The Journal of Vascular Access
OnlineFirst

https://doi.org/10.1177/11297298241239998

Sage Journals

Clinical trial protocol

Systematic application of SICA-PED protocol for central venous catheterization in neonates: A prospective clinical study on 104 cases

Ferdinando Spagnuolo [1], Anna Maietta [1], Umberto Pugliese [1], Emanuele Lettieri [1], Fabrizio Minopoli [1], Nicola Coppola [2], Marco La Verde [3], Margherita Macera [4], Caterina Monari [4], Lorenzo Onorato [2], and Mauro Carpentieri [1]

Background: Catheterization of central vessels can be associated with early and late, potentially fatal complications. A proactive approach is imperative to reduce the frequency and magnitude of adverse events. Recently, the GAVeCeLT has proposed a protocol called SICA-PED (i.e. Safe Insertion of Central Access in Pediatric patients) and includes seven evidence-based strategies.

Methods: Through a single-center prospective observational study, the authors wanted to consolidate the efficacy and safety of these protocol in newborns. In a series of 104 newborns, the seven steps of the protocol were applied (1) pre-procedural ultrasound study of the RaCeVA veins, (2) correct aseptic technique, (3) ultrasound-guided venipuncture, (4) intraprocedural localization of the tip of the catheter with TTE (ECHO TIP) and (iECG) intracavitary electrocardiogram, (5) reasoned choice of the implant exit site with the RAVESTO Tunneling technique, (6) anchoring without stitches, and (7) exit point protection with the use of glue and transparent semipermeable membrane. The authors have included a further precaution in point (6) the subcutaneous anchoring system has added the counter-fixation of the catheter wings that we will call 6Plus Point.

Results: All infants requiring implantation of elective us-guided central venous access were enrolled in the study. None of the 104 implanted central venous catheters experienced early complications (accidental arterial puncture, PNX, primary malposition); rare late complications such as ecchymosis, CRBSI, exit site infection or dislodgement were observed, No catheter-related thrombotic phenomena were observed. The CRBSI catheter-related infection rate was 2.47 × 1000 days catheter cases.

Conclusion: The results of this prospective study strengthen the feasibility and efficacy of the SICA-Ped Protocol. Demonstrating that the systematic application of the evidence-based seven-step implantation strategy increases the success rate, minimizes early and late complications, which result in increased patient safety.

Keywords
Central venous catheterization, neonates, protocol, intracavitary ECG, sutureless securement, echo tip location

[1]Terapia Intensiva Neonatale AOU Università degli Studi di Napoli "Luigi Vanvitelli" Napoli, Napoli, Campania, Italy
[2]UOC Malattie Infettive Dipartimento di Salute Mentale e Fisica e Medicina Preventiva AOU Università degli Studi di Napoli "Luigi Vanvitelli" Napoli, Napoli, Campania, Italy
[3]Dipartimento Materno infantile Ginecologia ed Ostetricia AOU Università degli Studi di Napoli "Luigi Vanvitelli" Napoli, Napoli, Campania, Italy
[4]UOC Malattie Infettive AOU Università degli Studi di Napoli "Luigi Vanvitelli" Napoli, Napoli, Campania, Italy

Corresponding author(s):
Ferdinando Spagnuolo, Neonatal Intensive Care AOU University of Naples "Luigi Vanvitelli" Largo Madonna delle Grazie,1, Naples, Campania 80138, Italy. Email: ferdinando.spagnuolo@policliniconapoli.it

Introduction

In the last decade, even in pediatric age, there has been a widespread use of central venous catheters (CVAD) in large caliber polyurethane (3–4 Fr) inserted into the brachiocephalic vein (BCV) or internal jugular vein (IJV) Centrally Inserted Central Catheter known as CICC or into the common femoral vein Femorally Inserted Central Catheter known as FICC.

Unlike smaller ECCs (1–2.7 Fr), CICCs and FICCs allow repeated blood sampling, infusion of high volumes of fluids and/or drugs or solutions not compatible with peripheral venous access and allow bloody hemodynamic monitoring when necessary.[1]

The higher success rate of the procedure, partly explained by the global use of the ultrasound technique and partly by the availability of more technically advanced materials (micro-introducer kits: 21G needle, floppy straight tip 0.018″ nitinol guidewire, micro-introducer-dilator and power injectable polyurethane catheters) has made it possible to extend the indications for the use of CICC and FICC also in the neonatal period, historically the prerogative of umbilical venous catheters (UVC) and epicutaneo-cava catheters (ECC).

The choice of a CICC or a FICC[2] is not only motivated exclusively by the "clinical criticality" but extends to any newborn who has a hypothetical duration of pharmacological/infusion treatment or parenteral nutrition of more than 2 weeks or every newborn in whom the attempt to place an ECC, with central tip, is repeatedly failed.

Insertion-related complications were divided into "immediate" during the implantation phase, related to venipuncture errors such as pneumothorax (PNX), hemothorax, arterial hematoma, or nerve damage or due to an incorrect location of catheter (primary malposition, arrhythmias), "early" (within 48 h) and "late" (after 48 h). Late complications could also be related to errors during the insertion maneuver and can result in early infections, venous thrombosis (CRT), secondary mispositioning up to true catheter dislodgement, or management-related complications that result in lumen occlusion or late infections.

Complications, however, always result in an interruption of treatment, which affects clinical

outcomes and causes a longer hospital stay, both factors underlying the increase in overall costs to the healthcare system.[3]

A reasoned approach to the choice of the most appropriate device,[2] the correct use of new technologies applied with a methodology structured in specific insertion and management "protocol" based on scientific evidence,[4–6] as has already happened in the world of adult vascular access, could contribute to reducing the incidence of complications. Not only catheter-related infections (CRBSI)[7] but also all complications were reduced, increasing the success rate and safety for the patient and overall increasing the cost-effectiveness of the CVAD implantation procedure.[8]

The GAVeCeLT (the Italian Group for Long Term Venous Access Devices) has developed a specific group of evidence-based recommendations for the insertion of CVAD in pediatric age named SICA-Ped (i.e. Safe Insertion of Central Access in Pediatric patients).[9,10]

These protocol is articulated in seven key points to minimize the different types of complications related to the insertion, thus to increase the safety and success of the maneuver: (1) pre-procedural ultrasound study of the veins using protocol RaCeVA,[11,12] (2) correct aseptic technique,[13] (3) ultrasound-guided venipuncture,[11] (4) intra-procedural tip location with a non-radiological method, but through ultrasound TTE (ECHOTIP-Ped, Neo-ECHOTIP),[14,15] and intracavity electrocardiogram (iECG),[16,17] (5) reasoned choice of the implant exit site with the Tunneling technique according to RAVESTO,[18–20] (6) anchorage without sutures,[21] and (7) protection of the exit site with the use of glue and transparent semipermeable membrane.[22,23] The authors have included a further precaution in point (6) the subcutaneous anchoring system has added the counter-fixation of the catheter's wings.

