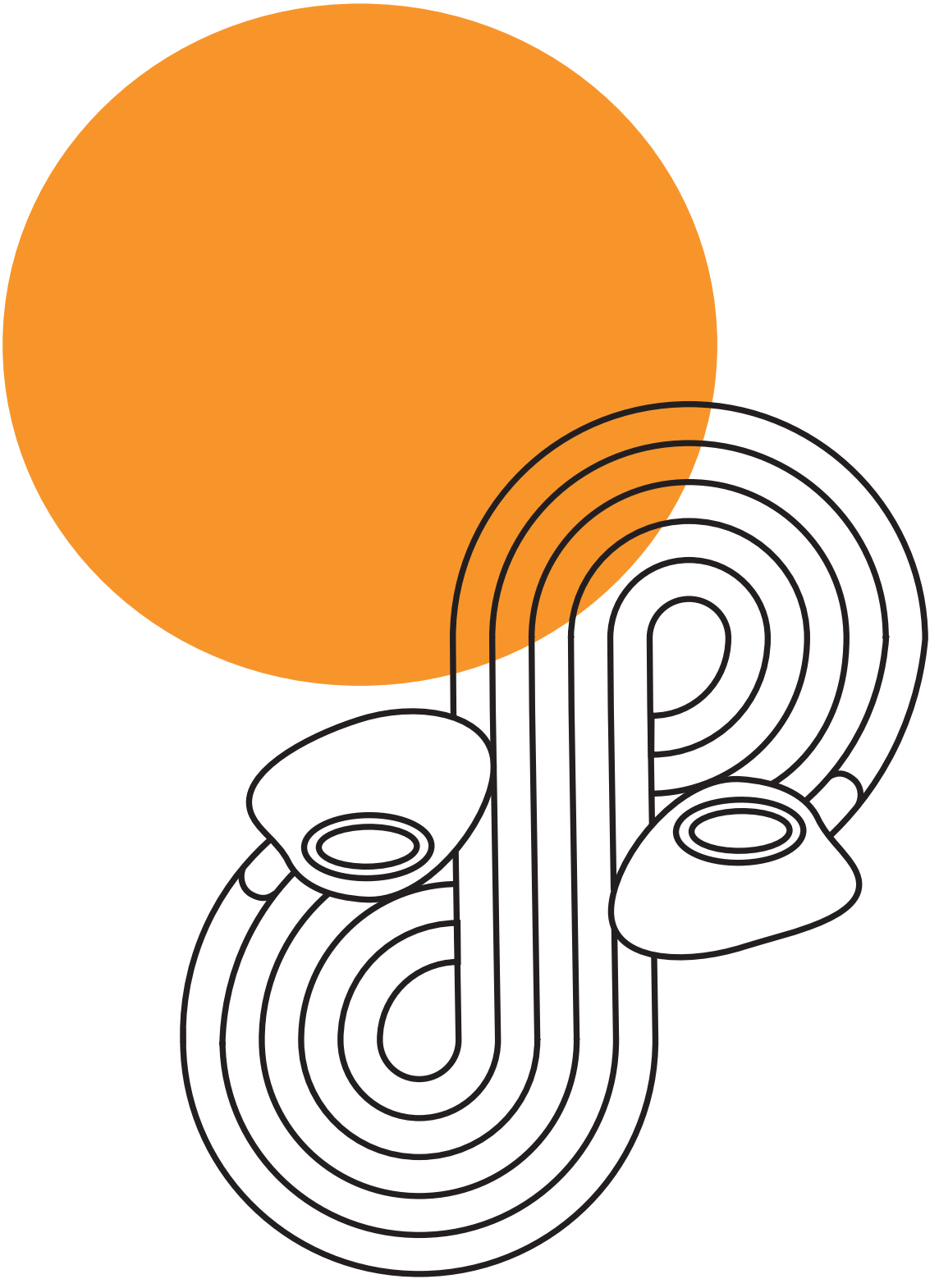

OPTIMIZATION OF CENTRAL VENOUS ACCESS CARE IN PEDIATRIC ONCOLOGY PATIENTS

Optimalisatie van de zorg rondom centraal veneuze toegang in kinderoncologie patiënten

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op

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door

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"When you come out of the storm, you won't be the same person who walked in. That's what this storm's all about."

