Cultured during a local infection, n (%)
Gram-positive		
Coagulase-negative staphylococci[a]	51 (32.9)	N.A.
Staphylococcus aureus	8 (5.2)	4 (40.0)
Viridans streptoccci[b]	12 (7.7)	1 (10.0)
Streptococcus pneumoniae	2 (1.3)	0 (0.0)
Enterococci[c]	22 (14.2)	N.A.
Other Gram-positive[d]	14 (9.0)	2 (20.0)
Gram-negative		
Enterobacteriaceae[e]	19 (12.3)	3 (30.0)
Nonfermenting Gram negative bacteria[f]	20 (12.9)	0 (0.0)
Candida		
Candida spp.[g]	6 (3.9)	0 (0.0)
Miscellaneous[h]	1 (6.5)	0 (0.0)
Total	155 (100.0)	10 (100.0)

CLABSI, central line associated blood stream infection; N.A., not applicable; spp., species. CoNS and Enterococci, if cultured from exit sites, were not reported by the clinical microbiology laboratory.

[a] *S. epidermidis* (32), *S. warneri* (1), *S. haemolyticus* (8), *S. hominis* (6), *S.capitis* (4).

[b] *S.mitis* (9), *S. salivarius* (2), *S. oralis* (1), *S. vestibularis* (1).

[c] *E. faecium* (14), *E. faecalis* (8).

[d] *Micrococcus luteus* (4), *Corynebacterium* spp. (3), *Microbacterium oxydans* (2), *Streptococcus dysgalactiae* (1), *Bacillus* spp. (3), *Clostridium terteus* (1), *Brevibacterium* spp. (1), *Rothia mucilaginosa* (1).

[e] *Escherichia coli* (11), *Klebsiella pneumoniae* (3), *Enterobacter cloacae complex* (3), *Serratia marcescens* (1), *Panthoea* spp. (3) , *Enterobacter asburiae* (1).

[f] *Stenotrophomonas maltophilia* (3), *Acinetobacter* spp. (7), *Chryseobacterium* spp. (1), *Flavobacterium* spp. (2), *Moraxella* spp. (3), *Pseudomonas aeruginosa* (2), *Roseomonas mucosa* (1), *Sphingomonas* (1).

[g] *Candida albicans* (5), *Candida lusitaniae* (1).

[h] *Mycobacterium chelonae* (1).

2.4. Risk factors for CVAD-related complications

To identify risk factors for all CVAD-related complications, univariate logistic regressions models were estimated. The insertion of an HB-CVAD compared to TIVAP appeared to be a significant risk factor for CLABSI (OR: 2.78, CI: 1.41–5.47, p = 0.005) and dislocations (OR: 4.03, CI: 1.32–12.33, p = 0.02), Table 5. No significant difference in the number of CLABSIs during severe neutropenia episodes was found between patients with an HB-CVAD and TIVAP (p = 0.79). Lumen number (double lumen) and lumen diameter (≥7) were risk factors for CLABSI (OR: 3.31, CI: 1.68–6.54, p = 0.001, and OR: 4.31, CI: 2.16–8.64, p<0.001), respectively. Lumen diameter (≥7 Fr) was a risk factor for local infections (OR: 2.54, CI: 1.07–6.02, p = 0.039). Diagnosis (hematooncologic diseases) was a risk factor for hematomas (OR: 4.93, CI: 1.96–12.41, p = 0.001). Age (≤2 years) was a risk factor for dislocations (OR: 4.69, CI: 1.04–21.12, p = 0.034). Introduction method (percutaneous vs. open), access vein (jugular vs. subclavian) and introduction site (right vs. left) were no significant risk factors for CVAD-related complications, results not shown.