The aim of this study is to test the feasibility of the SICA-Ped protocol in a cohort of newborn and to report the incidence of the outcomes in the studied population.

Methods

This is a prospective observational single-center study conducted in the Neonatal Intensive Care Unit NICU of the University of Campania "Luigi Vanvitelli" in Naples, Italy from October 2021 to November 2023. The study protocol has been approved by the local Ethics Committee (*n.ro of protocol 0018889/s*). The parents were explained the goal of the study and signed an informed consent form.

Inclusion criteria were all preterm or full-term infants aged 1–28 days of postnatal age or corrected age less than 42 weeks, with BCV diameter or common femoral vein ⩾3 mm and sinus rhythm on surface ECG candidates for elective implantation of a 3–4 Fr caliber polyurethane catheter from a deep vein of the supra/infraclavicular region (CICC) or lower extremities (FICC) in agree with the current nomenclature of CVADs,[11] and with a central tip, respectively at the cable-atrial junction (CAJ) for CICCs and at the outlet of the inferior vena cava (IVC) for FICCs.

Indications for implantation were considered: need for central venous access in every

hemodynamically unstable infant (need for repeated blood draws, infusion of high volumes of fluids, bloody hemodynamic monitoring), or in every stable infant with hypothetical duration of pharmacological/infusion or parenteral nutritional treatment greater than 2 weeks or need, need for surgery, and any infant in whom the attempted placement of an ECC and/or CVO, with a central tip he had repeatedly failed.[2]

Exclusion criteria were correct age ≥42 weeks, severe coagulation disorders with high hemorrhagic risk (e.g. severe thrombocytopenia), right or left BCV diameter < to 3 mm, thrombosis of BCV or superior vena cava (SVC) or common femoral vein, all catheters implanted urgently and umbilical venous catheters (UVC) and epicutaneous-caval catheters (ECC) since SICA-Ped protocol is applicable only with ultrasound-guided venipuncture.

Study design

This prospective observational study was designed to analyze the feasibility of the insertion protocol and the clinical impact on the rate of possible complications potentially related to central venous catheterization exclusively in the neonatal population.

The insertion protocol was articulated in seven strategic evidence base points:

(1) Pre-procedural ultrasound study: The choice of the most appropriate site for venipuncture was made after the systematic study of the veins using the protocol used in clinical practice called "RaCeVA"[12,24] Rapid Central Veins Assessment and "RaFeVA"[25,26] Rapid Femoral Veins Assessment. Determining criteria for the choice of venipuncture site are based on the caliber, depth of the vein, and relationships with surrounding structures potentially at risk of accidental puncture such as pleura, nerves, and arteries. An ideal catheter-to-vein ratio of at least 1:3 is acceptable according to the rule of Nifong,[27] which recommends cannulating veins whose internal diameter is at least three times greater than the outer diameter of the catheter, for the prevention of venous thrombosis. The principle behind the bundle's first recommendation is that there is no ideal vein for every pediatric patient and that the vein should be identified through careful ultrasound examination.[11,28–31]

(2) Correct aseptic technique: Hand hygiene preferably with hydroalcoholic gel, maximum protective barriers, antisepsis of the skin with 2% chlorhexidine in 70% isopropyl alcohol has been used. We consistently adopted in all infants the recommendation to cleanse and disinfect the skin with a single application for at least 30″ followed by a 30″ pause before starting the procedure.[32–34]

According to most guidelines,[29,30,35] the use of maximum barrier precautions included non-sterile hood, non-sterile mask, sterile gloves, sterile gown, life-size sterile drape on the patient and sterile ultrasound probe protection (long enough to cover the probe and wire). Protecting the insertion site from microbial contamination through proper hand hygiene, maximum barrier protection, and skin antisepsis is of paramount importance.[13,21]

(3) Ultrasound-guided: Real-time ultrasound-guided venipuncture of the chosen vein has been

systematically adopted, with different techniques in terms of vein visualization (short axis, long axis, oblique axis) and needle approach (in-plane, out-of-plane),[11] conforming to the protocol Neo-ECHOTIP, depending on the vein considered and the clinical situation, in order to get the best visualization of the vein and the needle.[15] Ultrasonography was also used to assess the correct direction of the guidewire and catheter (ultrasound tip navigation), according to the ECHOTIP-Ped[14] and the Neo-ECHOTIP protocol.[15,36] In case of CICC insertion, ultrasonography was also used to assess the absence of pneumothorax, and hemothorax, immediately after venipuncture, as currently recommended.[11] The third innovative component of our package is the "global" use of ultrasound for different purposes: to immediately rule out early pleuropulmonary complications (such as pneumothorax) and to verify the correct direction of the guidewire and/or catheter (tip navigation).[11,24] Ultrasound-guided venipuncture has quickly become the gold standard for central venous cannulation in newborns as well[11] as demonstrated in previous studies.[24,37] Several studies have shown that ultrasound guidance reduces the number of venipunctures and the risk of immediate complications. In particular, the number of puncture attempts is one of the factors most associated with complications.[38,39,40] US-guided supraclavicular BCV catheterization has been associated with the lowest rate of infections associated with the central line and deep vein thrombosis in pediatric patients admitted to PICU and carriers of a CVAD.[41]

(4) Intra-procedural verification of the central position of the tip with non-invasive methods: The intracavitary ECG technique has been used to check the correct position of the catheter tip, in almost all cases.[16,17] Ultrasonography has always been used as an adjunctive method to confirm tip position, in association with intracavitary ECG.[11,14,15,28,36] Post-procedural radiography was considered as an option only in case of failure (non-feasibility or non-applicability) of intracavitary ECG and ultrasound. Intracavitary ECG as a non-invasive intraprocedural method for tip localization has often been used in pediatric and neonatal patients.[42,43] The accuracy of the ECG IC technique was reported at 92.9%[42] and 95.8%[16] which is very close to the results of the multicenter study in adults.[44]

(5) Tunneling: In each case, the most appropriate exit site has been defined, using tunneling to move the exit site away from areas at high risk of bacterial contamination or displacement.[18,19] The tunneling options were decided according to the RAVESTO[20] protocol (Rapid Assessment of Venous Exit Site and Tunneling Options). Tunneling has been adopted not only to reduce the risk of extraluminal bacterial contamination in patients with long-term venous access but also to stabilize the device on flat surfaces, such as the infraclavicular region, to reduce the possibility of accidental dislodgement.

