Editorial

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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

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Abstract

Introduction: Central venous accesses devices (CVADs) have a fundamental importance for diagnostic and therapeutic purposes in pediatric onco-hematological patients. The treatment of pediatric onco-hematological diseases is complex and requires the use of integrated multimodal therapies. Long-lasting and safe central venous access is therefore a cornerstone for any successful treatment.

Methods: The aim of this work is to define pediatric guidelines about the management of CVADs in onco-hematology. A panel of experts belonging to the working groups on Infections and Supportive Therapy, Surgery and Nursing of the Italian Pediatric Hematology Oncology Association (AIEOP) revised the scientific literature systematically, scored the level of evidence and prepared these guidelines. The content of the following guidelines was approved by the Scientific Board of AIEOP.

Results and Conclusions: Important innovations have been developed recently in the field of CVADs, leading to new insertion methods, new materials and new strategy in the overall management of the device, especially in the adult population. These guidelines recommend how to apply these innovations in the pediatric population, and are directed to all physicians, nurses and health personnel active in the daily management of CVADs. Their aim is to update the knowledge on CVAD and improve the standard of care in pediatric patients with malignancies.

Keywords

PICC, CICC, pediatric, malignancy (or hematology, oncology), ± vascular access

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Table 1. Indications for the positioning of a central venous catheter.

Infusion of solutions potentially harmful to the endothelium and / or vesicants and /or irritants
Drugs with osmolarity > 500 mOsm/L and NPT with osmolarity>900 mOsm/L
Solutions with pH<5 or pH>9
Clinically unstable patients with complex infusion regimens (multiple infusions) or need to infuse large quantities of fluids
Daily Withdrawals or prolonged therapy
Hemodynamic monitoring
Blood exchange procedures
Poor peripheral venous heritage

Introduction

Central venous access devices (CVAD) have a fundamental importance for the treatment of pediatric onco-hematological patients. The management of pediatric onco-hematological diseases is complex and requires the use of integrated multimodal therapies. Considering the limitation of peripheral venous access (multiple sticks, pain, risk of extravasation), long-lasting venous access has became mandatory in the last three decades to administer safely intravenous complex therapy and improving the quality of care.[1–3] Table 1 shows the most frequent indications to the positioning of central venous access (CVAD). However, CVAD can be associated with several complications such as malfunctions, infections, and thrombosis that may lead to prolonged hospitalizations, increased costs and sometimes require the adoption of additional systemic treatments (antibiotics, antifungal, heparin) or the removal of the catheter itself.[2,4] The prevalence of CVAD-related complications is of 14% to 36% in the first 2 years after its placement.[5] The risk of catheter-related complications can be however widely modulated by the method of CVAD insertion and by the-insertion management of the CVAD itself.[6] Early catheter-related complications (i.e. within 24–48 h after insertion) range between 7% and 18%.[7,8] Late complications, 48 or more hours after insertion, can be divided into infective and non-infective. Catheter related infections are an important cause of morbidity in patients with CVADs; the most frequently isolated pathogens are Gram positive, coagulase negative staphylococci (CONS) and *Staphylococcus Aureus*, followed by *Candida spp*.[9] Literature data report an incidence of central line associated blood stream infection catheter-related infections (CLABSI) between 1.7 and 11.3 cases for 1000 days catheter. In the onco-hematological setting the incidence is of 1.4 per 1000 catheter days for totally implantable ports and of 1–4.6 per 1000 catheter days for external catheters.[4] Moreover, CLABSI affect about 25% of pediatric patients with onco-hematological disease,[7] and its estimated mortality rate is between 12.5% and 25%.[6]

The incidence of CLABSI is variable according to patient factors (age, underlying disease) and also to modifiable factors such as correct hand hygiene and compliance with aseptic measures during and after insertion, type of CVAD, choice of the insertion site, technique of CVAD placement, dwelling time of CVAD, and-last but not least-management of the CVAD and the related devices (proper handling of line, correct preparation and administration of infusion fluids, correct dressing, appropriate technique of drug delivery).[10–12]

When choosing the CVAD, the clinician must considerer the patient demographic characteristics, the type of underlying disease, the cost-effectiveness and efficiency of each device. Moreover, in order to early identify or even prevent CVAD-related complications, it is important to define the correct practices for accessing the CVAD and maintaining its patency (flushing and locking).[13] Despite few randomized controlled trials have defined the standard best practice, the maximum adherence to the evidence is fundamental, especially in relation to the availability of new tools and materials. Considering that the adherence to guidelines in CVAD management significantly reduces the incidence of catheter-related complications, in particular infections and thrombosis,[14] a panel of Italian Pediatric Hematology Oncology Association (AIEOP) experts has developed these guidelines about the management of CVADs in pediatric onco-hematology.

Methods

This project was a joint effort of different Working Group (WG) of AIEOP: Infectious Disease WG, Supportive Therapy WG, Surgery WG, and Nursing WG. Each WG designed 2 to 4 of its to be included in the expert panel group (EPG) of this project. The selection criteria were: wide experience on CVAD in the daily practice, previous participation in developing policies and procedures on this topic, activity as speakers and tutors in scientific meetings and training courses, authorship or co-authorship of publications and/or guideline on this area. The EPG was coordinated by MC and SC who identified three subgroups of experts in charge for the literature search on three different topics: (1) medical management of CVADs; (2) nurse management of CVADs; (3) insertion of CVADs and insertion-related complications. The work of each group was divided in three steps: (a) literature search and summary of evidences; (b) scoring of evidences and proposal of recommendations; (c) discussion of recommendations, approval

Table 2. Grading of evidence based medicine according to the European society of microbiology and infectious diseases.

Strenght of recommendation (SoR)	
Grade	Definition
A	AIEOP strongly supports a recommendation for use
B	AIEOP moderately supports a recommendation for use
C	AIEOP marginally supports a recommendation for use
D	AIEOP supports a recommendation against use
Quality of evidence	
Level	Definition
I	Evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)
II*	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from > 1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index for source of level II evidence	
*	Source
r	Meta-analysis or systematic review of randomized controlled trial
t	Transferred evidence, that is result from different patient cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting

and writing the manuscript. For these purposes, the whole panel got together in four different occasion during 18-month period, while the rest of the discussion and exchange of information was carried out by e-mail and conference calls. The bibliographic research was performed on PubMed data base (https://pubmed.ncbi.nlm.nih.gov/) using the keywords "central venous catheter" and "pediatric malignancy"; only publications in English language were considered while case reports and case series where excluded. Further publications were identified by the reference list of selected publications. In the process of writing the manuscript, publications available by December 2019 were added if considered relevant. Literature evidences were scored according to the system proposed by the European Society for Clinical Microbiology and Infectious Disease that is based on 4 levels for the strength of recommendation (capital letter A, B, C, D), three levels for the evidence of recommendation (roman numbers I, II, III) and an index to specify the source of level II of evidence (Table 2). When there was insufficient data for a quality assessment, the panel of experts gave a recommendation, without indicating the quality of evidence. After editing the recommendations, the document was circulated among AIEOP members for 1 month for observations or suggestions and submitted for the final approval and endorsement by the scientific board of AIEOP.

Results and discussion

In our literature search, we selected 54 articles on pediatric patients: 29 out of 54 were focused on oncological diseases. Out of 68 articles on CVAD management only 10 articles were focused on pediatric oncology patients, seven on pediatric patients with non-oncological disease and eight on a mixed population of both oncological and non-oncological patients. We collected 22 study on choice and insertion of the CVAD: among these, six were on for pediatric oncology patients, five on non-oncological pediatric patients and 11 on a mixed pediatric population. We also considered one previous AIEOP position paper about the choice and insertion CVAD in the pediatric onco-hematology population[1] and two consensus documents about the diagnosis and management of thrombosis and infections on pediatric oncological patients[4,5] Furthermore, we have also considered other guidelines on CVAD management, even if not specifically addressing the pediatric onco-hematological population.