Two multivariable logistic regression models with possible risk factors for CVAD-related complications in general and CLABSIs in particular were estimated (Table 6). Age at insertion (≤2 vs. >2 years), diagnosis (hematooncologic diseases vs. solid tumors), and CVAD type (HB-CVAD vs. TIVAP), were included in the analysis. CVAD type (HB-CVAD) (OR: 2.02, CI: 1.02–3.97, p = 0.043) and diagnosis (hematooncologic diseases) (OR: 2.20, CI: 1.09–4.47, p = 0.029) were significant risk factors for CVAD-related complications in general. CVAD type (HB-CVAD) (OR: 3.05, CI: 1.49–6.32, p = 0.002) was a significant risk factor for CLABSI.

3. Discussion

The incidence of CVAD-related complications in pediatric oncology patients is high. This resulted in frequent dispense of SAT, removal of multiple CVADs, and even intensive care unit (ICU) admission. The most common complications in this study were malfunctions, CLABSIs, and local infections. The incidence of CVAD-related complications in pediatric oncology patients per 1000 CVAD-days described in literature ranged from 0.8 to 2.0 for malfunctions, 0.1 to 1.6 for bloodstream infections related to the CVAD, and 0.1 to 0.3 for local infections [4–11]. The incidence of less common complications described in literature is comparable to that found in this study [5–7,9,12]. The high incidence of CVAD-related complications compared to the literature might be explained by the variety in CVAD-types analyzed, the underlying diseases in the patients observed (e.g. hematooncologic or solid malignancies),

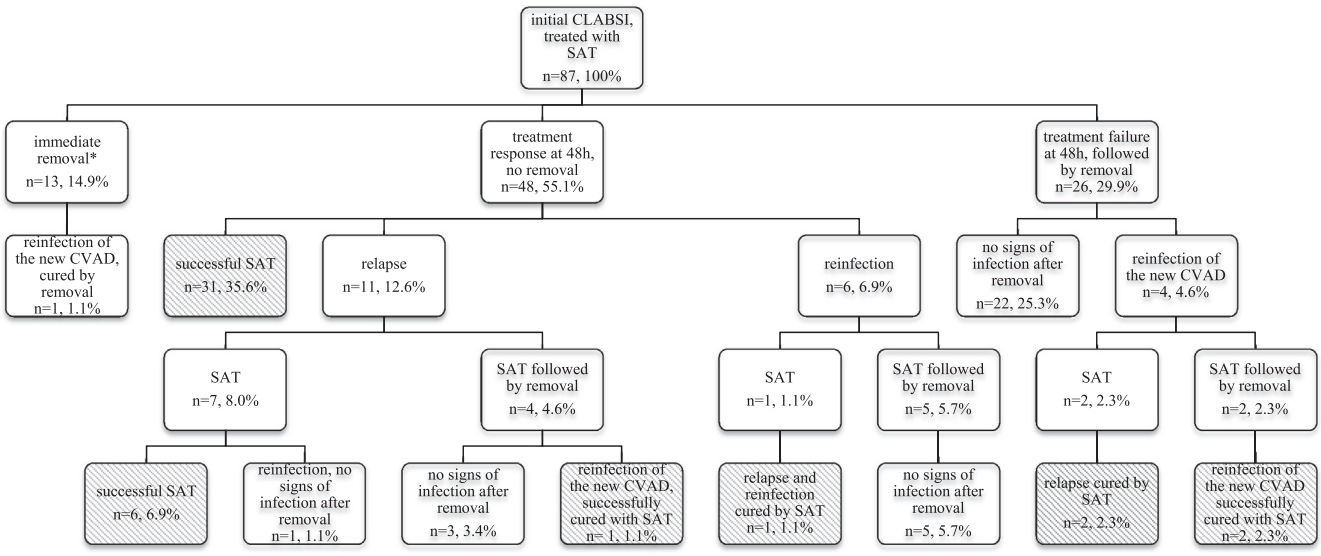

Fig. 1. CLABSI treatment results CLABSI, Central Line Associated Blood Stream Infection; SAT, Systemic Antibiotic Treatment; n, number; h = hour *Following the protocol of our institution, immediate removal is indicated owing to CLABSI caused by positive blood cultures with *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida* spp. In total 103 CLABSI events are described, initial CLABSIs ($n=87$), reinfections ($n=16$), relapses were not scored as a new CLABSI events. Striped blocks are CLABSI events cured successfully with SAT only ($n=43$). In total, 43/103 (41.7%) of the CLABSIs were successfully treated with SAT.