The rationale for tunneling is to ensure the most appropriate location of the exit site.[20,31,45,46] For example, many complications of central venous access to the cervicothoracic site (CICC) or femoral site (FICC) are related to difficulty in exit site management and/or catheter instability because of a higher risk of dislodgement (difficulty stabilizing and fixation), a

higher risk of infection (difficulty disinfecting and maintaining a clean dressing), higher risk of venous thrombosis (excessive catheter mobility)[47,48] that the tunnelization is capable of decreasing.[20,31,45,46,49,50]

(6) Catheter fixation without sutures: As currently recommended, sutures have never been used for catheter fixation that may also have favorable effects on the risk of infection.[13,21] Safety was achieved exclusively by subcutaneous anchoring (SecurAcath, Interrad). In our experience, the most effective safety was subcutaneous anchorage that minimizes the risk of dislodgement and can theoretically reduce the risk of infection and venous thrombosis.[23,51,52]

(7) Exit site protection with glue and semi-permeable transparent membranes: Cyanoacrylate glue has been consistently used to seal the exit site to stabilize the catheter, reduce oozing/bleeding, and decrease the risk of extraluminal bacterial contamination.[19,22] Butyl or octyl-butyl cyanoacrylate were used interchangeably. The exit site was constantly covered with a transparent dressing with high permeability (high MVTR = high water vapor transfer rate) (IV3000, Smith & Nipote); in agreement with literature an MVTR value >1500 was considered acceptable.[53]

Recent data have already suggested that octyl-and/or butyl-cyanoacrylate are very effective in reducing bleeding from the exit site. In addition, the glue helps to stabilize the catheter effectively, albeit for a limited period.[23,29,54] Data from the literature also suggest that glue may act as a barrier against bacterial contamination, reducing the risk of infection in line with what has been described by other groups,[19] there are no reports that cyanoacrylate may have undesirable effects on the skin of infants[23] or that it may alter the chemical-physical characteristics of polyurethanes.[55] The stabilization of the catheter becomes even safer by combining glue-free and sutureless fixation with the use of transparent semi-permeable membranes, which obviously also have a favorable impact especially on reducing the risk of bacterial contamination. The use of transparent membranes is strongly recommended by several guidelines.[33] In this regard, although skin damage can be a problem in infants and infants, no cases of Catheter Associated Skin Injury (CASI) have been reported in the first 2 weeks after CVAD insertion. Our current CASI prevention strategy includes the use of clear membranes with a high MVTR (Moisture Vapor Transfer Rate), the use of minimal amounts of cyanoacrylate glue, an appropriate dressing change policy, and an appropriate skin antisepsis policy.

All procedures were performed within the neonatal intensive care unit (NICU) directly inside the incubator or on the Infant Warmer in hybrid incubators in case of hypothermic treatment in place.

Sedation, analgesia and/or anesthesia were used in all patients with fentanyl citrate intranasal (i.n.) nebulized (3 γ/kg) and midazolam (i.n.) nebulized 0.5 mg/kg 15 min prior to puncture and/or dexmedetomidine 2–3 mcg/kg (i.n.), while shortly before, the operative field was infiltrated with 1% buffered lidocaine 0.2 mL/kg according to recent guidelines.[56]

Different levels of intraprocedural monitoring of vital signs were used, depending on the clinical condition, but ECG monitoring was always included, as intracavitary ECG was adopted as the first option for tip localization. Using an ECG monitor with adequate shielding, the ECG trace was recorded with an output velocity of 50 mm/s and a sensitivity of 10 mm/mV, switching from a surface lead II to an intracavitary floating catheter-II when intracavitary ECG was required; the CVAD was connected to the ECG monitor via a dedicated sterile cable (Vygocard, Vygon).

Ultrasound imaging was performed with a Fujifilm Sonosite PX ultrasound device, equipped with the following translators: HSL 25xp/13-6 MHz linear probes, L 25xp/13-6 MHz micro-linear probe, C11xp/8-5 MHz micro convex probe, P10xp/8-4 MHz pediatric cardiology probe, to meet all requirements for venous evaluation, venipuncture, tip navigation, tip position, and determination of insertion-related complications.

Several central VADs from many different brands were used. In most cases, 3 Fr monolume new generation polyurethane power injectable catheters were used. Catheters currently marketed as PICCs have also been used "off label" as CICC or FICC, as described above.[45,46,49,50] This allowed us to use micro-introducer kits: 21G needle, floppy straight tip 0.018″ nitinol guidewire, micro-introducer-dilator with 3.5–4.5 Fr/5 cm dilator for all procedures.

After insertion, the management of all CVADs was carried out according to our department policies (routine dressing change every week), first if dirty or unglued, needle-free connectors with neutral displacement, medicated caps, saline washing only, daily surveillance of the exit site, PIPP[57]pain scale monitoring, N-pass.[58]

All CVAD insertions were performed by a single operator specifically trained in neonatal and pediatric vascular access (two pediatric nurses, two neonatologists in training). Data analysis was performed by a clinician external to NICU.

Infectious disease surveillance by a stewardship of the hospital infectious disease specialists.

Endpoint

The primary endpoint was to assess the incidence of any immediate complications occurring during the procedure: venipuncture failure, success after more than two attempts, pneumothorax, accidental arterial injury, local hematoma, hemothorax, hemo-mediastinum, nerve injury, lymphatic duct damage, gas embolism, hemopericardium, intraprocedural arrhythmias, failure to place the catheter tip in the planned position (primary malposition).

The secondary endpoint was to assess the incidence of any early (within 48 h of insertion) or late (after 48 h and within 14 days or until removal when no longer needed) complications potentially related to the insertion maneuver. Potential early complications included local hematoma, tunnel hematoma, exit site bleeding, early catheter malfunction, relevant local pain detected with PIPP Pain Scale in preterm and N-PAS in term infant. Late complications, within the first 2 weeks, potentially related to insertion included infectious (exit site infection, tunnel infection, or CRBSI) and non-infectious (CRT catheter-related venous thrombosis, catheter

rupture, tip migration, displacement) complications.

Local skin infection was defined by the presence of erythema and/or tenderness at the exit site or tunnel, regardless of the presence of fever or purulent discharge. The diagnosis of CRBSI was based on the differential time to positivity (DTP).[59] Catheter-related thrombosis (CRT) was diagnosed by ultrasound examination, which was performed only based on a clinical suspicion. Catheter malfunction was defined as the persistent inability to infuse normal saline despite manual pressure performed by a 10 mL syringe. Dislodgement was defined as the misplacement of the catheter's tip outside of the target zone.

A specific database was developed to collect relevant patient details (demographics, medical history, reason for CVAD insertion), insertion maneuver (type of venous access, type of catheter, etc.) and periprocedural complications. Follow-up of each catheter lasted if it was in place, but it was assumed that complications occurring after 2 weeks (in particular, infection) were less likely to be related to the insertion maneuver.

Statistical analysis

The statistical analysis of the anamnestic characteristics of the sample and the incidence of intra- and post-procedural complications was performed on Excel files. The incidence of complications was compared with data reported in the literature. The data were normalized considering the different characteristics of the individual devices used and the other characteristics reported in the data collection form. The X square test was performed. Variables were expressed as mean ± SD.