— Haruki Murakami, Kafka on the Shore

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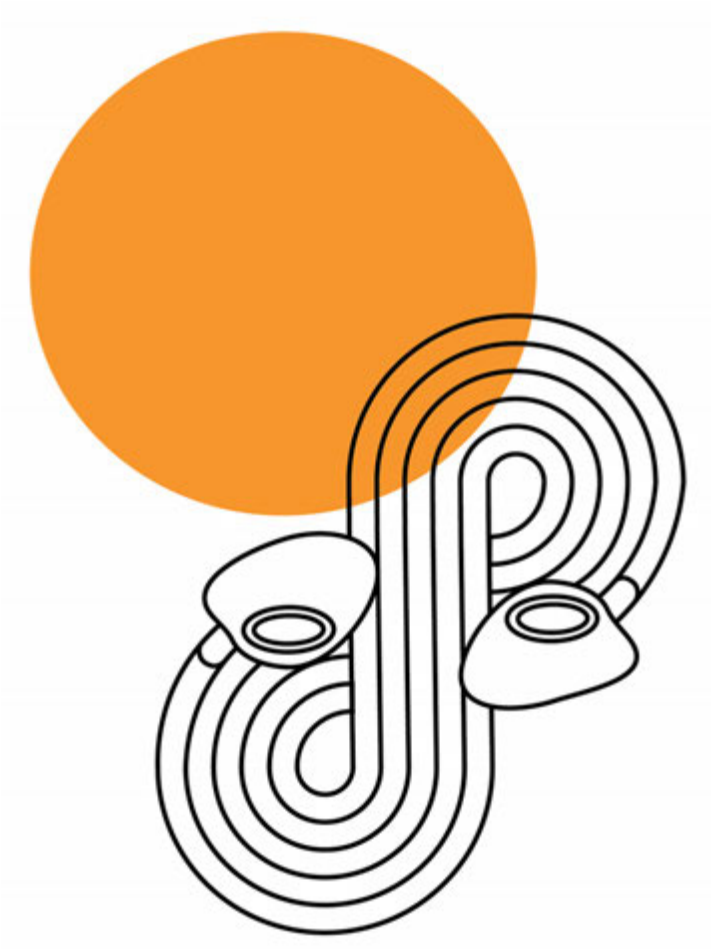
CHAPTER 1

Introduction and thesis outline



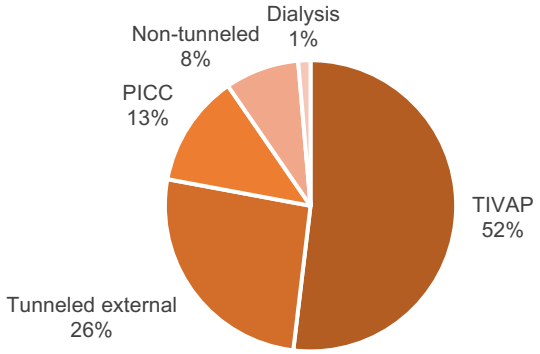
INTRODUCTION AND THESIS OUTLINE

PART 1 – COMPREHENSIVE ANALYSIS OF CENTRAL VENOUS ACCESS CARE

CENTRAL VENOUS ACCESS SURGERY

Paediatric oncology patients receiving chemotherapy require reliable and safe venous access during their treatment. Since treatment is often necessary for months up to years the insertion of a long-term tunnelled central venous catheter (CVC) creates a reliable access route to the venous system. From the beginning of the centralization of the paediatric oncologic care in the Netherlands, nearly all CVCs are inserted at the Princess Máxima Centre in Utrecht, the Netherlands; approximately 700 CVCs each year. (1) The most inserted CVCs in this patient group are the totally implantable venous access port (TIVAP) and double lumen tunnelled external CVC (brand name: Powerline®, previously Hickman®), see **Figure 1**. These long-term tunnelled CVCs are implanted by paediatric surgeons at the operation theatre under general anaesthesia.

Figure 1 CVC types implanted at the Princess Máxima Centre for paediatric oncology (1)



PICC; Peripherally Inserted Central Catheter, TIVAP; Totally Implantable Venous Access Port.
Data from the CVC registry of the Princess Máxima Centre for paediatric oncology over a five-year period from 2019-2023.