General recommendations about CVADs management

1. Periodic staff training is recommended for the maintenance and updating of skills in the management of VADs. (AII)

Maintaining skills related to the management of central venous access and updating knowledge in line with "evidence-based practice" must be an integral part of the training of any new employee and of the annual assessment of skills for all operators.[15] The literature shows that adherence to optimized guidelines with periodic staff refreshes (at least yearly) reduces the incidence of related catheter complications, mainly infectious-related.[14,16,17]

2. The use of bundles with checklists for the safe management of the CVAD in the pediatric oncohematology patient is recommended. (AII)

In recent years, the concept of "bundle" has increasingly been established in this area; a "bundle" is a set of recommendations and good behavior which, applied in systematic and consistently, can significantly improve the outcome of a procedure.[14,16–18]

3. It is recommended a constantly updated training also for the staff of auxiliary services (Radiology, Transfusion, Anesthesia and Resuscitation etc.) (A)

Although not based on formal clinical studies, the expert panel considered very important this recommendation in order to ensure an adequate expertise about the management of CVC among personnel of services that contribute in and cooperate with diagnostic and treatment procedures on the patients.

4. It is recommended that detailed documentation about the insertion site, the type of CVAD, the material of the catheter, the dead space and the length of external part of the catheter should be quickly and constantly accessible to the staff managing the patient. (AI)

Although not based on formal clinical studies, the expert panel considered very important this recommendation in order to give all key information about the CVAD to all personnel involved in the daily management and care of patient.

5. The home management of the CVAD is feasible and safe only after proper planning, which includes also proper training of the caregiver and/or of the patient himself. (AI t)

The possibility of home care of the CVAD must be considered after proper discussion among healthcare providers, caregivers and patients when the age of the patient allows to do it.[19,20]

Indications for insertion and selection of the CVAD

The choice of the VAD is of great importance and should be based upon patient's needs, particularly in relation to:

- Diagnosis, management plan and expected duration of the intravenous treatment
- Age of the patient
- Possible patient's preference for the type or location of the device (especially in the case of adolescent patients)
- Venous patrimony
- Family skills and resources available for maintaining and managing the CVAD

The choice of the most suitable CVAD must arise from the collaboration between all team's professionals (nurses, anesthesiologists, pediatric surgeons, pediatric oncologists, vascular access team) sharing this decision, if possible, also with the patient (e.g. adolescents and young adults) and with their caregivers, illustrating the pros and cons of each device. There is not sufficient evidence to absolutely recommend one device over another in each category of patients; Usually, it is recommended to use the device with the least number of lumens as far as possible for therapeutic needs.[21] The CVAD currently available, based on the new nomenclature,[22] can be divided as follows:

PICCs (peripherally inserted central catheters): That is, central catheters inserted, by puncture and cannulation of veins in the arm (basilica, brachial, cephalic, axillary).

CICCs (centrally inserted central catheters): That is, central catheters inserted by puncture and cannulation of deep veins of the supraclavicular and infraclavicular area (innominate, internal and external jugular, subclavian and axillary).

FICCs (femoral inserted central catheters): That is, central catheters inserted by puncture and cannulation of the veins of the inguinal region (common femoral and superficial femoral).

The use of FICCs is mainly limited to patients with mediastinal mass or anatomical lesions or thrombosis of the superior vena cava that contraindicate insertion of the catheter through cannulation of the veins of the arms or the cervico-thoracic area; it may be considered also in some patients at high risk for accidental dislodgment.

PORTs: are totally implantable CVAD, that consist of a catheter (PICC or CICC) connected to a reservoir, placed

in a subcutaneous pocket, accessible by puncture of a silicone membrane. Insertion and removal or ports require minor surgical procedures; also, access to the reservoir implies a skin puncture. Though, the advantage of ports is represented by the fact that—being totally implanted—they allow an easier body hygiene; also, they are associated with a better impact on body image.

For continuous use (daily access or at least one access per week) external catheters such as PICC, CICC and FICC are more appropriate. PICCs are traditionally considered to be adequate for medium-short term use; however, there is increasing evidence in favor of use of PICC also as long-term access, in particular for the latest generation polyurethane devices, with a lower incidence of infectious and thrombotic complications. The lumen size of these devices in relation to the vascular caliber limits their use only to cases where the diameter of the arm veins is appropriate.[23–25]

For intermittent use (less frequently than once per week), totally implantable systems (ports) are preferred. Typical indications are the intermittent long-term use such as in solid tumors, in patients with hemoglobinopathies, in hemophilic patients under prophylactic treatment, in the case of neuropsychiatric disease or syndromic patients with special needs.

After the selection of the device, the **insertion of the CVAD** is a procedure that requires a dedicated planning. Previously,[26,27] many pediatric CVADs were placed by venous cutdown. This technique is associated with several complications (infective and mechanical), so it must be strongly discouraged.[28–31] It also requires specialist surgical skills[31,32] and has higher performance costs.[33] Last but not least, in the event of repeated insertions, venous cutdown is inevitably associated with a progressive depletion of the vascular patrimony due to venous thrombosis and/or stenosis.[34–37] Venous cutdown is currently replaced by ultrasound-guided techniques, which are safer, more effective and more cost-effective.[38–40]

Today, the gold-standard in terms of technique of CVAD insertion is represented by the **ultrasound-guided percutaneous technique**,[3,41–43] which is based on ultrasound (US) use to locate the vein, study its characteristics (course, caliber, presence of valves / endoluminal formations), measure the distance of the same from the skin surface, direct the path of the needle and also control the introduction of the guide wire in real time.[44–46]

Recommendations about positioning and selecting CVADs

1) A tunneled catheter is recommended for continuous use. (AI r)

Given the simplicity of most tunneling techniques, it is suggested to always tunnel the catheters inserted in the election regimen, given the high impact that this technique has in reducing immediate and late complications.[21,42,47]

2) For discontinuous use, a totally implanted CVAD (Port) is recommended. (A II)

It is possible to implant either a chest- PORT, with catheter inserted in veins of the cervical-thoracic district, or a PICC-Port, in which the catheter is inserted in a deep vein of the arm and the pocket for the reservoir obtained possibly in the green area according to Dawson RB.[48] The choice of the vein depends exclusively on the venous patrimony and on the general conditions of the patient. Even for totally implantable systems, it is necessary to use micro-introduction kits, which may not always be provided in the PORT package.