Results

Over a period of 3 years, 104 consecutive CVAD insertions were included in the study. The neonatal population included preterm or full-term patients of 1–28 days of postnatal age or corrected age less than 42 weeks, with BCV brachiocephalic vein diameter or common femoral vein ⩾3 mm and sinus rhythm on surface ECG candidates for elective implantation of a 3–4 Fr caliber polyurethane catheter.

Table 1 shows CVADs inserted in infants: mean gestational age was 35.7 weeks (±4.5) and mean weight was 2466 g (±1.08), mean length 45.3 cm (±5.02), mean size of BCV cannulated was 3.4 mm (SD 0.22), the only right femoral vein cannulated was 5 mm, mean duration of CVADs was 12 days (±2–90). All insertions were performed in the NICU. As shown in Table 1, the vast majority of CVADs were CICCs inserted into the right brachiocephalic vein because based on my experience the right BVC is easier to scan, more direct access to V.C.S., offer higher success rate of cannulation and lower rate of incorrect direction of the guidewire and catheter. The catheter tip was placed at the junction between the superior vena cava and the right atrium, by intracavitary ECG and ultrasound. The only FICC was inserted into the right common femoral vein and the tip located at the outlet of the VCI in the right atrium. All CICCs were tunneled into the infraclavicular area, to move the exit site to a clean and stable position. The

FICC was tunneled mid-thigh. Intracavitary ECG was used in all patients (100%), but only in the patient with a device implanted in the right femoral vein the maximal P wave was not useful to locate the tip at the inferior cavo-atrial junction and the correct position was confirmed by ultrasound; in all of them, the position of the tip was further verified by ultrasound, with a double method (100%). Radiographic confirmation was never requested. Several brands of catheters were used, mostly 3 Fr, single-lumen, always non-cuffed polyurethane catheters. A catheter was inserted by substitution on a guidewire: also in this case, ultrasound was used for tip navigation and intracavitary ECG for tip localization. Subcutaneous anchorage was used in all patients (100%). Counter-fixing of the wings in all cases (100%).

Tab 1. Central venous access devices in neonates.

	CICC	FICC	Total
	n = 103	*n* = 1	*N* = 104
Vein			
Right brachiocephalic	103		103
Right femoral		1	1
Technique			
Ultrasound-based tip location	103	1	104 (100%)
i-EKG based tip location	103	1	103 (99%)
Agreement Eco-iEKG	103		103 (99%)
Primary malpositioning	0	0	0
Tunneling	103	1	104 (100%)
Exchange by guide wire	1		1
Catheter caliber (Fr = French)			
3 Fr	103		103
4 Fr		1	1
Lumen			
Single lumen	103	1	104
Patients			
Weight, mean ± SD (range) (g)	2486 ± 1087 (629–5000)		
Length, mean ± SD (range) (cm)	45.3 ±6.4 (31–55)		
Gestational age, mean ± SD (range) (weeks)	36.0 ± 4.4 (26–42)		
Gender (male/female)	50/53	1	104
Venous size (range) (mm)	3.4 ± 0.29 (3.1–4.2)	5	

Table 2 shows that no immediate or early complications were recorded in any of the patients. In particular, 98% central veins were successfully drilled on the first attempt.

Tab 2. Post-procedural complications: early.

	CICC = 103	FICC = 1
Double attempt	2 (1.9%)	—
Arterial puncture	—	—
Pnx	—	—

Among the late complications shown was tunnelitis in a single patient in septic shock from Klebsiella pneumoniae with multi-organ involvement, who later died.

In the same patient, catheter dislodgement occurred with secondary migration, due to the accidental partial opening of the subcutaneous anchoring system during medication.

Seven episodes of bacteremia were detected during the observation period, but in four cases DTP excluded the diagnosis of CRBSI. In three case was confirmed diagnosis of CRBSI (Klebsiella pneumoniae, Staphylococcus aureus, Candida Guilliermondii) started at 12-day average from the implant, treated with target antibiotic therapy after catheter removal (2.8% of non-elective removal for CRBSI).

In summary, considering the entire population of patients enrolled in our study, there was no episode of accidental arterial puncture or pleural-pulmonary injury during the insertion maneuver. The correct position of the tip was successfully verified with a double intraprocedural Rx-free method by intracavitary ECG and ultrasound in 99% of cases, without any need for post-procedural radiography. Rare post-procedural complications were reported during the first 2 weeks follow-up (see Table 3). The overall rate of CRBSI was 2.47 × 1000 catheter days. No CRTs have been registered. No complications occurred following the first 2 weeks.

Tab 3. Post-procedural complications: late.

	CICC = 103	FICC = 1
Dislodgment	1 (0.96%)	—
Secondary misplacement	1 (0.96%)	—
Local ecchymosis	—	—
Infection of exit site	1 (0.96%)	—
Local pain at exit site	—	—
Lumen occlusion	—	—
CRT	—	—
CRBSI	3	—

Discussion

The present study is the first prospective study to verify the feasibility of the protocol adopting an appropriate evidence-based strategy of insertion and incidences of adverse outcomes related to insertion in a large sample size of newborns.

CVAD-related complications have been reported in the literature with an incidence of 7–18%[60,61] and approximately 25% of pediatric CVADs develop complications prior to completion of treatment.[3] Most CVAD-related complications result in serious consequences, such as premature catheter removal, discontinuation of therapy, and/or the onset of secondary clinical problems, with prolonged hospital stay and an increased risk of mortality.[60,61]

In infants in general and in preterm infants in particular, a severe systemic infection increases hospital costs,[62] with a huge risk for neurological prognosis[63] and for the severity of distant outcomes.[64]

There is growing evidence in the adult literature that most complications are preventable with appropriate operator training and the use of evidence-based recommendations for inclusion and management.[65]

However, studies in the pediatric population are limited, even more so in the neonatal population.[41,66,67,68]

Our previous study[69] is a retrospective observational study conducted in NICU on 40 newborns received CICC. We also evaluated the safety of an ultrasound guided puncture using our NICU insertion bundle. The venipuncture proved to be easy and safe while tip location was 100% accurate with iECG. No pneumothorax or pleural effusion occurred.

Barone et al.[37] had published work on CICC implanted in preterm neonates with weight below 1500 g demonstrating zero complication rate with a bundle insertion application on thirty patients. The success rate of the procedure was100%. No case of accidental arterial or pleural puncture war was registered. In the Barone study the catheters were placed in three hospitals using the same procedure, that is a well definite insertion bundle demonstrating that even different operators in different hospitals can have zero complication if they follow the same insertion bundle.

The SICA ped protocol used in this study agreed with the GAVeCeLT study published in 2022 by Pittiruti et al.[10] that analyzed a seven steps bundle for CVC insertion in the pediatric population (SIC-PED bundle). Pittiruti's prospective study evaluated 729 central lines in hospitalized neonates, infants, and children. Out of 729 central line insertions, there were no immediate complications (no pneumothorax, no arterial puncture, no malposition); the incidence of early and late complications (local ecchymosis, dislodgment, local pain, exit site infection) was 3.7%; in the first 2 weeks after insertion, no catheter-related bacterial infection or catheter-related thrombosis was recorded.