PRACTICAL CONSIDERATIONS FOR CVC SURGERY

Surgical CVC implantation guidelines for the paediatric oncologic population have been published in the past. (2, 3) However, these guidelines neither discussed the practical execution of CVC surgery or the management of per-operative complications in this specific population. A paediatric oncology "tips and tricks" CVC implantation manuscript might be of value for less specialized paediatric centres to reduce complications. Therefore, the aim of **Chapter 2** was to bundle the surgical CVC implantation expertise of the specialized surgeons from our centre, incorporating insights from the currently available literature. The goal is to add on to the knowledge of paediatric oncologic surgeons regarding CVC implantation and per-operative CVC complication management.

We concluded that one specific part of the TIVAP implantation method is less studied, i.e., the positioning of the port. When a TIVAP is implanted, the position of the port needs to be chosen, a position at the anterior thoracic wall, above the breast, or at the lateral thoracic wall, below the breast. Literature on the most preferable port position regarding satisfaction, scar-formation and complications was still inconclusive. **Chapter 3** describes our cross-sectional study investigating satisfaction of patients, parents, survivors, and nurses with an anterior versus lower lateral thoracic wall port.

INCIDENCE, BURDEN, AND PREVENTION OF CENTRAL VENOUS ACCESS COMPLICATIONS

The implantation of a CVC can result in serious complications that can have an enormous impact on patients and their caregivers. From previously performed studies, we already knew that the incidence and impact of these complications in the paediatric oncology population is high. (4, 5) CVC-related complications can be divided in surgical complications (e.g., arterial punctures or cardiac arrhythmias) and complications related to CVC use (e.g., bloodstream infections or central venous

thromboses (CVT)). (5) These complications may result in prolonged hospital admissions, CVC removals, and postponement of treatment. They can even result in high rates of paediatric intensive care unit (PICU) admissions, and mortality. Consequently, the complications have a major impact on the quality of life of this group of patients, who already face many hurdles during their treatment period. Additionally, these complications, especially CVC-related bloodstream infections, result in increased health care costs. (4, 6)

Chapter 4 describes the current clinical burden of CVC-related complications (i.e., surgical complications and complications related to CVC use) in our hospital. This chapter thereby underlines the importance of complication prevention. The results of this study were used to narrow our focus on areas of future study regarding the prevention of complications.

Risk factors for CVC-related complications can be divided into three categories: patient-related factors (e.g., neutropenia), health care provider-related factors (e.g., CVC manipulation frequency) and device-related risk factors (e.g., CVC type). (6) See **Table 1** for an overview of risk factors specifically for CVC-related bloodstream infections. (6, 7) Patient-related factors are least modifiable, therefore most preventative strategies target device- and health care provider-related factors.

Health care provider-related factors were targeted in our hospital by updating and aligning all CVC care protocols in the Netherlands, and by training providers on these protocols. Regarding device-related factors, we performed the study discussed in **Chapter 5**. Specifically for the Hodgkin lymphoma group, a high risk of CVC-related CVT was observed and suspected to be related to a commonly used CVC type in this group, i.e., peripherally inserted central venous catheters (PICC). The objective of this study therefore was to determine the most optimal CVC for paediatric patients

diagnosed with Hodgkin lymphoma by comparing the incidence of CVC-related complications per CVC type. (5, 8)

Table 1 Risk factors for CVC-related bloodstream infections specified for paediatric oncology patients (6, 7)

Patient-related factors
Diagnosis (e.g., acute myeloid leukaemia)
High-intensity chemotherapy
Bone-marrow transplant <100 days ago
Red blood cell or platelet transfusion <1 week ago
Neutropenic (ANC <500)
Previous CVC-related bacteraemia
Health care provider-related factors
Emergency CVC implantation
Non-aseptic technique during CVC care
Frequent CVC manipulations
Failure to remove unnecessary CVC
Device-related factors
CVC type (i.e., external tunnelled CVCs and PICCs)
CVC implantation <1 month ago
Multiple CVCs (i.e., >1 CVC)
CVC implantation site (i.e., femoral vein)

ANC; Absolute Neutrophil Count, CVC; Central Venous Catheter, PICC; Peripherally Inserted Central Catheter.