Despite their small size, these devices allow the administration of fluids for hydration, blood products, parenteral therapies, chemotherapy drugs. PORT which allow the administration of high flows and contrast media should be preferred.[49,50]

3) It is recommended that the ratio of catheter caliber to vein diameter should not exceed 1/3. (A II)

In younger children insertion of catheters into supraclavicular veins is strongly recommended as they are of a more generous size, ensuring greater safety of the procedure. Puncture of subclavicular vessels (i.e. axillary vein) is recommended only in older children.[26,34,51–54]

4) Multiple lumen CVADs should be inserted only in few selected patients, based on the intensity of care and on the therapeutic program. (A)

The use of a multiple lumens catheter, although indicated in some specific categories of patients[1,10,28,42,55] (bone marrow transplantation, apheresis) is associated with an increased risk of infection[53,56] for multiple manipulation. The expert panel recommend that the choice of this device must be customized to the patient's needs.[11,28,47,54,57–59]

5) The choice of material must be based on high performance in terms of guaranteed flows and pressure resistance as well as device endurance. (A II)

For the short- and medium-term venous catheterization, both in children and infants, the tendency to use "off label" PICC power injectable has also developed in the past for the placement of catheters in veins of the cervical-thoracic district and in the femoral vein (CICC/FICC). In fact, the introduction kits contained in the PICC power injectable packs are generally built with more modern materials suitable for the pediatric patient:

- Third generation polyurethane catheters with power injectable technology that allow flows up to 5 ml/sec and the possibility of being used for injection of contrast medium via "power injector."
- Echogenic needles of small caliber (21 G).
- guidewires in nitinol (nickel-titanium) with a soft straight tip ("floppy-straight tip"), with a thickness of 0.018." These guide wires are particularly thin and non-traumatic in order to minimize risk of endothelial damage.
- micro-introducer dilator of suitable size and length for the pediatric patient from 3 Fr upwards
- the insertion of CICC/PICC or FICC catheters, using J-type metal guides wires, is strongly discouraged, especially in newborn babies where the arc of the J-type often exceeds the diameter of the canned vessel.[60,61]

6) Insertion by surgical venous cutdown is not recommended.[1,34,35,38,42,44,59,62,63] (AI)

Veins cannulation by venous cutdown is not recommended as standard procedure, especially in patients suffering from onco-hematological diseases. This technique, born in the 70s[27,64] together with the first CVAD designed for long-term use, has gradually lost its validity due to the high incidence of both short and long-term complications as well as for the permanent damage induced by surgical sacrifice to the vessel.[35]

7) The ultrasound-guided technique represents the current standard for venipuncture and venous cannulation for insertion of a CVAD. (AIt)

The ultrasound-guided percutaneous technique now represents the procedure of choice for the insertion of most CVAD even in the pediatric / neonatal age. This evidence is corroborated by numerous randomized studies that have shown how the use of ultrasound, increases the probability of successful cannulation of the target vessel while reducing both mechanical complications and the infectious ones associated with "blind" percutaneous venipuncture or venous cutdown.[38,42,44,59,62,63] Ultrasound also allows early diagnosis of any insertion-related complications (hematoma, hemorrhage, pneumothorax) and with the permanence of the catheter.[5,41,45,60,65,66]

8) The use of cyanoacrylate tissue glue is recommended (AII).

It is appropriate to apply cyanoacrylate glue at the exit site soon after catheter insertion; repeated post-insertion applications are not recommended, since the glue may deposit on the CVAD and may be difficult to remove. The glue allows rapid and complete hemostasis at the exit site, reduces the incidence of dressing change, decrease the micro-macro movements of the catheter and may be useful in prevention of thrombosis and infections. The use of glue alone does not seem to reduce the risk of dislocation but—when used in association with other securement devices—it seems to improve the dwelling time of the CVADs.[59,67–70] A recent study shows that the use of glue on polyurethane catheters for long periods does not cause alterations to the structure of the device. The same study underlines the possibility of damage induced by cyanoacrylate on silicone, therefore not advising use of glue on silicone catheters.[71]

9) The use of an insertion BUNDLE and of a maintenance bundle[21,72], as described in Tables 3 and 4,[3,40,43,46,73–75] is recommended (A1).

Management of the infusion lines

The management of the infusion lines and the exit site is part of the care of patients with a CVAD. Routine inspections of the infusion line and the exit site must be scheduled; skin antisepsis and dressings changes must be performed at pre-established intervals. Indications and protocols for the management of these devices, must be specified in the hospital policies and / or in the local protocols. General behavioral rules such as routine hand hygiene during all care actions and the education of family members and patients in this practice are to be considered a strong recommendation in all circumstances.[11,76–79]

Recommendations about infusion lines management

1. Minimize the number of CVAD accesses to prevent infections, doing diagnostic and therapeutic procedures at the same time.[3] (A)

Although not based on formal clinical studies, the expert panel considered very important this recommendation in order to sensitize patient, health personnel and caregiver on the importance to avoid unnecessary manipulation of CVC.

2. Limit intermittent infusion (AII).

Repeated disconnection and reconnection of an intermittent infusion line increases the risk of contamination at all connection points, with an increased risk of CLABSI.[80–82]

3. Use NFC (needle free connectors) (A II t).

Use transparent NFC, with neutral/negligible displacement, minimum dead space and luer-lock connection, for closing the access to the CVAD.[11,40,81,83,84]

Table 3. BUNDLE for CVAD positioning.

Implant BUNDLE
a) Hand washing, aseptic technique, and maximum barrier protection during the procedure.[59] Hand washing before the procedure must be done with alcoholic gel or with disinfectant soap if visibly dirty or contaminated. The maximum precautions are also meant for the sterile and adequately length coverage of the ultrasound probe.[40]
b) Appropriate selection of the insertion site: an ultrasound scan of all veins of the arm and neck is performed bilaterally before the procedure.[46]
c) Choice of the most appropriate vein in terms of caliber, collapsibility, depth and proximity to structures at risk.[46]
d) Use of 2% chlorhexidine in 70% isopropyl alcohol for skin disinfection before insertion. Sterile single-dose applicators are recommended.[3]
e) US-guided system.[43]
f) Use the intracavitary ECG method to check the position of the catheter tip.[73]
g) Use non-cuffed external catheter stabilization systems (or cuffed until cuff stabilization), of the sutureless or subcutaneous implant type.[74,75]
h) Use of cyanoacrylate glue for the protection of the exit site
i) Use of transparent semipermeable dressings wherever possible.

Table 4. BUNDLE for CVAD maintenance.

General recommendations
- Daily re-evaluation of the need for a central venous access
- Hand hygiene before any contact with the venous access device, with the insertion site or with any part of the infusion line
- Replacement of the skin adhesive sutureless device at least weekly (subcutaneously anchored securement devices do not require replacement)
Care of the exit site
- Daily inspection/palpation of the exit site
- Replacement of the transparent dressing at least weekly or more frequently if soiled, wet or detached
- Replacement of the skin adhesive sutureless device at least weekly (subcutaneously anchored securement devices do not require replacement)
- Skin antisepsis with 2% chlorhexidine in 70% isopropyl alcohol at each dressing change
Care of the infusion lines
- Close with a needle free connector any hub used discontinuously
- Active disinfection of the needle free connector before each access, using 2% chlorhexidine in 70% alcohol; as an alternate option, passive disinfection with port protectors (disinfecting caps)
- Flush and lock all lumens with normal saline: catheters not in use should be flushed at least weekly
- Periodic replacement of the infusion lines, with a frequency depending on the solution delivered

4. Respect the aseptic technique in the management of CVAD and during dressings changes, using only sterile, single use devices.[3,82,85] (A r)
5. Disinfect the access surface of the NFC before each use by friction of 5-15 seconds with 2% chlorhexidine in alcoholic solution.[11,40,82,85] (AI t)

Single-dose 2% chlorhexidine preparations reduce the risk of microbial contamination. As an alternative to manual / active disinfection, use port protectors, that is, disinfecting caps containing 70% isopropyl alcohol which have been proven to reduce bacterial growth at the hub level and the incidence of CLABSI.[82,83,85–88]

6. Replace the NFC at the same time as the administration set (for CVADs in use see frequency in point 9) or at the end of the infusion of blood products or in the presence of evident blood residues.[11,84,89] (AII r t)
7. Adopt the flush-clamping-disconnection sequence when replacing the NFC. After replacing the NFC, leave the clamp open (BIII).