In the book "Vascular Access in Neonates and Children,"[9] Biasucci et al described the "SICA Ped protocol" (Safe insertion of central access in Pediatric patient") a seven steps protocol developed by GAVeCeLT for CVC insertion. The seven steps were always: (1) pre-procedural ultrasound study of the RaCeVa veins, (2) correct aseptic technique, (3) ultrasound-guided venipuncture, (4) intraprocedural tip location with ECHO or iECG (intracavitary electrocardiogram) (5) reasoned choice of the implant exit site with the RAVESTO Tunneling technique, (6) anchoring without stitches, and (7) exit point protection with the use of glue and transparent semipermeable membrane.

In our prospective study we were able to systematically apply the SICA Ped protocol for insertion of ultrasound guided CVAD in a cohort of newborns and we recorded a very low rate of complications.

Indeed, the careful choice of the vein by preprocedural ultrasound (point 1) and the constant use of ultrasound guidance (point 3) may have impacted the complications related to the puncture.

The tip location with intraprocedural, non-invasive, Rx-free techniques, such as iECG and ultrasound (point 4) may have avoided primary mispositioning; the combined method has always been feasible and applicable, post-procedural control by X-ray has never been required.

The iECG method was used in almost all patients with 99% accuracy, compared to 100% when combined with ultrasound-based tip location. The disagreement between two methods probability can be explained by the fact that in the implantation of catheters coming from the lower half of the body (femoral veins) the tip location technique with iECG is not able to correctly localize the position of the tip. While there is a well-defined electrophysiological correlate between CAJ and the atrium (maximum peak of the P wave), as is the electrophysiological correlate of the right atrium (biphasic P wave), the electrophysiological

correlate of the junction between VCI and the right atrium (i.e. the position where to place the tip of the catheter coming from below) is not at all well-defined. It happens that when the tip is in the middle of the right atrium, the P is biphasic, but when the tip descends toward the atrio-caval junction, several possibilities occur in an unpredictable way (flattening of the P, or complete negativization of the P) without the certainty of what is the precise indicator of the position of the tip at the inferior atrio-caval junction. Also, for this reason, in pediatric patients, and even more so in newborns, ultrasound is considered the second and most reliable method for verifying the tip location.[11,14,15,24,28,38] A micro-convex probe (4–8 MHz) or a small sector probe (3–7 MHz) was used for tip location, in most cases with a right parasternal projection (Figure 1). The maneuver was particularly feasible in newborns, as reported in the literature.[14,15,21,24,28,38]

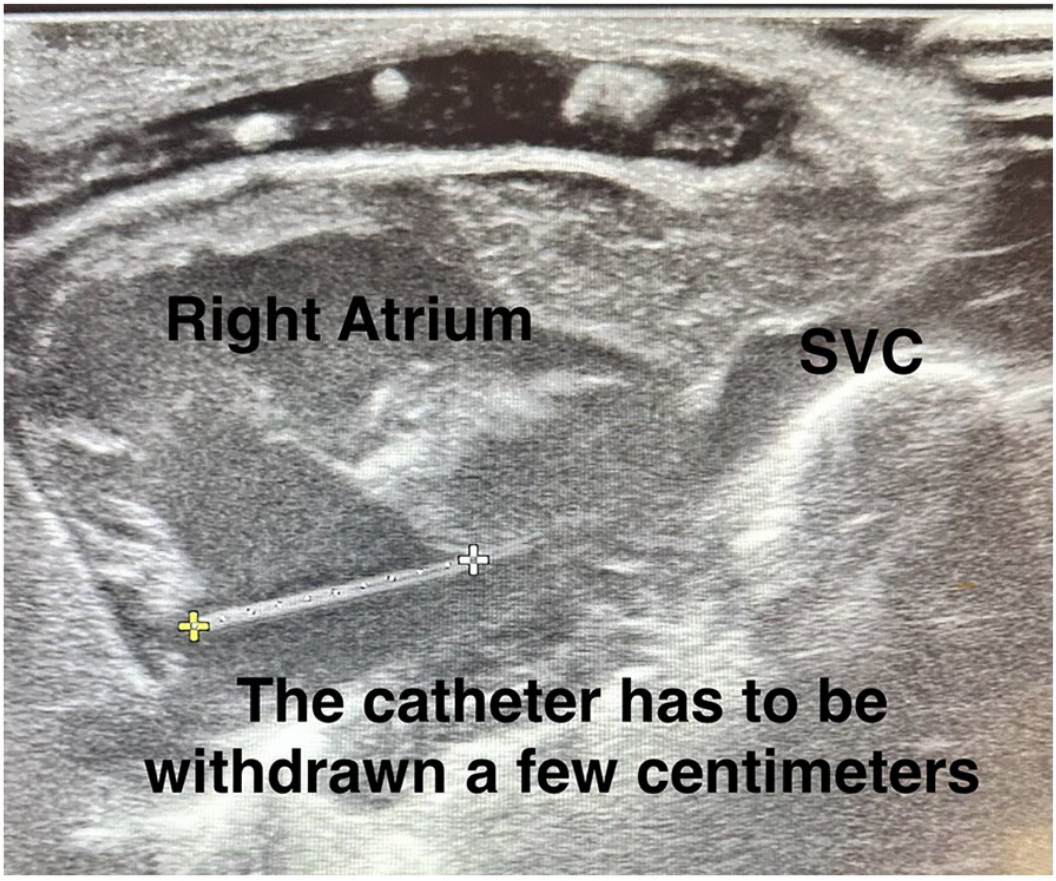

Figure 1. Echo tip location.

The simultaneous adoption of three different strategies could explain the almost total absence of dislodgement: tunneling (to move the exit site to a stable area) (point 5) and sutureless fixation (subcutaneous anchoring is particularly effective in this sense) (point 6). In fact, the only case observed occurred due to an accidental opening of the anchoring system, which is indirect proof of its effectiveness.

The advisability of tunneling remains controversial, although always feasible, in infants under 1 kg of body weight or in cases of brief therapies in cases where the CICC/FICC has been

implanted only for the failure of a “peripheral” ECC or CVO.

The tunnelitis observed in a single patient in fatal septic shock from Klebsiella pneumoniae with multi-organ involvement it was probably a sign of a serious impairment of the immune system.

In these insertion’s protocol we included an additional precaution (labeled as 6 Plus) to the subcutaneous anchoring system with the counter-fixation of the catheter wings with the use of adhesive sutureless skin devices (StatLock, BD) to avoid dangerous accidental twists on itself (Figure 2). Based on our experience we have observed that the manipulation of the infusion lines and the continuous involuntary movements of newborns can cause screwing of the catheter on itself that over time can seriously injure it.

Figure 2. Counter-fixation of the catheter wings.