PART II – CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING PREVENTION

Epidemiology and burden

CVC-related bloodstream infections are among the most observed complications and result in a high morbidity and mortality burden worldwide. (6, 9) The incidence rate of CVC-related bloodstream infections within the time-frame that the CVC was in situ (i.e., CVC-days) ranges between 0.1-2.3 per 1,000 CVC-days. This rate depends

on patient population, CVC type and infection definitions used. Patients are hospitalised for salvage treatment of these bloodstream infections. The aim of salvage treatment is to cure the infection with antibiotics, avoid CVC removal, and prevent severe sepsis. (10) The mean success rate of salvage treatment has been described as 67% for long-term CVCs and depends mostly on the microbe causing the infection and the site of infection. Failure of infection treatment could result in severe sepsis, which could lead to prolonged hospitalisation, intensive care unit admission, and even mortality. (6) Altogether, CVC-related bloodstream infections pose a high clinical burden on paediatric oncology patients and their families, and result in high hospital costs. (4)

Aetiology and pathogenesis

Two microbial contamination routes can be identified 1) extra-luminal and 2) intra-luminal. In case of extra-luminal contamination, bacteria migrate from the exit-site to the CVC tip via the outer layer of the catheter. Intra-luminal contamination happens by CVC manipulation, by injection of a contaminated infusate or via haematogenous seeding from another infection site. (6) The microbes form a biofilm on the CVC surface consisting of an extracellular matrix, due to which much higher concentrations of antibiotics are needed to kill these microbes as compared to free-living bacteria. (10) As previously described in our retrospective study, the most identified micro-organisms during CVC-related bloodstream infections are coagulase-negative staphylococci. (11)

Preventive strategies

CVC-related infection prevention is of the utmost importance given the clinical outcomes caused by these infections. Preventive strategies are mostly aimed at the "provider" and "device" risk factors as described in **Table 1**, since these are mostly amendable. The most important strategies that have been described in literature are

the following eight: the use of checklists, hand hygiene, using maximal sterile barrier precautions, chlorhexidine skin disinfection/washes, chlorhexidine dressings, hub decontamination, frequent insertion site checks, needleless intravascular CVC systems, and limiting both the CVC dwell time and CVC replacements. (6, 12)

Furthermore, the use of anti-microbial substances, such as systemic prophylaxis and lock solutions, have previously been studied. **Chapter 6** describes the effect of these antimicrobials against Gram-positive CVC-related bloodstream infections in adults and children diagnosed with cancer in a meta-analysis. No benefit was observed in the use of systemic antimicrobial prophylaxis prior to CVC insertion. Nevertheless, this meta-analysis did show promising results for the prevention of CVC-related bloodstream infections by using antimicrobial lock solutions, more specifically, taurolidine-containing lock solutions.

Based on the available literature, experts described taurolidine as the most promising prophylactic lock substance for the prevention of CVC-related infections. (13) Taurolidine has anticoagulant, antimicrobial, and anti-biofilm properties. No antimicrobial resistance to taurolidine has been reported, which makes the substance a more attractive option as compared to other antimicrobial lock solutions. Taurolidine causes a chemical reaction with the bacterial cell wall, endotoxins, and exotoxins, resulting in irreversible damage to the bacteria, minimization of bacterial pathogenicity and inhibition of bacterial surface adhesion. (14, 15) In **Chapter 7** a meta-analysis was performed describing the efficacy of taurolidine for the prevention of CVC-related bloodstream infections in a variety of patient populations.

For taurolidine containing lock solutions, it is advised to aspirate and discard the lock before drawing a blood culture. The hypothesis was that taurolidine can lead to a delayed or even false negative blood culture result if it ends up in the blood culture.

This potentially has an impact on clinical decision making, infection surveillance systems, and research results. **Chapter 8** describes the impact of taurolidine on the detection of microbial growth in blood culture vials.

Although challenging, it is necessary to accurately differentiate between CVC-related and non CVC-related bloodstream infections. (6) For this differentiation and due to practical considerations, the CLABSI definition of the Infectious Diseases Society of America (IDSA) is mostly used in paediatric oncology. (16) The applicability of this definition for the paediatric oncology populations, however, was still unknown. Specifically for clinical studies, such as the CATERPILLAR-study, it is important to be aware of the accuracy of this definition in this patient group. **Chapter 9** therefore focussed on the applicability of the CLABSI criteria in this population.