Table 5
Univariate analysis of the HB-CVAD vs. TIVAP.

	HB-CVAD ($n=123$) vs. TIVAP ($n=166$)	
Complications	OR (95% CI)	p-value
Surgical complications		
• Pneumothorax	-	-
• Hemothorax	-	-
• Other[a]	1.89 (0.63–5.63)	0.26
Hematoma	0.60 (0.23–1.60)	0.36
CLABSI	2.78 (1.41–5.47)	0.005*
Local Infection	2.16 (0.90–5.20)	0.104
Malfunction	0.66 (0.33–1.31)	0.24
Thrombosis	5.60 (0.57–54.86)	0.13
Mechanical complications		
• Dislocation	4.03 (1.32–12.33)	0.02*
• Breakage/rupture	3.84 (0.93–15.88)	0.07
• Detachment	0.53 (0.19–1.51)	0.34

CVAD, central venous access device; HB, Hickman–Broviac; TIVAP, totally implantable venous access port; CLABSI, central line associated blood stream infection; CI, confidence interval; OR, odds ratio; p-value, probability value.

[a] Other surgical complications: failure of puncturing the vein, accidentally puncturing an artery, cardiac arrhythmias, a bleeding or hematoma, dislocation of the catheter-tip (detected by radiology) and negative blood return after insertion.

* Significant values.

Table 6
Multivariate analysis.

	CVAD-related complications		CLABSI	
Risk factors	OR (95% CI)	p-value	OR (95% CI)	p-value
Age at insertion				
≤2 Years	1			
>2 Years	0.55 (0.29–1.04)	0.070	0.96 (0.46–2.01)	0.070
Diagnosis				
Solid	1			
Hematooncologic	2.20 (1.09–4.47)	0.029*	0.94 (0.46–2.01)	0.900
CVAD-type				
TIVAP	1			
HB-CVAD	2.02 (1.02–3.79)	0.043*	3.05 (1.49–6.32)	0.002*

CVAD, central venous access device; HB, Hickman–Broviac; TIVAP, totally implantable venous access port; CLABSI, central line associated bloodstream infection; CI, confidence interval; OR, odds ratio; p-value, probability value.

* Significant values.