The real effectiveness of the wings counter-fixing is a starting point for further studies.

The low incidence of CRBSI in the first 2 weeks of follow-up could be secondary to the appropriate use of currently recommended infection prevention strategies during the maneuver

(point 2), the adoption of the tunneling technique to optimize the exit site (point 5), sutureless fixation (point 6), and proper protection of the exit site (point 7).

Despite the systematic application of strategies evidence based we observed an overall rate of CRBSI of 2.47 × 1000 catheter days. Positive blood culture for Candida G. can be an expected complication in a severe hypoxic-ischemic encephalopathy in protracted total parenteral nutrition (NPT). In the other two cases, the onset of severe septic shock was prior to catheter implantation. Probably the early positivity of the catheter's blood culture may be due to the increased amount of bacteremia during catheter insertion.

The absence of any case of bleeding from the exit site and the very low rate of local complications could be related to the constant use of glue at the exit site.

Catheter-related thrombosis (CRT) has not been observed throughout the life of CVADs, probably a consequence of a "reasoned" strategy. The synergistic action of the pre-procedural choice of the most appropriate vein by ultrasound examination: the vein size in addition to respecting the ratio of vein caliber to device caliber (point 1), to the minimization of trauma to the venous wall by ultrasound-guided venipuncture (point 3), to correct position of the catheter tip, verification by intraprocedural methods (point 4) and optimal stabilization of the catheter using a multimodal strategy that includes the choice of the exit site (point 5), sutureless fixation (point 6), cyanoacrylate glue and transparent semi-permeable dressing (point 7). The absence of any case of tip migration with secondary malposition is likely related to the very accurate localization of the tip by intraprocedural methods and the prevalent use of polyurethane catheters.

Conclusion

The paper's strength lies in its plan implementation in all cases.

This study, among the first for simple size, shows the minimization of complications related to the insertion of CVADs in a cohort of newborns as the result of a synergistic role of the seven points contained in the insertion protocol.

In terms of cost-effectiveness, it should be noted that the SICA-Ped protocol stood out not only for an extremely low rate of complications, but also for its low procedural costs. All implants were performed in the NICU avoiding expensive environments such as the operating room or the X-ray room for fluoroscopy or post-procedural radiography.

The widespread diffusion of the procedure will clarify how much is linked to the individual skills of the individual operator and how much to the goodness of the protocol itself. This could turn out to be a weakness of the paper.

Limitations of the study

A major limitation of the study is that all insertions were performed by a single specifically qualified physician; for example, the operator's personal preference may have conditioned the exclusive choice of the right BCV for the implantation of the CICCs, rather than the contralateral

one of the same size; literature proves that the same results can only be reproduced by physicians adequately trained in the use of ultrasound and/or the use of intracavitary ECG.

In addition, the subdivision of complications, related to the procedure, into phases: preimplantation related to the choice of the device, complications in the immediate and early or late implantation phase related to management, certainly useful from a methodological point of view, may not reflect the real etiopathogenesis in clinical reality, resulting in a false causal link between the points of the protocol and the observed endpoints.

The SICA-PED protocol, due to its peculiar pre- and intra-procedural articulation, may not be the first choice outside of the election, that is, in emergency conditions.

Authors' note

The corresponding author is affiliated with GAVeCeLT.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Ferdinando Spagnuolo https://orcid.org/0000-0002-4850-406X

Note

Abbreviations CVC Central Venous Catheter.
CICC Centrally Inserted Central Catheter.
FICC Femoral Inserted Central Catheter.
ECC. Epicutaneo-Cava Catheter
UVC. Umbilical Venous Catheter
nPICC. Neonatal Peripherally Inserted Central Catheter
CRBSI. Catheter Related Blood Stream Infection
GAVeCeLT Italian Group for Long Term Venous Access Devices
SICA-Ped Safe Insertion of Central Access in Pediatric patients
RaCeVA Rapid Central Vein Assessment.
RaFeVA Rapid Femoral Vein Assessment.
CASI Catheter Associated Skin Injury
RAVESTO Rapid Assessment of Venous Exit Site and Tunneling Options
TTE Transthoracic Echocardiogram
iECG intracavitary electrocardiogram
MVTR Moisture Vapor Transfer Rate
SVC. Superior Vein Cava

CAJ Cavo Atrial Junction.
IJV. Internal Jugular Vein.
IVC. Inferior Vein Cava
BCV. Brachiocephalic vein
FV. Femoral vein
PNX Pneumothorax.
CVADs. Central Venous Access Devices,
NICU. Neonatal Intensive Care Unit
DTP differential time to positivity

References

1. Barone G, Pittiruti M. Epicutaneo-caval catheters in neonates. New insight and new suggestion from the recent literature. *J Vasc Access* 2020; 21: 805–809. Crossref. PubMed. ISI.
2. Barone G, D'Andrea V, Ancora G, et al. The neonatal DAV-expert algorithm: a GAVeCeLT/GAVePed consensus for the choice of the most appropriate venous access in newborns. *Eur J Pediatr* 2023; 182: 3385–3395. Crossref. PubMed.
3. Ullman AJ, Marsh N, Mihala G, et al. Complications of central venous access devices: a systematic review. *Pediatrics* 2015; 136(5): e1331–e1344. Crossref. PubMed.
4. Brescia F, Pittiruti M, Ostroff M, et al. The SIC bundle: a seven-step strategy to minimize complications potentially related to the insertion of centrally inserted central catheters. *J Vasc Access*. Epub ahead of print 29 July 2021. Crossref
5. Emoli A, Cappuccio S, Marche B, et al. Il protocollo 'ISP' (Inserzione Sicura dei PICC): un "bundle" di otto raccomandazioni per minimizzare le complicanze legate all'impianto dei cateteri centrali ad inserimento periferico (PICC) [The ISP (safe insertion of PICCs) protocol: a bundle of 8 recommendations to minimize the complications related to the peripherally inserted central venous catheters (PICC)]. *Assist Inferm Ric* 2014; 33(2): 82–89. PubMed.
6. Brescia F, Pittiruti M, Ostroff M, et al. The SIF protocol: a seven-step strategy to minimize complications potentially related to the insertion of femorally inserted central catheters. *J Vasc Access*. Epub ahead of print 29 August 2021. Crossref
7. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *New Engl J Med* 2006; 355(26): 2725–2732. Crossref. PubMed. ISI.
8. Bell T, O'Grady NP. Prevention of central line-associated bloodstream infections. *Infect Dis Clin North Am* 2017; 31(3): 551–559. Crossref. PubMed.
9. Biasucci G, Disma NM, Pittiruti M. Vascular access in neonates and children. Book. Springer International Publishing, 2022 Switzerland AG. Crossref.
10. Pittiruti M, Celentano D, Barone G, et al. A GAVeCeLT bundle for central venous catheterization in neonates and children: a prospective clinical study on 729 cases. *J Vasc Access* 2023 Nov; 24(6):1477-1488.
11. Lamperti M, Biasucci DG, Disma N, et al. European Society of Anaesthesiology guidelines on peri-operative use of ultrasound-guided for vascular access (PERSEUS vascular access). *Eur J Anaesthesiol*

2020; 37(5): 344–376. Crossref. PubMed.