The two meta-analyses that we performed showed us the possible potential of taurolidine, but the evidence in paediatric oncology patients remained scarce. Therefore, an assessor blinded randomized controlled trial comparing the taurolidine-citrate-heparin lock to the heparin lock for the prevention of CVC-related bloodstream infections in paediatric oncology patients, the CATERPILLAR-study, was designed. In **Chapter 8** we describe the protocol of the CATERPILLAR-study and **Chapter 9** describes the results.

PART III - CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING TREATMENT

Enterobacterales are cultured during 12% of the reported CLABSIs in paediatric oncology patients, as observed by our retrospective study. (11) The current guidelines provided poor evidence to support a treatment recommendation in these cases, i.e. salvage treatment with antibiotics versus CVC removal. (10) **Chapter 12**

therefore describes whether salvage treatment with systemic antibiotics is a safe and effective strategy in these cases.

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PART I

COMPREHENSIVE ANALYSIS OF CENTRAL VENOUS ACCESS CARE

CHAPTER 2

Tunneled vascular access surgery in pediatric oncology; Experience from a national pediatric oncology center

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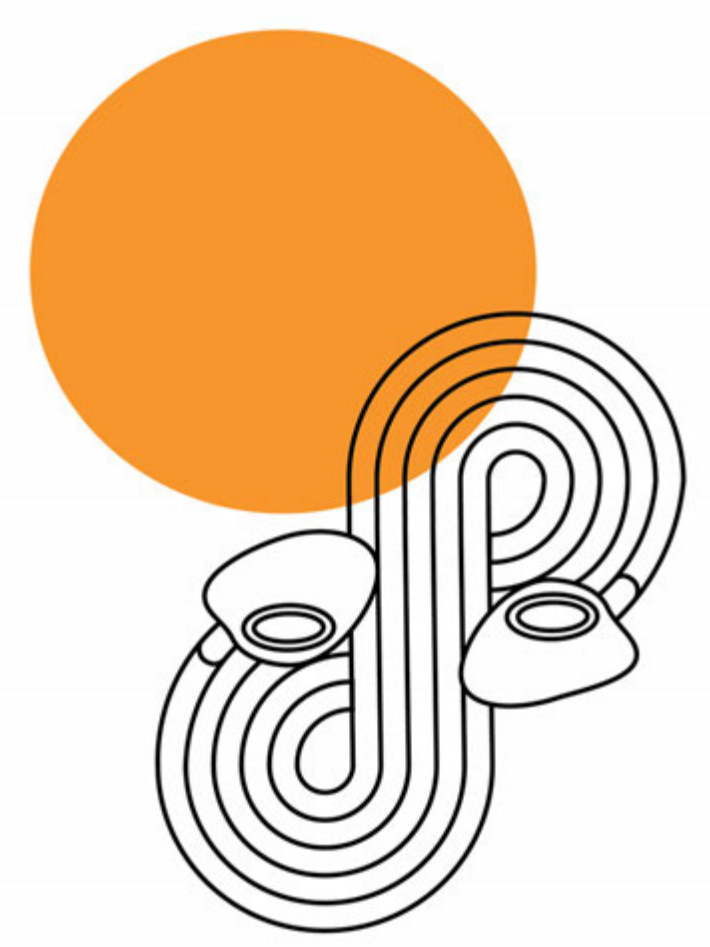
EJC Paediatric Oncology. 2023; (2)100127



ABSTRACT

Central venous access is essential in the treatment of children diagnosed with cancer. Therefore, as a paediatric oncologist/surgeon, it is important to identify the most optimal central venous catheter (CVC) for each patient, to accurately perform CVC surgery and to be aware of the possible complications that can occur and how to prevent and treat them. The aim of this article is to provide an overview of recommendations for CVC choice, methods for tunneled CVC surgery and strategies for perioperative complication treatment. This is based on the experience of the surgeons from our national paediatric oncology center in the Netherlands, inserting 700 CVCs each year.

INTRODUCTION

Since 2018, all pediatric oncology care in the Netherlands has been centralized in the Princess Máxima Center for Pediatric Oncology, Utrecht. In the Netherlands, around 600 children are diagnosed with cancer each year. Central venous access is an integral part of the treatment of these children. Since centralization, approximately 700 central venous catheters (CVC) are inserted each year. The most commonly inserted CVCs in this patient group are vascular access ports (VAP) and tunneled external CVCs. The aim of this article is to provide an overview of recommendations for CVC choice, methods for long-term tunneled CVC surgery and strategies for perioperative complication treatment, from the surgery department of our national pediatric oncology center in the Netherlands.