the nonuniform complication criteria used, and the different CVAD-maintenance protocols used (e.g. CVAD flush/lock protocols) [4–11]. Malfunction was the most common complication in this study. Currently in the Netherlands, CVADs are locked with heparin. However, the heparin lock appears to be of limited value in the prevention of malfunction [29]. Preventing malfunction of the CVAD should instead be accomplished by the education of health care providers about the maintenance of CVADs and by working more protocolized; use more proper flushing policies, needle-free connectors, and no-reflux strategies (e.g. a no-reflux syringe) [29]. Future research needs to address the best lock solution for the prevention of CVAD malfunction in this patient population. The high incidence of CLABSIs might be associated with the CVAD-types inserted (i.e. a large number of HB-CVADs), the CVAD-maintenance protocols used (e.g. CVAD flush/lock protocols), or factors related to the underlying malignancy, such as endogenous infections, high-risk chemotherapy, and the supplementation of total parenteral nutrition (TPN) [28]. The high incidence might also be explained by the arguable issue of the definition of bloodstream infections related to the CVAD. During the past years, many variations of definitions for bacteremia caused by the CVAD were used in literature. In this study, the CLABSI criteria were used instead of the central line related bloodstream infection (CRBSI) criteria, being the most practical definition considering the lack of peripheral blood cultures and catheter tip cultures in this patient group, which are required for the definition of a CRBSI. Additionally, in clinic, a bacteremia is often being treated as associated to the CVAD, even though the CRBSI criteria are not met. Therefore, we accept a possible overestimation of the incidence rate using the CLABSI criteria. However, it is also possible that the amount of CLABSIs is underestimated, since the BSIs that were not scored as a CLABSI owing to an insufficient number of blood cultures, could also have been scored as CLABSIs if more blood cultures were obtained. Other authors scored all positive blood cultures drawn from the CVAD, including bloodstream infections caused by infections located elsewhere in the patient, which can result in an overestimation of CVAD-related infections [30,31]. To eliminate bacteremias that were the result of the weakened mucosal barrier of the gut in immunocompromised patients, the MBI-LCBIs were excluded in this analysis. Pediatric oncology patients frequently have a weakened mucosal barrier; therefore, physicians are often unsure if the bloodstream infection has originated from the weakened mucosal barrier or the CVAD. These criteria might be useful in practice to differentiate between CLABSIs and MBI-LCBIs to avoid unnecessary removal of the CVAD [25–27]. SAT was successful in 42% of the CLABSI episodes. This indicates that SAT in combination with clinical observation is an acceptable strategy in case of CLABSI caused by microorganisms other than *Candida* spp., *Pseudomonas aeruginosa,* or *Staphylococcus aureus.* Unfortunately, a great deal of the CLABSI episodes will still result in removal of the CVAD owing to continuing symptoms, relapses or reinfections. In the prevention of CLABSIs, the use of lock solutions containing taurolidine, ethanol or citrate appears to be promising; however, further research on this subject is needed and strongly recommended [11,29,32–35]. Patients diagnosed with hematooncologic malignancies were more at risk for CVAD-related complications in general; this might be because of more frequent CVAD-manipulation in this patient group [1,7,9]. The insertion of an HB-CVAD appeared to be a significant risk factor for CVAD-related complications in general, dislocations and CLABSIs in particular. Dislocations are probably less common during the use of a TIVAP since it is inserted underneath the skin. Possible explanations for the high incidence of CLABSIs in HB-CVADs are the open access to the bloodstream through the external parts of the HB-CVAD, the frequent occurrence of double lumen HB-CVADs, the higher frequency of TPN supplementation, and the dispense of more high-risk chemotherapy in HB-CVADs. However, no significant difference was found in the incidence of severe neutropenia during CLABSIs in patients with HB-CVADs or TIVAPs. HB-CVADs were also found to be a risk factor for infections in other studies [4,8,19–21]. Owing to the higher risk of CVAD-related complications associated with the HB-CVAD, the insertion of other double lumen CVADs (i.e. double-lumen TIVAP) instead of an HB-CVAD might be considered in the future if a double lumen is indicated. Lumen number and diameter correlated with the CVAD-type inserted, and were therefore also found as significant risk factors. Lumen diameter was a risk factor for local infections. A lumen diameter of ≥7 Fr is associated with the HB-CVAD, which has external parts, and could therefore be more at risk for local infections. Age was a risk factor for dislocations, probably owing to a higher risk of self-removal by these younger patients [9]. Limitations of this study were the retrospective design, the fact that some CVADs were still in situ at the end of the study, and that some patients were treated in a different hospital in the Netherlands or at home for a period of time. Major complications appearing in other institutions were documented in our institution, although it is possible that minor complications are missing since the medical files of other institutions were not reviewed. Additionally, CRBSI is technically the most accurate definition of describing infections related to the CVAD; however, as described above, this definition is not an option in this population. In conclusion, compared to literature we detected a high incidence of CVAD-related complications in pediatric oncology patients. Therefore, CVAD-related complication prevention and treatment are important and could reduce the incidence of CVAD-related complications, SAT dispense, CVAD-removal and ICU admission. We recommend that professionals need to be educated more in CVAD-maintenance, work more

protocolized, and perform further research to observe the efficacy of lock solutions (e.g. locks containing taurolidine and citrate) and other double-lumen CVADs (e.g. double-lumen TIVAPs) on the decrease of the most common CVAD-related complications.