12. Spencer TR, Pittiruti M. Rapid central vein assessment (RaCeVA): a systematic, standardized approach for ultra- sound assessment before central venous catheterization. *J Vasc Access* 2019; 20(3): 239–249. Crossref. PubMed. ISI.
13. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011; 52(9): e162–e193. Crossref.
14. Zito Marinosci G, Biasucci DG, Barone G, et al. ECHOTIP-Ped: a structured protocol for ultrasound-based tip navigation and tip location during placement of central venous access devices in pediatric patients. *J Vasc Access*. Epub ahead of print 13 July 2021. Crossref
15. Barone G, Pittiruti M, Biasucci DG, et al. Neo-ECHOTIP: a structured protocol for ultrasound-based tip navigation and tip location during placement of central venous access devices in neonates. *J Vasc Access*. Epub ahead of print 5 April 2021. Crossref
16. Rossetti F, Pittiruti M, Lamperti M, et al. The intracavitary ECG method for positioning the tip of central venous access devices in pediatric patients: results of an Italian multicenter study. *J Vasc Access* 2015; 16(2): 137–143. Crossref. PubMed. ISI.
17. Mastroianni R, Capasso A, Ausanio G. The intracavitary electrocardiography method for tip location of jugular internal vein access device in infants of less than 5 kg: a pilot study. *J Vasc Access* 2018; 19(6): 639–643. Crossref. PubMed. ISI.
18. Moureau NL, Marsh N, Zhang L, et al. Evaluation of skin colonization and placement of vascular access device exit sites (ESCAPE study). *J Infect Prev* 2019; 20(1): 51–59. Crossref. PubMed.
19. Gilardi E, Piano A, Chellini P, et al. Reduction of bacterial colonization at the exit site of peripherally inserted central catheters: a comparison between chlorhexidine-releasing sponge dressings and cyano-acrylate. *J Vasc Access* 2021; 22(4): 597–601. Crossref. PubMed. ISI.
20. Ostroff MD, Moureau N, Pittiruti M. Rapid assessment of vascular exit site and tunneling options (RAVESTO): a new decision tool in the management of the complex vascular access patients. *J Vasc Access* 2021. Epub ahead of print 21 July 2021. Crossref
21. Gorski LA, Hadaway L, Hagle ME, et al. Infusion therapy standards of practice, 8th edition. *J Infus Nurs* 2021; 44(1S Suppl 1): S1–S224. Crossref. PubMed.
22. D'Andrea V, Pezza L, Barone G, et al. Use of cyanoacrylate glue for the sutureless securement of epicutaneo-caval catheters in neonates. *J Vasc Access* 2021. Epub ahead of print 8 April 2021. Crossref
23. D'Andrea V, Barone G, Pezza L, et al. Securement of central venous catheters by subcutaneously anchored suturless devices in neonates. *J Matern Fetal Neonatal Med*. Epub ahead of print 9 May 2021. Crossref
24. Spagnuolo F. Global use of ultrasound in newborn vascular access: Ra.Ce.Va: implantation and management of complications. *J Ultrasound*. Epub ahead of print 1 September 2023. Crossref
25. Breschan C, Graf G, Arneitz C, et al. Feasibility of the ultrasound-guided supraclavicular cannulation of the brachiocephalic vein in very small weight infants: a case series. *Paediatr Anaesth* 2020; 30(8): 928–933. Crossref. PubMed.
26. Brescia F, Pittiruti M, Ostroff M, et al. Rapid femoral vein assessment (RaFeVA): a systematic protocol

for ultrasound evaluation of the veins of the lower limb, so to optimize the insertion of femorally inserted central catheters. *J Vasc Access* 2021; 22(6): 863–872. Crossref. PubMed. ISI.

27. Nifong TP, McDevitt TJ. The effect of catheter to vein ratio on blood flow rates in a simulated model of peripherally inserted central venous catheters. *Chest* 2011; 140: 48–53. Crossref. PubMed. ISI.
28. Lamperti M, Bodenham AR, Pittiruti M, et al. International evidence-based recommendations on ultrasound-guided vascular access. *Intensive Care Med* 2012; 38(7): 1105–1117. Crossref. PubMed. ISI.
29. Cellini M, Bergadano A, Crocoli A, et al. Guidelines of the Italian Association of Pediatric Hematology and Oncology for the management of the central venous access devices in pediatric patients with onco-hematological disease. *J Vasc Access*. 2021 May; 22(3):344–352. Crossref
30. Crocoli A, Tornesello A, Pittiruti M, et al. Central venous access devices in pediatric malignancies: a position paper of Italian Association of Pediatric Hematology and Oncology. *J Vasc Access* 2015; 16(2): 130–136. Crossref. PubMed. ISI.
31. Barone G, D'Andrea V, Vento G, et al. A systematic ultrasound evaluation of the diameter of deep veins in the Newborn: results and implications for clinical practice. *Neonatol* 2019; 115(4): 335–340. Crossref. PubMed.
32. Yokoe DS, Anderson DJ, Berenholtz SM, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. *Infect Control Hosp Epidemiol* 2014; 35(8): 967–977. Crossref. PubMed.
33. Loveday HP, Wilson JA, Pratt RJ, et al. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2014; 86(Suppl 1): S1–70. Crossref.
34. Johnson J, Bracken R, Tamma PD, et al. Trends in chlorhexidine use in US neonatal intensive care units: results from a follow-up national survey. *Infect Control Hosp Epidemiol* 2016; 37(9): 1116–1118. Crossref. PubMed.
35. Wendel D, Mezoff EA, Raghu VK, et al. Management of central venous access in children with intestinal failure: a position paper from the NASPGHAN intestinal rehabilitation special interest group. *J Pediatr Gastroenterol Nutr* 2021; 72: 474–486. Crossref. PubMed.
36. Grasso F, Capasso A, Pacella D, et al. Ultrasound guided catheter tip location in neonates: a prospective cohort study. *J Paediatric* 2022; 244: 86–91. Crossref. PubMed.
37. Barone G, Pittiruti M, Ancora G, et al. Centrally inserted central catheters in preterm neonates with weight below 1500g by ultrasound-guided access to the brachio-cephalic vein. *J Vac Access* 2021 May; 22(3):344–352. Crossref. PubMed.
38. Froehlich CD, Rigby MR, Rosenberg ES, et al. Ultrasound-guided central venous catheter placement decreases complications and decreases placement attempts compared with the landmark technique in patients in a pediatric intensive care unit. *Crit Care Med* 2009; 37(3): 1090–1096. Crossref. PubMed.
39. Oulego-Erroz I, González-Cortes R, García-Soler P, et al. Ultrasound-guided or landmark techniques for central venous catheter placement in critically ill children. *Intensive Care Med* 2018; 44: 61–72. Crossref. PubMed.
40. Oulego-Erroz I, Fernández-García A, Álvarez-Juan B, et al. Ultrasound guided supraclavicular

cannulation of the brachiocephalic vein may reduce central line-associated blood- stream infection in preterm infants. *Eur J Pediatr* 2020; 179(11): 1655–1663. Crossref. PubMed.