CVC CHOICE

The decision to insert a long-term tunneled CVC, is based on the duration of treatment, number of lumens needed, the clinical status of the patient and the caliber of the veins, see **Table 1**. The VAP is the first CVC of choice in children requiring long-term access, due to the low incidence of complications when compared to other CVC types. (1, 2) If a multi-lumen CVC is needed (e.g., acute myeloid leukemia, non-Hodgkin lymphoma, neuroblastoma, or patients requiring stem cell transplantation) an external tunneled CVC is inserted since double lumen VAP use has been rarely described in children. The tunneled external CVCs inserted in our hospital are cuffed, pressure resistant, and made of polyurethane. Polyurethane was preferred over silicone for tunneled external CVCs due to the higher rate of mechanical complications observed, possibly related to the fragility of the silicone catheter. (2)

The VAPs however, still consist of an epoxy/titanium port with a silicone catheter. Silicone is preferred by the surgeons in our hospital for patients with a VAP due to easier handling, since the incidence of mechanical complications in patients with a silicone catheter VAP has been described as very low (2) and since polyurethane catheters have been shown to be difficult or impossible to remove in the paediatric population after insertion for multiple years in the past(17-19). (3-5) Since tunneled external CVCs are often inserted for a much shorter duration when compared to VAPs this problem doesn't occur. (2-5) However, robust evidence in pediatric oncology patients regarding the complication rate in silicone versus new generation polyurethane CVCs is still lacking, and requires further research. Cuffed catheters together with a suture less securement device are preferred to prevent dislocations. A switch to polyurethane catheters was made after experiencing a high rate of catheter shears during infusion requiring repair or replacement when a silicone type of tunneled external CVC was used. (2) Antimicrobial impregnated catheters are expensive and there is currently not enough evidence to support their use in pediatric oncology patients. (6)

SURGICAL TECHNIQUE

The surgical steps for CVC insertion and removal are described stepwise in **Table 2**.

CVC INSERTION

Preoperative preparation

Before CVC insertion, patients and parents are prepared for surgery by a pedagogue who demonstrates the working mechanism of the CVC on a doll. A pre-operative ultrasound with Doppler of the insertion veins is performed in patients with a history of CVC-related thrombosis or infections. If the number of available veins is (expected to be) limited, magnetic resonance venography can be performed. A thrombocyte threshold of $50x10^9$/L for platelet transfusion is adhered to, but the evidence is

scarce(20). Neutropenia at the time of CVC insertion is not considered a contra-indication since it does not appear to increase the risk of CVC-related infections in pediatric oncology patients and treatment delays should be prevented. (8, 9) Insertion is preferably performed in the absence of a bacteraemia. (6)

TABLE 1 Vascular access device indications

	Type	Indications
CVC	Tunneled CVC	Central access needed Long-term access >4-6 months Tunneled CVC type depending on: Number of lumen needed (single lumen: vascular access port (VAP), multiple lumen: cuffed external CVC) Fear of needles Estimated duration of access (multiple years: VAP)
	Peripherally Inserted Central Catheter (PICC)	Central access needed Planned insertion of >6 weeks and <4-6 months Suitable veins (i.e. CVC diameter <33-45% of venous diameter) One of the following reasons: Diagnosis unclear Preference for avoidance of general anesthesia Recurrent CVC infections Extra lumen needed next to tunneled CVC Radiotherapy
	Non-tunneled CVC	Central access needed Planned insertion of >1 week or <6 weeks One of the following reasons: Emergency setting Tunneled CVC or PICC needed but positive blood cultures Stem cell apheresis Insertion of a tunneled CVC or PICC not possible
Non-CVC	Midline	No central access needed in the upcoming months (e.g. only blood withdrawals or infusion of non-irritable substances) Planned insertion of >1 week or <4-6 months Suitable veins (i.e. CVC diameter <33-45% of venous diameter) Frequent blood withdrawals or antibiotic administration for a period of >1 week
	Peripheral vein access	No central access needed No frequent blood withdrawals Insertion duration of <1 week

CVC; Central Venous Catheter, PICC; Peripherally Inserted Central Catheter, VAP; Vascular Access Port

Preparation

The patient is positioned in Trendelenburg position to increase the vein diameter and to reduce the risk of air emboli. A shoulder roll is used to improve access to and position of the veins. Although the evidence is scarce, intravenous cefazolin is administered before insertion in order to prevent early postoperative infections. (10) An aseptic technique is used throughout the procedure.