Declarations of interest

None.

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References

[1] Carraro F, Cicalese MP, Cesaro S, et al. Guidelines for the use of long-term central venous catheter in children with hematooncological disorders. On behalf of supportive therapy working group of Italian Association of Pediatric Hematology and Oncology (AIEOP). Ann Hematol 2013;92(10):1405–12.
[2] Farrelly JS, Stitelman DH. Complications in pediatric enteral and vascular access. Semin Pediatr Surg 2016;25(6):371–9.
[3] Ullman AJ, Marsh N, Mihala G, et al. Complications of central venous access devices: a systematic review. Pediatrics 2015;136(5):e1331–44.
[4] Allen RC, Holdsworth MT, Johnson CA, et al. Risk determinants for catheter-associated blood stream infections in children and young adults with cancer. Pediatr Blood Cancer 2008;51(1):53–8.
[5] Cesaro S, Cavaliere M, Pegoraro A, et al. A comprehensive approach to the prevention of central venous catheter complications: results of 10-year prospective surveillance in pediatric hematology–oncology patients. Ann Hematol 2016;95(5):817–25.
[6] Cesaro S, Corro R, Pelosin A, et al. A prospective survey on incidence and outcome of Broviac/Hickman catheter-related complications in pediatric patients affected by hematological and oncological diseases. Ann Hematol 2004;83(3):183–8.
[7] Fratino G, Molinari AC, Parodi S, et al. Central venous catheter-related complications in children with oncological/hematological diseases: an observational study of 418 devices. Ann Oncol 2005;16(4):648–54.
[8] Hord JD, Lawlor J, Werner E, et al. Central line associated blood stream infections in pediatric hematology/oncology patients with different types of central lines. Pediatr Blood Cancer 2016;63(9):1603–7.
[9] Pinon M, Bezzio S, Tovo PA, et al. A prospective 7-year survey on central venous catheter-related complications at a single pediatric hospital. Eur J Pediatr 2009;168(12):1505–12.
[10] Journeycake JM, Buchanan GR. Catheter-related deep venous thrombosis and other catheter complications in children with cancer. J Clin Oncol 2006;24(28):4575–80.
[11] Simon A, Ammann RA, Bode U, et al. Healthcare-associated infections in pediatric cancer patients: results of a prospective surveillance study from university hospitals in Germany and Switzerland. BMC Infect Dis 2008;8:70 https://bmcmedicine.biomedcentral.com/about.
[12] Fratino G, Mazzola C, Buffa P, et al. Mechanical complications related to indwelling central venous catheter in pediatric hematology/oncology patients. Pediatr Hematol Oncol 2001;18(5):317–24.
[13] al-Hathal M, Malmfors G, Garwicz S, et al. Port-A-Cath in children during long-term chemotherapy: complications and outcome. Pediatr Hematol Oncol 1989;6(1):17–22.
[14] Fratino G, Molinari AC, Mazzola C, et al. Prospective study of indwelling central venous catheter-related complications in children with Broviac or clampless valved catheters. J Pediatr Hematol Oncol 2002;24(8):657–61.
[15] Sarper N, Zengin E, Corapcioglu F, et al. Totally implantable central venous access devices in children with hemato-oncologic malignancies: evaluation of complications and comparison of incidence of febrile episodes with similar patients without central venous access devices. Pediatr Hematol Oncol 2006;23(6):459–70.
[16] Viana Taveira MR, Lima LS, de Araujo CC, et al. Risk factors for central line-associated bloodstream infection in pediatric oncology patients with a totally implantable venous access port: a cohort study. Pediatr Blood Cancer 2016;64(2):336–42.