This practice reduces blood reflux in the catheter lumen and the risk of intraluminal occlusions from clots.[81]

8. Minimize the number of additional devices (ramps, filters, caps, extensions) to reduce the risk of contamination and accidental disconnections.[87,90–93] (AI t)
9. Replace the infusion lines with a frequency based on the solution administered or the type of administration (continuous vs intermittent), or in case of contamination or compromised integrity of the materials. (A r)

The recommended frequency based on the type of infusion is as follows:

a. solutions for parenteral nutrition: at least every 24 h or every time a new bag of nutrition is connected[11,80,82,84]
b. Blood transfusions: at the end of each blood unit [3]
c. Propofol every 6 or 12 hours and whenever the container is changed with propofol[3]
d. Lipid emulsions: every 12 hours[80]
e. Continuous infusion set: not more than 96 hours[11,80,87,94]

Exit/insertion site management

Exit site management includes skin antisepsis and periodic dressing replacement at pre-established intervals or in an extemporaneous way as soon as the dressing appears moist, loose, or visibly dirty.

Recommendations for external CVADs

1. Always respect the aseptic technique in the management of the emergency site.[3,82,85] (A r)
2. Carefully examine the catheter exit site and the surrounding area daily (without removing the dressing if not necessary) to identify any redness, tenderness, edema, and secretions.[11,40,95,96] (A II)
3. Always evaluate any skin lesions associated with medical adhesives (MARSI = Medical Adhesive Related Skin Injury) secondary to the use of dressing devices or skin adhesion stabilization devices.[3,96,97] (A r)
4. Use 2% chlorhexidine gluconate in 70% isopropyl alcohol as a skin antiseptic to clean the exit site. Single-dose preparations of chlorhexidine reduce the risk of microbial contamination.[11,40,82,96,98,99] (AI t)

Note: in premature infants, excess of chlorhexidine or alcohol may cause skin irritation and chemical burns.[11,40,98,99] : in these patients, use only the minimal necessary amount of antiseptic and remove after 30 s. Do not use iodine or povidone-iodine in premature newborns, since it may interfere with thyroid metabolism[87,96,98–101]

5. The use of transparent films with high index of transpirability (high MVTR = moisture vapor transfer rate) is recommended; replace them every 7 days. (AII t)
6. Document all routine and extraordinary management actions on the CVAD for correct monitoring.[102,103] (A)

Recommendations for totally implantable CVADs (Ports)

1. Examine the region of the skin pocket, to assess the presence of signs of swelling, erythema, or secretion. [89,96,104,105] (A I)

Use 2% chlorhexidine gluconate in 70% isopropyl alcohol for skin antisepsis before inserting the non-coring Huber needle respecting the time of action.[102–104]

2. Flush the port preferably orienting the bevel of the Huber needle in the opposite direction from the connection between the catheter and the reservoir, so to facilitate the removal of deposits.[3](B III)

Use Huber needles of appropriate length to reduce the risk of dislocation: the wing of the needle must rest on the skin and at the same time the tip of the needle must touch the bottom of the reservoir.

3. Check the functionality of the catheter and the correct positioning of the needle with blood aspiration and flush before every use of the device. (A r).
4. Replace the Huber needle at least every 7 days.[105] (A)
5. Cover the Huber needle and the access to the reservoir using sterile, transparent, semi-permeable dressings with a high MVTR when the port is in use.
6. Flush the port (if not in use) with saline, every month.[103,106,107] (AI)

In adult population it is well accepted that extending the flushing interval to up to 3 months remains medically safe and drastically reduces the costs. On the contrary, pediatric patients may be more prone to either mechanical and thrombotic complications for several reasons (type of disease with related thrombophilic condition, smaller vessels and smaller catheters etc.). For these reasons, monthly flushing of the catheter should be recommended.

Furthermore, prospective randomized controlled trials showed that the use of heparinized solutions had no significant advantage compared to normal saline in the reduction of catheter malfunction due to clots.[102,105,106,108,109]

7. Replace the dressing every 7 days or at each replacement of the Huber needle.[102,106] (AII)

Choice of securement devices

Securement of CVAD is an important safeguard as it reduces one of the most important complications, that is, dislodgment. Securement must be chosen according to the following characteristics: it must prevent movements of the CVAD and avoid dislocation, prevent accidental removal, prevent micro-movements that generate damage to the vascular walls and protect the insertion site from microbial contamination maintaining skin integrity around the insertion site. The chosen device must be compatible with alcohol-based solutions, chlorhexidine gluconate and iodophors such as povidone-iodine. Also, it must ensure visibility of the insertion site and the administration of therapies; it must be comfortable and non-irritating for the

patient, easy to use and with a favorable cost-benefit ratio.[3,110,111]

Recommendations about the use of Securement Devices

1) Stabilization is essential to prevent complications, especially CVAD dislodgment, (AI r) and can be obtained by different devices such as: (a) securement system integrated in the dressing, (b) sutureless systems with skin adhesion, (c) subcutaneously anchored securement (SAS).[3,65,105,107–113,114–117]

There is currently no strong evidence to indicate the superiority of one securement i device over another.[116–122]

2) The application of CVAD securement requires asepsis. (B II)
3) The use of sutures for CVAD stabilization is contraindicated as it is associated with a greater risk of infectious and accidental puncture.[3,67,110,111,123](AII)

Evaluate the integrity of sutureless devices with skin adhesion at each dressing change. The devices must be replaced weekly, or earlier if they are wet, dirty, or even partially detached.

4) Subcutaneously anchored securement devices must be of appropriate caliber, suitable to the external diameter of the catheter (CICC-PICC-FICC). (IIA)[118–121]

The use of SAS is recommended for CVADs with a duration of more than 15 days or in situation at high risk for dislodgment; they must be removed in the event of an exit site infection.[116] The application of gauze between the skin and the SAS can be advantageous to reduce the risk of pressure decubitus skin lesions.[113,124,125]

Flushing and locking the CVAD

The recent literature shows[102,106,108,109,126,127] that maintaining the patency of a CVAD does not require the use of heparin but the adoption of strategies such as (a) an adequate protocol for rinsing the device (FLUSH) and closing it (LOCK) with normal saline, and (b) the adoption of NFC able to prevent blood reflux (backflow) inside the catheter at the time of disconnection from the venous line (Neutral displacement NFC).

Recommendations about flushing the CVAD

1) Prior to any infusion, especially in case of administration of antiblastic/vesicant, check the patency of the CVAD by aspirating blood and infusing normal saline. Flush with the pulsatile technique (push and pause).[3,126,128–130] (A r)

It is recommended to flush using disposable, single-dose pre-filled syringes.[3,127,129]

Flushing with saline after each infusion will eliminate drugs precipitate inside the lumen and reduce the risk of interaction between incompatible drugs. Flushing must be enforced after infusion of blood products or infusion of lipids or after drawing blood samples from the catheter or after infusing contrast medium.[128,129,131] In case of drugs incompatible with sodium chloride, flush first with 5% glucose solution and then with normal saline. Do not leave glucose in the lumen of the catheter, since this will enhance the formation of the biofilm.

The start-stop flushing technique is recommended, in order to create turbulence inside the catheter lumen and to prevent blood product from adhering to the inner catheter wall.

2) It is recommended to use a “no reflux” strategy to prevent blood reflux.[93,126,130] (AII)

It is recommended to use pre-filled syringes with stops at the end of the run (or alternatively normal syringes but leaving 1 ml at the end of the flush) adopting start-stop technique leaving the clamp open after disconnection. Adopt a proper sequence of flush-clamping-disconnection if neutral displacement NFC are not available.