Venous access

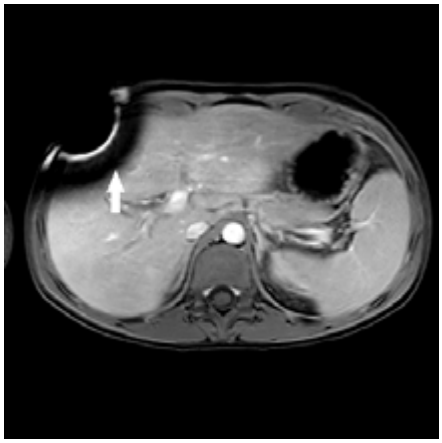
The access route to be used for catheterization is chosen by the surgeon based on ultrasound assessment of the veins (for which Spencer et al. (11) described a useful rapid assessment method), tumor location, and CVC-history of the patient. (12, 13) In general, the internal jugular vein on the right side is preferred due to the straighter route to the superior vena cava and in order to prevent the rare occurrence of thoracic duct injury. (6)

In patients with tumors of the liver or chest, the CVC is preferably inserted on the contralateral side to avoid interference during radiological imaging, see **Figure 1**, and resection in the future. If the CVC is re-inserted soon after removal due to an infection, the CVC is preferably inserted on the contralateral side. (6)

The Seldinger technique is used to get venous access. (14) Ultrasound-guided insertion, see **Figure 2**, is preferred over insertion based on anatomical landmarks due to the higher success and lower complication rate. (15) Furthermore, it is preferred over an open cut-down technique due to the lower risk of vessel damage resulting in stenosis. (16) To obtain access to the subclavian/brachiocephalic vein specifically, an ultrasound-guided supraclavicular approach is used. (17)

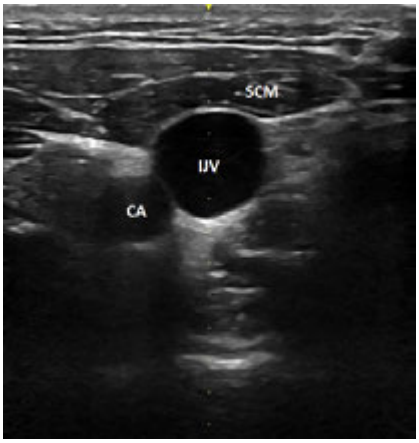
Patency of the vein is confirmed with ultrasound by excluding the presence of a thrombus using compression; if a thrombus is present, the vein will not collapse. During puncturing, the vein and tip of the needle should always be visible in the center of the ultrasound view for the prevention of an accidental arterial puncture, vessel damage or pneumothorax/hematothorax. In young children, be aware that the veins are located very superficially and due to a very compliant vessel wall, the vein can easily be pushed forward by the bevel of the needle instead of being punctured.

Figure 1 VAP artefact



Artefact from VAP causing difficult assessment of the liver (arrow).

Figure 2 Ultrasound CVC insertion



Ultrasound image of the relationship between the right sternocleidomastoid muscle (SCM), internal jugular vein (IJV) and carotid artery (CA). Carotid artery located on the lateral side of the internal jugular vein.

Guidewire insertion

During guidewire insertion, no resistance should be felt. Extra systoles or arrhythmias can be caused by the guidewire and are sometimes used to confirm a right atrial position of the guidewire. Be aware, however, that this may also occur when the guidewire is inserted through the carotid artery. Therefore, it is advised that the location of the guidewire is checked by ultrasound and/or fluoroscopy. The skin around the guidewire is incised to create space for the dilator. A small pocket is

created through the incision for the prevention of catheter kinking and to make sure the catheter will eventually be located deep from the incision site.

Creation of exit site

The VAP pocket is created directly above the fascia of the pectoral muscle. If the pocket is created in the subcutaneous tissue, rotation can easily occur. The location is discussed with the patient and caregivers, however, the lower lateral position under the inframammary fold is preferred since we suspect that scars can become very broad when located above the nipple line due to tensile forces on the wound caused by arm movements and breast formation.