[17] Viscoli C, Castagnola E, Giacchino M, et al. Bloodstream infections in children with cancer: a multicentre surveillance study of the Italian Association of Paediatric Haematology and Oncology. Supportive Therapy Group-Infectious Diseases Section. Eur J Cancer 1999;35(5):770–4.
[18] Wesenberg F, Flaatten H, Janssen Jr CW. Central venous catheter with subcutaneous injection port (Port-A-Cath): 8 years clinical follow up with children. Pediatr Hematol Oncol 1993;10(3):233–9.
[19] Adler A, Yaniv I, Steinberg R, et al. Infectious complications of implantable ports and Hickman catheters in paediatric haematologyoncology patients. J Hosp Infect 2006;62(3):358–65.
[20] La Quaglia MP, Lucas A, Thaler HT, et al. A prospective analysis of vascular access device-related infections in children. J Pediatr Surg 1992;27(7):840–2.
[21] Mirro Jr J, Rao BN, Kumar M, et al. A comparison of placement techniques and complications of externalized catheters and implantable port use in children with cancer. J Pediatr Surg 1990;25(1):120–4.
[22] White AD, Othman D, Dawrant MJ, et al. Implantable versus cuffed external central venous catheters for the management of children and adolescents with acute lymphoblastic leukaemia. Pediatr Surg Int 2012;28(12):1195–9.
[23] Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49(1):1–45.
[24] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–13.
[25] Centers for Disease Control and Prevention. Device associated module BSI. http://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf; 2018, Accessed date: March 2018.
[26] See I, Soe MM, Epstein L, et al. Impact of removing mucosal barrier injury laboratory-confirmed bloodstream infections from central line-associated bloodstream infection rates in the National Healthcare Safety Network, 2014. Am J Infect Control 2017;45(3):321–3.
[27] Simon A, Furtwangler R, Graf N, et al. Surveillance of bloodstream infections in pediatric cancer centers — what have we learned and how do we move on? GMS Hyg Infect Control 2016;11 [Doc11] https://www.egms.de/static/en/journals/dgkh/authors.htm.
[28] Kakkos A, Bresson L, Hudry D, et al. Complication-related removal of totally implantable venous access port systems: does the interval between placement and first use and the neutropenia-inducing potential of chemotherapy regimens influence their incidence? A four-year prospective study of 4045 patients. Eur J Surg Oncol 2017;43(4):689–95.
[29] Pittiruti M, Bertoglio S, Scoppettuolo G, et al. Evidence-based criteria for the choice and the clinical use of the most appropriate lock solutions for central venous catheters (excluding dialysis catheters): a GAVeCeLT consensus. J Vasc Access 2016;0:453–64.
[30] Tomlinson D, Mermel LA, Ethier MC, et al. Defining bloodstream infections related to central venous catheters in patients with cancer: a systematic review. Clin Infect Dis 2011;53(7):697–710.
[31] Simon A, Bode U, Beutel K. Diagnosis and treatment of catheter-related infections in paediatric oncology: an update. Clin Microbiol Infect 2006;12(7):606–20.
[32] Dumichen MJ, Seeger K, Lode HN, et al. Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. J Hosp Infect 2012;80(4):304–9.
[33] Handrup MM, Moller JK, Schroder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. Pediatr Blood Cancer 2013;60(8):1292–8.
[34] Schoot RA, van Ommen CH, Stijnen T, et al. Prevention of central venous catheter-associated bloodstream infections in paediatric oncology patients using 70% ethanol locks: a randomised controlled multi-centre trial. Eur J Cancer 2015;51(14):2031–8.
[35] Schoot RA, vDE, van Ommen CH, et al. Antibiotic and other lock treatments for tunnelled central venous catheter-related infections in children with cancer. Cochrane Database Syst Rev 2013;6:CD008975.