Recommendations about locking the CVAD

1) The use of normal saline is recommended for locking CVADs.[127] (A I)

Randomized controlled trials have shown no difference between saline and heparinized solution; saline is preferable due to the greater handling and the lower risk of side effects compared to heparin especially in the newborn.[3,106,108]

2) Locking with non-antibiotic antibacterial substances (in particular, 2% taurolidine) has been proven effective in pediatric patients in reducing the risk of infection.[126,132–135] Data on the pediatric cancer population are still limited.[136,137] (BI)
3) The use of thrombolytic substances (urokinase 5000 IU/ml or the tissue activator of plasminogen - rTPA 1 mg/ml) is recommended only in case of occlusion of the catheter lumen due to clots.[5] (A II)

The diagnosis of lumen occlusion is suspected after performing the following assessments:

A) Impossibility in aspiration or difficulty in blood return, impossibility or difficulty in infusion;
B) Exclusion of extraluminal causes such as kinking of the catheter, pinch-off, fibroblastic sleeve, non-functioning

valved catheter, venous thrombosis at the tip of the catheter.

Lumen occlusion may be secondary to clots, drug precipitates, lipids, or contrast medium. The nature of the occlusion is usually identified by investigating the recent maneuvers performed on the CVAD. Attempts to pharmacological unblocking include the use of thrombolytics (clot occlusion), 50-75% ethanol (lipid occlusion), 8.4% sodium bicarbonate (occlusion due to drugs or contrast medium).

The solution used for unblocking the catheter should be removed as much as possible, so to reduce the risk of undesirable side effects.[138,139]

Conclusion

Over the past few years, we have observed important innovations in relation to the use of CVADs in the pediatric field linked to new insertion technique, use of new materials and news concepts in the general management of the device. For this reason, we decide to develop guidelines that could be of reference in the daily practice of pediatric oncohemathology.

From all the literature analyzed, some fundamental bundles emerge (highlighted in Appendix 1) especially in relation to CVAD insertion techniques, the use of securement systems and the need for a correct training of the new staff and periodic refreshes of the old staff (including the patient's caregivers) so to maintain a proper level of skills in CVAD management.

The aim of these guidelines is to help every clinician taking care of pediatric onco-hematological patients requiring CVADs; also, we hope that this may be the basis for a process of revision and updating of management practices of CVADs in any center of pediatric oncology.

Appendix 1. BUNDLE for the management of the CVAD.

a.Hand washing, aseptic technique and maximum barrier protections during the implantation procedure. Hand washing before the procedure must be done with alcoholic gel or with disinfectant soap if visibly dirty or contaminated. The maximum precautions are also meant for the sterile and adequately length coverage of the ultrasound probe
b.Appropriate selection of the insertion site: an ultrasound scan of all veins of the arm and neck is performed bilaterally before the procedure.
c.Choice of the most appropriate vein in terms of size, collapsibility, depth and proximity to structures at risk.
d.Use of 2% chlorhexidine in 70% isopropyl alcohol for skin disinfection before insertion. Sterile single-dose applicators are recommended.
e.US-guided system
f.Use the intracavitary ECG method to check the position of the catheter
g.Use non-cuffed external catheter stabilization systems (or cuffed until cuff stabilization), of the sutureless or subcutaneous implant type.
h.Use of cyanoacrylate glue for the protection of the exit site.
i.Daily re-evaluate the need for catheter permanence.
j.Carry out hand hygiene before any contact with the catheter, the insertion site and the infusion lines.
k.Disinfect the needle-free connector access port (hub) before each access with 2% chlorhexidine solution in 70% alcohol solutions.
l.Flush and lock with normal saline. Washing should be done every 7 days.
m.The dressing (sterile, transparent, semipermeable) must remain intact (dry, not detached, clean) and must be replaced every 7 days.
n.Use 2% chlorhexidine gluconate in 70% alcohol for disinfection of the insertion site when changing the dressing.
Always keep in mind the times for replacing the infusion lines according to the solutions administered.

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References

1. 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: 130–136.
2. Redfern W and Braby J. *Plumer's Principles and practice of infusion therapy*. Philadelphia, PA, USA: Wolters Kluwer/ Lippincott Williams and Wilkins. 2014; pp. 678–742.
3. Gorski LA. The 2016 infusion therapy standards of practice. *Home Heal Now* 2016; 35: 10–18.
4. Carraro F, Cicalese MP, Cesaro S, et al. Guidelines for the use of long-term central venous catheter in children with hemato-oncological disorders. on behalf of supportive therapy working group of Italian Association of Pediatric

Hematology and Oncology (AIEOP). *Ann Hematol* 2013; 92: 1405–1412.
5. Giordano P, Saracco P, Grassi M, et al. Recommendations for the use of long-term central venous catheter (CVC) in children with hemato-oncological disorders: management of CVC-related occlusion and CVC-related thrombosis. On behalf of the coagulation defects working group and the supportive the. *Ann Hematol* 2015; 94: 1765–1776.
6. Baskin KM, Mermel LA, Saad TF, et al. Evidence-based strategies and recommendations for preservation of central venous access in children. *J Parenter Enter Nutr* 2019; 43: 591–614.
7. Ullman AJ, Marsh N, Mihala G, et al. Complications of central venous access devices: a systematic review. *Pediatrics* 2015;136:e1331–e1344.
8. Rey C, Álvarez F, De La Rua V, et al. Mechanical complications during central venous cannulations in pediatric patients. *Intensive Care Med* 2009; 35: 1438–1443.
9. 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: 1–45.
10. 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: 1505–1512.
11. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011; 52: e162–e193.
12. 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: 648–654.
13. Rickard CM and Ullman AJ. Bloodstream infection and occlusion of central venous catheters in children. *Lancet Infect Dis* 2018; 18: 815–817.
14. Choi SW, Chang L, Hanauer DA, et al. Rapid reduction of central line infections in hospitalized pediatric oncology patients through simple quality improvement methods. *Pediatr Blood Cancer* 2013; 60: 262–269.
15. Secola R, Azen C, Lewis MA, et al. A crossover randomized prospective pilot study evaluating a central venous catheter team in reducing catheter-related bloodstream infections in pediatric oncology patients. *J Pediatr Oncol Nurs* 2012; 29: 307–315.
16. Rinke ML, Chen AR, Bundy DG, et al. Implementation of a central line maintenance care bundle in hospitalized pediatric oncology patients. *Pediatrics* 2012; 130: e996–1004.
17. Duffy EA, Rodgers CC, Shever LL, et al. Implementing a daily maintenance care bundle to prevent central line–associated bloodstream infections in pediatric oncology patients. *J Pediatr Oncol Nurs* 2015; 32: 394–400.
18. Dandoy CE, Hausfeld J, Flesch L, et al. Rapid cycle development of a multifactorial intervention achieved sustained reductions in central line-associated bloodstream infections in haematology oncology units at a children's hospital: a time series analysis. *BMJ Qual Saf* 2016; 25: 633–643.
19. Rinke M, Chen AR, Milstone AM, et al. Bringing central-line associated bloodstream infection Prevention Home: catheter maintenance practices and beliefs of pediatric oncology patients and families. *Jt Comm J Qual Patient Saf* 2015; 41: 177–185.
20. Møller T and Adamsen L. Hematologic patients' clinical and psychosocial experiences with implanted long-term central venous catheter: self-management versus professionally controlled care. *Cancer Nurs* 2010; 33: 426–435.
21. Schiffer CA, Mangu PB, Wade JC, et al. Central venous catheter care for the patient with cancer: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 2013; 31: 1357–1370.
22. Pittiruti M and Scoppettuolo G *The GAVeCeLT manual of PICC and midline: Indications, insertion, management*. Milan, Italy: Edra 2017; pp. 1–240.
23. Abedin S and Kapoor G. Peripherally inserted central venous catheters are a good option for prolonged venous access in children with cancer. *Pediatr Blood Cancer* 2008; 51: 251–255.
24. Cotogni P, Pittiruti M, Barbero C, et al. Catheter-related complications in cancer patients on home parenteral nutrition. *J Parenter Enter Nutr* 2013; 37: 375–383.
25. Cotogni P, Barbero C, Garrino C, et al. Peripherally inserted central catheters in non-hospitalized cancer patients: 5-year results of a prospective study. *Support Care Cancer* 2015; 23: 403–409.
26. Broviac JW, Cole JJ and Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. *Surg Gynecol Obstet* 1973; 136: 602–606.
27. Hickman RO, Buckner CD, Clift RA, et al. A modified right atrial catheter for access to the venous system in marrow transplant recipients. *Surg Gynecol Obstet* 1979; 148: 871–875.
28. Ares G and Hunter CJ. Central venous access in children: indications, devices, and risks. *Curr Opin Pediatr* 2017; 29: 340–346.
29. Perdikaris P, Petsios K, Vasilatou-Kosmidis H, et al. Complications of HickmanBroviac catheters in children with malignancies. *Pediatr Hematol Oncol* 2008; 25: 375–384.
30. Blum L-V, Abdel-Rahman U, Klingebiel T, et al. Tunneled central venous catheters in children with malignant and chronic diseases: a comparison of open vs. percutaneous implantation. *J Pediatr Surg* 2017; 52: 810–812.
31. Dzierzega M, Ossowska M, Chmiel D, et al. The malposition of central venous catheters in children. *Polish J Radiol* 2014; 79: 275–278.
32. Kamra K and Hammer GB. Central venous catheter placement in children: 'How good is good enough?' *Pediatr Anesth* 2013; 23: 971–973.
33. Hancock-Howard R, Connolly BL, McMahon M, et al. Cost-effectiveness analysis of implantable venous access device insertion using interventional radiologic versus conventional operating room methods in pediatric patients with cancer. *J Vasc Interv Radiol* 2010; 21: 677–684.
34. Davidson J, Paul A, Patel S, et al. Central vein preservation in critical venous access. *Eur J Pediatr Surg* 2015; 26: 357–362.
35. Cameron GS. Central venous catheters for children with malignant disease: surgical issues. *J Pediatr Surg* 1987; 22: 702–704.
36. Kim S, Kim Y and Moon S-B. Histological changes of the unligated vein wall adjacent to the central venous catheter after open cutdown in rats. *J Pediatr Surg* 2015; 50: 1928–1932.