41. Habas F, Baleine J, Milési C, et al. Supraclavicular catheterization of the brachiocephalic vein: a way to prevent or reduce catheter maintenance-related complications in children. *Eur J Pediatr* 2018; 177: 451–459. Crossref. PubMed.
42. Raffaele A, Segal A, Romano P, et al. Intracavitary electrocardiography-guided positioning of central vascular access device can spare unnecessary ionizing radiation exposure in pediatric patients. *J Vasc Access* 2021; 22(1): 64–68. Crossref. PubMed. ISI.
43. Pittiruti M, Pelagatti F, Pinelli F. Intracavitary electrocardiography for tip location during central venous catheterization: a narrative review of 70 years of clinical studies. *J Vasc Access* 2021; 22(5): 778–785. Crossref. PubMed. ISI.
44. Pittiruti M, Bertollo D, Briglia E, et al. The intracavitary ECG method for positioning the tip of central venous catheters: results of an Italian multicenter study. *J Vasc Access* 2012; 13: 357–365. Crossref. PubMed. ISI.
45. Pittiruti M, Scoppettuolo G (eds). *Manuale GAVeCeLT dei PICC e dei midline*. 1st ed. Milan: Edra SpA, 2016, pp. 1–240.
46. Lawson BT, Zealley IA. Adult 'PICC' device may be used as a tunneled central venous catheter in children. *Cardiovasc Intervent Radiol* 2018; 41(4): 645–652. Crossref. PubMed.
47. Tsai MH, Lien R, Wang JW, et al. Complication rates with central venous catheters inserted at femoral and non-femoral sites in very low birth weight infants. *Pediatr Infect Dis J* 2009; 28(11): 966–970. Crossref. PubMed.
48. Sze Yong T, Vijayanathan AA, Chung E, et al. Comparing catheter related bloodstream infection rate between cuffed tunnelled and non-cuffed tunnelled peripherally inserted central catheter. *J Vasc Access*. Epub ahead of print 13 January 2021. Crossref
49. Bernasconi F, Zanaboni C, Dato A, et al. Atypical use of PICC in infants and small children: a unicentric experience. *J Vasc Access* 2017; 18(6): 535–539. Crossref. PubMed. ISI.
50. Pittiruti M. The "off-label" use of PICCs. In: Sandrucci S, Mussa B (eds) *Peripherally inserted central venous catheters*. 1st ed. Milan: Springer/Verlag, 2014, pp.127–144. Crossref.
51. Pinelli F, Pittiruti M, Van Boxtel T, et al. GAVeCeLT- WoCoVA consensus on subcutaneously anchored securement devices for the securement of venous catheters: current evidence and recommendations for future research. *J Vasc Access* 2021; 22(5): 716–725. Crossref. PubMed. ISI.
52. Crocoli A, Martucci C, Sidro L, et al. Safety and effective- ness of subcutaneously anchored securement for tunneled central catheters in oncological pediatric patients: a retrospective study. *J Vasc Access*. Epub ahead of print 4 June 2021. Crossref
53. Bainbridge P, Browning P, Bernatchez SF, et al. Comparing test methods for moisture-vapor transmission rate (MVTR) for vascular access transparent semipermeable dressings. *J Vasc Access* 2021. Epub ahead of print 8 October 2021. Crossref PubMed.
54. Wilkinson JN, Sheikh N, Jayamaha J. Tissue adhesive as an alternative to sutures for securing central venous catheters. *Anaesthesia* 2007; 62(9): 969–970. Crossref. PubMed. ISI.

55. Di Puccio F, Giacomarro D, Mattei L, et al. Experimental study on the chemico-physical interaction between a two-component cyanoacrylate glue and the material of PICCs. *J Vasc Access* 2018; 19(1): 58–62. Crossref. PubMed. ISI.

56. Lago P. Neonatal procedural pain management (vol II). *Front Paediatr* 2023; 11: 1270055. Crossref. PubMed.

57. Stevens B, Johnston C, Petryshen P, et al. Premature Infant Pain Profile: development and initial validation. *Clin J Pain* 1996; 12(1): 13–22. Crossref. PubMed.

58. Hummel P, Puchalski M, Creech SD, et al. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol* 2008; 28(1): 55–60. Crossref. PubMed. ISI.

59. Mermel LA, Allon M, Bouza E, et al. Clinical practice guide- lines 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. Crossref. PubMed. ISI.

60. Rey C, Alvarez F, De La Rua V, et al. Mechanical complications during central venous cannulations in pediatric patients. *Intensive Care Med* 2009; 35(8): 1438–1443. Crossref. PubMed.

61. Alexandrou E, Spencer TR, Frost SA, et al. Central venous catheter placement by advanced practice nurses demonstrates low procedural complication and infection rates: a report from 13 years of service. *Crit Care Med* 2014; 42(3): 536–543. Crossref. PubMed.

62. Payne NR, Carpenter JH, Badger GJ, et al. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. *Pediatrics* 2004; 114(2): 348–355. Crossref. PubMed.

63. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004; 292(19): 2357–2365. Crossref. PubMed.

64. Wheater M, Rennie JM. Perinatal infection is an important risk factor for cerebral palsy in very-low-birthweight infants. *Dev Med Child Neurol* 2000; 42: 364–367. Crossref. PubMed.

65. Pronovost P. Interventions to decrease catheter-related bloodstream infections in the ICU: the keystone intensive care unit project. *Am J Infect Control* 2008; 36(10): S171. e1–S171.e5. Crossref. PubMed.

66. Smulders CA, van Gestel JP, Bos AP. Are central line bundles and ventilator bundles effective in critically ill neonates and children? *Intensive Care Med* 2013; 39: 1352–1358. Crossref. PubMed. ISI.

67. Matysiak K, Szewczuk M, Sobocki J, et al. Complications of tunneled peripherally inserted and tunneled-cuffed central catheters in home parenteral nutrition. *Nutrition* 2021; 91–92: 111354. Crossref. PubMed.

68. Taylor JE, McDonald SJ, Earnest A, et al. A quality improvement initiative to reduce central line infection in neonates using checklists. *Eur J Pediatr* 2017; 176: 639–646 Crossref. PubMed.

69. Spagnuolo F, Vacchiano T. Ultrasound-guided cannulation of the brachiocephalic vein in newborns: a novel approach with a supraclavicular view for tip navigation and tip location. *J Vasc Access* 2022; 23(4): 515–523. Crossref. PubMed. ISI.