37. Kim S, Kim Y, Hwang JW, et al. Inhibitory effect of sustained perivascular delivery of paclitaxel on neointimal hyperplasia in the jugular vein after open cutdown central venous catheter placement in rats. *Ann Surg Treat Res* 2017; 92(2): 97.
38. Moureau N, Lamperti M, Kelly LJ, et al. Evidence-based consensus on the insertion of central venous access devices: definition of minimal requirements for training. *Br J Anaesth* 2013; 110: 347–356.
39. Avanzini S, Guida E, Conte M, et al. Shifting from open surgical cut down to ultrasound-guided percutaneous central venous catheterization in children: learning curve and related complications. *Pediatr Surg Int* 2010; 26: 819–824.
40. 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: S1–70.
41. Gurien LA, Blakely ML, Russell RT, et al. Real-time ultrasonography for placement of central venous catheters in children: a multi-institutional study. *Surgery* 2016; 160: 1605–1611.
42. Lamperti M, Bodenham AR, Pittiruti M, et al. International evidence-based recommendations on ultrasound-guided vascular access. *Intensive Care Med* 2012; 38: 1105–1117.
43. Pittiruti M. Ultrasound guided central vascular access in neonates, infants and children. *Curr Drug Targets* 2012; 13: 961–969.
44. Bruzoni M, Slater BJ, Wall J, et al. A prospective randomized trial of ultrasound- vs landmark-guided central venous access in the pediatric population. *J Am Coll Surg* 2013; 216: 939–943.
45. Dassinger MS, Renaud EJ, Goldin A, et al. Use of real-time ultrasound during central venous catheter placement: results of an APSA survey. *J Pediatr Surg* 2015; 50: 1162–1167.
46. Spencer TR and Pittiruti M. Rapid central vein assessment (RaCeVA): a systematic, standardized approach for ultrasound assessment before central venous catheterization. *J Vasc Access* 2019; 20: 239–249.
47. Shulman RJ, Smith EO, Rahman S, et al. Single- vs double-lumen central venous catheters in pediatric oncology patients. *Am J Dis Child* 1988; 142: 893–895.
48. Dawson RB. PICC Zone Insertion Method™ (ZIM™): a systematic approach to determine the ideal insertion site for PICCs in the upper arm. *J Assoc Vasc Access* 2011; 16: 156–160.
49. Bonciarelli G, Batacchi S, Biffi R, et al. Gavecelt consensus statement on the correct use of totally implantable venous access devices for diagnostic radiology procedures. *J Vasc Access* 2011; 12: 292–305.
50. Burbridge B, Plewes C, Stoneham G, et al. Randomized clinical trial evaluating complications and complication-related removal of arm-situated power-injectable and non-power–injectable totally implanted venous access devices among cancer patients. *J Vasc Interv Radiol* 2018; 29: 648–656.
51. Journeycake JM and Buchanan GR. Thrombotic complications of central venous catheters in children. *Curr Opin Hematol* 2003; 10: 369–374.
52. Matsuzaki A, Suminoe A, Koga Y, et al. Long-term use of peripherally inserted central venous catheters for cancer chemotherapy in children. *Support Care Cancer* 2006; 14: 153–160.
53. Skinner R, Koller K, McIntosh N, et al. Prevention and management of central venous catheter occlusion and thrombosis in children with cancer. *Pediatr Blood Cancer* 2008; 50: 826–830.
54. Thurman CB, Abbott M, Liu J, et al. Risk for health care-associated bloodstream infections in pediatric oncology patients with various malignancies. *J Pediatr Oncol Nurs* 2017; 34: 196–202.
55. Marcy P-Y. Central venous access: techniques and indications in oncology. *Eur Radiol* 2008; 18: 2333–2344.
56. Dezfulian C, Lavelle J, Nallamothu BK, et al. Rates of infection for single-lumen versus multilumen central venous catheters: a meta-analysis. *Crit Care Med* 2003; 31: 2385–2390.
57. Chen S-H, Yang C-P, Jaing T-H, et al. Catheter-related bloodstream infection with removal of catheter in pediatric oncology patients: a 10-year experience in Taiwan. *Int J Clin Oncol* 2012; 17: 124–130.
58. Gonzalez G, Davidoff AM, Howard SC, et al. Safety of central venous catheter placement at diagnosis of acute lymphoblastic leukemia in children. *Pediatr Blood Cancer* 2012; 58: 498–502.
59. Biasucci DG, Pittiruti M, Taddei A, et al. Targeting zero catheter-related bloodstream infections in pediatric intensive care unit: a retrospective matched case-control study. *J Vasc Access* 2018; 19: 119–24.
60. Omid M, Rafiei MH, Hosseinpour M, et al. Ultrasound-guided percutaneous central venous catheterization in infants: learning curve and related complications. *Adv Biomed Res* 2015; 4: 199.
61. Nakayama S, Takahashi S and Toyooka H. Curved-end guidewire for central venous cannulation in neonate. *Anesth Analg* 2003; 97: 917–918.
62. Lau CSM and Chamberlain RS. Ultrasound-guided central venous catheter placement increases success rates in pediatric patients: a meta-analysis. *Pediatr Res* 2016; 80: 178–184.
63. Nardi N, Wodey E, Laviolle B, et al. Effectiveness and complications of ultrasound-guided subclavian vein cannulation in children and neonates. *Anaesth Crit Care Pain Med* 2016; 35: 209–213.
64. Niederhuber JE, Ensminger W, Gyves JW, et al. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. *Surgery* 1982; 92: 706–712.
65. Raman D, Sharma M, Moghekar A, et al. Utilization of thoracic ultrasound for confirmation of central venous catheter placement and exclusion of pneumothorax: a novel technique in real-time application. *J Intensive Care Med* 2019; 34: 594–598
66. 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: 344–376.
67. Emoli A, Cappuccio S, Marche B, et al. Il protocollo "ISP" (Safe Insertion of Picc): un 'bundle' di otto raccomandazioni per minimizzare le complicanze legate all'impianto dei PICC [Italian]. *Assist Inferm e Ric* 2014; 33(2): 82–90.

68. Pittiruti M, Scoppettuolo G, Emoli A, et al. Cyanoacrylate glue and central venous access device insertion. *J Assoc Vasc Access* 2016; 21: 249.
69. Scoppettuolo G, Annetta M, Marano C, et al. Cyanoacrylate glue prevents early bleeding of the exit site after CVC or PICC placement. *Crit Care* 2013; 17: P174.
70. Corley A, Marsh N, Ullman AJ, et al. Tissue adhesive for vascular access devices: who, what, where and when? *Br J Nurs* 2017; 26: 4–17.
71. 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: 58–62.
72. Walz JM, Ellison RT, Mack DA, et al. The bundle "plus": the effect of a multidisciplinary team approach to eradicate central line-associated bloodstream infections. *Anesth Analg* 2015; 120: 868–876.
73. 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: 137–143.
74. Bugden S, Shean K, Scott M, et al. Skin glue reduces the failure rate of emergency department–inserted peripheral intravenous catheters: a randomized controlled trial. *Ann Emerg Med* 2016; 68: 196–201.
75. Scoppettuolo G, Dolcetti L, Emoli A, et al. Further benefits of cyanoacrylate glue for central venous catheterisation. *Anaesthesia* 2015; 70: 758.
76. Boyce JM and Pittet D. Healthcare infection control practices advisory committee, HICPAC/SHEA/APIC/IDSA hand hygiene task force. Guideline for hand hygiene in healthcare settings. Recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force. Society for healthcare epidemiology of America/Association for professionals in infection control/infectious diseases society of america. *MMWR Recomm Reports Morb Mortal Wkly Report Recomm Reports* 2002; 51(RR-16): 1–45
77. World Health Organization (WHO). *WHO guidelines on hand hygiene in health care*. Geneva: Switz WHO, 2009.
78. (WHO) WHO. Hand Hygiene in outpatient and home-based care and long term care facilities, 2012.
79. Ellingson K, Haas JP, Aiello AE, et al. Strategies to prevent healthcare-associated infections through hand hygiene. *Infect Control Hosp Epidemiol* 2014; 35: 937–960.
80. Ullman AJ, Cooke ML, Gillies D, et al. Optimal timing for intravascular administration set replacement. *Cochrane Database Syst Rev* 2013; 9: CD003588.
81. Hadaway L. Needleless connectors for IV catheters. *Am J Nurs* 2012; 112: 32–44.
82. Velasquez Reyes DC, Bloomer M and Morphet J. Prevention of central venous line associated bloodstream infections in adult intensive care units: a systematic review. *Intensive Crit Care Nurs* 2017; 43: 12–22.
83. Casey AL, Karpanen TJ, Nightingale P, et al. An in vitro comparison of standard cleaning to a continuous passive disinfection cap for the decontamination of needle-free connectors. *Antimicrob Resist Infect Control* 2018; 7(1): 50.
84. Sherertz RJ, Karchmer TB, Palavecino E, et al. Blood drawn through valved catheter hub connectors carries a significant risk of contamination. *Eur J Clin Microbiol Infect Dis* 2011; 30: 1571–1577.
85. Bell T and O'Grady NP. Prevention of central line–associated bloodstream infections. *Infect Dis Clin North Am* 2017; 31: 551–559.
86. Inchingolo R, Pasciuto G, Magnini D, et al. Educational interventions alone and combined with port protector reduce the rate of central venous catheter infection and colonization in respiratory semi-intensive care unit. *BMC Infect Dis* 2019; 19(1): 215.
87. Marschall J, Mermel LA, Fakih M, et al. Strategies to prevent central line–associated bloodstream infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014; 3: 753–771.
88. Moureau NL and Flynn J. Disinfection of needleless connector hubs: clinical evidence systematic review. *Nurs Res Pract* 2015; 2015: 796762.
89. Sandora TJ, Graham DA, Conway M, et al. Impact of needleless connector change frequency on central line-associated bloodstream infection rate. *Am J Infect Control* 2014; 42: 485–489.
90. González López JL, Arribi Vilela A, Fernández del Palacio E, et al. Indwell times, complications and costs of open vs closed safety peripheral intravenous catheters: a randomized study. *J Hosp Infect* 2014; 86: 117–126.
91. Tamura N, Abe S, Hagimoto K, et al. Unfavorable peripheral intravenous catheter replacements can be reduced using an integrated closed intravenous catheter system. *J Vasc Access* 2014; 15: 257–263.
92. Administration UF and D. Safety considerations to mitigate the risks of misconnections with small-bore connectors intended for enteral applications, 2015
93. Hadaway L.Infusion therapy equipment. In: Alexander M, Corrigan A, Gorski L, Hankins J, Perucca R. (eds). *Infusion nursing: An evidence based approach*. 3rd ed.St Louis, MO: Saunders/Elsevier, 2010.
94. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. parenteral nutrition safety consensus recommendations. *J Parenter Enteral Nutr* 2014; 38: 296–333.
95. Alexandrou E, Ramjan LM, Spencer T, et al. The use of midline catheters in the adult acute care setting—clinical implications and recommendations for practice. *J Assoc Vasc Access* 2011; 16: 35–41.
96. Broadhurst D, Moureau N and Ullman AJ. World congress of vascular access (WoCoVA) skin impairment management advisory panel. management of central venous access device-associated skin impairment: an evidence-based algorithm. *J Wound Ostomy Continence Nurs* 2017; 44: 211–220.
97. McNichol L, Lund C, Rosen T, et al. Medical adhesives and patient safety: state of the science: consensus statements for the assessment, prevention, and treatment of adhesive-related skin injuries. *Orthop Nurs* 2013; 32: 267–281.
98. Paglialonga F, Consolo S, Biasuzzi A, et al. Reduction in catheter-related infections after switching from povidone-iodine to chlorhexidine for the exit-site care of tunneled central venous catheters in children on hemodialysis. *Hemodial Int* 2014; 18: S13–S18.
99. Yamamoto N, Kimura H, Misao H, et al. Efficacy of 1.0% chlorhexidine-gluconate ethanol compared with 10% povidone-iodine for long-term central venous catheter care in

hematology departments: a prospective study. *Am J Infect Control* 2014; 42: 574–576.
100. Tamma PD, Aucott SW and Milstone AM. Chlorhexidine use in the neonatal intensive care unit: results from a national survey. *Infect Control Hosp Epidemiol* 2010; 31: 846–849.
101. Alam MA, Ali NA, Sultana N, et al. Newborn umbilical cord and skin care in Sylhet District, Bangladesh: Implications for the promotion of umbilical cord cleansing with topical chlorhexidine. *J Perinatol* 2008; 28 (Suppl 2): S61–S68.
102. Baram A, Majeed G, Abdullah H, et al. Heparin versus saline solution for locking of totally implantable venous access port (TIVAP): cohort study of the first kurdistan series of TIVAP. *Adv Lung Cancer* 2014; 03(04): 67–74.
103. Devrim İ, Oruç Y, Demirağ B, et al. Central line bundle for prevention of central line-associated bloodstream infection for totally implantable venous access devices (ports) in pediatric cancer patients. *J Vasc Access* 2018; 19: 358–365.
104. Guiffant G, Durussel JJ, Flaud P, et al. Flushing ports of totally implantable venous access devices, and impact of the Huber point needle bevel orientation: experimental tests and numerical computation. *Med Devices* 2012; 5: 31–37.
105. Goossens GA, Jérôme M, Janssens C, et al. Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: a randomised, non-inferiority, open trial. *Ann Oncol Off J Eur Soc Med Oncol* 2013; 24: 1892–1899.
106. Rosenbluth G, Tsang L, Vittinghoff E, et al. Impact of decreased heparin dose for flush-lock of implanted venous access ports in pediatric oncology patients. *Pediatr Blood Cancer* 2014; 61: 855–858.
107. Conway MA, McCollom C and Bannon C. Central venous catheter flushing recommendations. *J Pediatr Oncol Nurs* 2014; 31: 185–190.
108. López-Briz E, , Ruiz Garcia V, Cabello JB, et al. Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults. *Cochrane Database Syst Rev* 2018; 7: CD008462.
109. Solinas G, Platini F, Trivellato M, et al. Port in oncology practice: 3-monthly locking with normal saline for catheter maintenance, a preliminary report. *J Vasc Access* 2017; 18: 325–327.
110. Ullman AJ, Cooke M and Rickard CM. Examining the role of securement and dressing products to prevent central venous access device failure: a narrative review. *J Assoc Vasc Access* 2015; 20: 99–110.
111. Krenik KM, Smith GE and Bernatchez SF. Catheter securement systems for peripherally inserted and nontunneled central vascular access devices: clinical evaluation of a novel sutureless device. *J Infus Nurs* 2016; 39: 210–217.
112. Cordovani D and Cooper RM. A prospective trial on a new sutureless securement device for central venous catheters. *Can J Anesth Can d'anesthésie* 2013; 60: 504–505.
113. Pittiruti M, Scoppettuolo G, Dolcetti L, et al. Clinical experience of a subcutaneously anchored sutureless system for securing central venous catheters. *Br J Nurs* 2019; 28: S4–14.
114. Toh LMHW, Mavili E, Moineddin R, et al. Are cuffed peripherally inserted central catheters superior to uncuffed peripherally inserted central catheters? a retrospective review in a tertiary pediatric center. *J Vasc Interv Radiol* 2013; 24: 1316–1322.
115. Egan GM, Siskin GP, Weinmann R, et al. A prospective postmarket study to evaluate the safety and efficacy of a new peripherally inserted central catheter stabilization system. *J Infus Nurs* 2013; 36: 181–188.
116. Macmillan T, Pennington M, Summers JA, et al. SecurAcath for securing peripherally inserted central catheters: a nice medical technology guidance. *Appl Health Econ Health Policy* 2018; 16: 779–791.
117. Luo X, Guo Y, Yu H, et al. Effectiveness, safety and comfort of StatLock securement for peripherally-inserted central catheters: a systematic review and meta-analysis. *Nurs Health Sci* 2017; 19: 403–413.
118. Hatakeyama N, Hori T, Yamamoto M, et al. An evaluation of peripherally inserted central venous catheters for children with cancer requiring long-term venous access. *Int J Hematol* 2011; 94: 372–377.
119. Yamamoto AJ, Solomon JA, Soulen MC, et al. Sutureless securement device reduces complications of peripherally inserted central venous catheters. *J Vasc Interv Radiol* 2002; 13: 77–81.
120. Waterhouse J, Bandisode V, Brandon D, et al. Evaluation of the use of a stabilization device to improve the quality of care in patients with peripherally inserted central catheters. *AACN Adv Crit Care* 2014; 25: 213–220.
121. Dolcino A, Salsano A, Dato A, et al. Potential role of a subcutaneously anchored securement device in preventing dislodgment of tunneled-cuffed central venous devices in pediatric patients. *J Vasc Access* 2017;18:540–545.
122. Patanella I and Papa A. SecurAcath VS Statlock per la sicurezza dei PICC in ambito pediatrico. *Hematol Rep* 2018; 10: s1.
123. Griswold S, Bonaroti A, Rieder CJ, et al. Investigation of a safety-engineered device to prevent needlestick injury: why has not StatLock stuck? *BMJ Open* 2013; 3(4): e002327.
124. Elen Hughes M. Reducing PICC migrations and improving patient outcomes. *Br J Nurs* 2014;23(2):S12, S14-8.
125. 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* 2020; 2020; 1129729820924568
126. 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; 17: 453–464.
127. Zhong L, Wang H-L, Xu B, et al. Normal saline versus heparin for patency of central venous catheters in adult patients - a systematic review and meta-analysis. *Crit Care* 2017; 21(1): 5.
128. Bertoglio S, Rezzo R, Merlo FD, et al. Pre-filled normal saline syringes to reduce totally implantable venous access device-associated bloodstream infection: a single institution pilot study. *J Hosp Infect* 2013; 84: 85–88.

129. Dolan SA, Arias KM, Felizardo G, et al. APIC position paper: Safe injection, infusion, and medication vial practices in health care. *Am J Infect Control* 2016; 44: 750–757.
130. Goossens GA. Flushing and locking of venous catheters: available evidence and evidence deficit. *Nurs Res Pract* 2015; 2015: 1–12.
131. Celetti SJ, Vaillancourt R, Pascuet E, et al. Taste and/or odour disturbances in pediatric patients undergoing iv flush with normal saline administered by prefilled syringe. *Can J Hosp Pharm* 2012; 65: 368–372.
132. Tribler S, Brandt CF, Petersen AH, et al. Taurolidine-citrate-heparin lock reduces catheter-related bloodstream infections in intestinal failure patients dependent on home parenteral support: a randomized, placebo-controlled trial. *Am J Clin Nutr* 2017; 106: 839–848.
133. Handrup MM, Møller JK and Schrøder H. Central venous catheters and catheter locks in children with cancer: A prospective randomized trial of taurolidine versus heparin. *Pediatr Blood Cancer* 2013; 60: 1292–1298.
134. Simon A, Ammann RA, Wiszniewsky G, et al. Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer patients. *BMC Infect Dis* 2008; 8: 8–15.
135. Gudiol C, Nicolae S, Royo-Cebrecos C, et al. Administration of taurolidine-citrate lock solution for prevention of central venous catheter infection in adult neutropenic haematological patients: a randomised, double-blinded, placebo-controlled trial (TAURCAT). *Trials* 2018; 19(1): 264.
136. Zacharioudakis IM, Zervou FN, Arvanitis M, et al. Antimicrobial lock solutions as a method to prevent central line–associated bloodstream infections: a meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014; 59: 1741–1749.
137. Bradshaw JH and Puntis JWL. Taurolidine and catheter-related bloodstream infection: a systematic review of the literature. *J Pediatr Gastroenterol Nutr* 2008; 47: 179–186.
138. Bookstaver PB, Rokas KEE Norris LB, et al. Stability and compatibility of antimicrobial lock solutions. *Am J Heal Pharm* 2013; 70: 2185–2198.
139. Landry DL, Braden GL, Gobeille SL, et al. Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clin J Am Soc Nephrol* 2010; 5: 1799–1804.