Tunneling of the CVC

Tunneling is done laterally on the thoracic wall; be aware that the mammary glands can be damaged if the tunnel is created too medially. If the distance from the neck incision to the exit-site is very long, the tunnel can be created in two steps. While tunneling, a wide bend needs to be made to the insertion vein to avoid possible kinking of the catheter. The position of the external jugular vein should be taken into account during tunneling.

Catheter insertion and assembly of the CVC parts

Measuring the appropriate catheter length is important to avoid malfunctions and dislocations. Multiple techniques are available and used to determine the optimal position of the catheter tip: the landmark insertion (i.e., cut the catheter at the level half-way from the sternal head of the clavicle to the nipple line on the right side and on two thirds on the left side) with a post-procedure X-ray, intra-procedural fluoroscopy (most commonly used in our hospital), ultrasound and intracavity electrocardiography-guided tip allocation. The landmark method and fluoroscopy are commonly used but both give an indirect view of the catheter tip, fluoroscopy

requires ionizing radiation and ultrasound requires training from experienced operators. Therefore, intracavity electrocardiography shows promising results in infants and children, but is not yet implemented in our centre. (18, 19)

The peel-away technique is used for catheter insertion; make sure the dilator never exceeds the length of the guidewire. The (back)flow of blood through the CVC is checked and the CVC is either locked or connected with continuous infusion. In case of a cuffed external CVC, the catheter is secured with a suture less securement device. A transparent dressing with high moisture vapor transfer rate is applied over the exit site. (12) No evidence in literature is available regarding specific postoperative instructions after CVC insertion or removal, the instructions given by our team of surgeons are detailed in **Table 2**.

CVC removal

In case of VAP removal, the old scar is incised (or excised in case of a displeasing scar) and the port and catheter are removed using electrocautery while ensuring the catheter is not damaged and completely removed. In order to prevent hemorrhage into the port site during VAP removal, a suture can be placed over the fibrin sheet after catheter removal. In case of a tunneled external cuffed CVC, most commonly the CVC can be removed by a gentle pull, preferably taking the cuff with it.

Guidewire exchange

Guidewire exchanges are ideally performed in the absence of a bacteraemia (6) and are associated with a high success rate and low risk of postoperative complications (20). Instead of a venous puncture, the neck scar is opened and the catheter is found and clamped proximally. The catheter is cut distally to the clamp, and a guidewire is passed through the catheter after releasing the clamp. The old catheter and/or port are removed and a new catheter is inserted over the guidewire.

TABLE 2a Stepwise insertion and removal of tunnelled central venous catheters (CVC)

Stepwise insertion of tunneled CVC	**Stepwise removal of tunneled CVC**
1. Preparation • General anesthesia • Trendelenburg position • Shoulder roll • Chlorhexidine wash • Surgical drapes • Flush catheter with saline • Intravenous cefazolin 2. Venous puncture • Check relevant structures by ultrasound (**Figure 2**) • Mark location of planned venous puncture • Attach 5cc syringe with 2-3cc saline loosely to the needle • Ultrasound-guided puncture • Check venous blood flow in syringe 3. Guidewire insertion • Insert guidewire and remove needle • Check position of guidewire with ultrasound and/or fluoroscopy • Clip guidewire to surgical drapes • Incision of skin over guidewire and create small pocket through the incision 4. Create exit-site • Incision of the skin • Create a pocket in case of a vascular access port (VAP) 5. Tunneling of the CVC • Local anesthetics • Tunneling of the catheter 6. Assembly of the CVC (VAP) • Adjust the catheter to reach the appropriate length • Fixate catheter on port • Suture port to pectoral fascia • Suture subcutaneous tissue and skin • *Check definitive position of catheter with fluoroscopy*[a] 7. Catheter insertion • Measuring the appropriate length • Insert dilator including peel-away sheet over guidewire • Remove dilator and guidewire • Insert catheter • Remove peel-away sheet • Check definitive position of catheter with fluoroscopy 8. Final check • Insert VP needle in port • Aspirate and flush with saline • Clean site • Wound closure strips • Apply transparent dressing • Lock CVC or attach a running infusion	1. Preparation • Deep sedation • Local anesthetics around exit site • Chlorhexidine wash • Surgical drapes 2. CVC removal • Retake old scar and clearing the catheter with electrocautery (VAP) • Gentle pull or blunt dissection and removal of cuff (tunneled external CVC) • Removal of catheter • Suture over CVC sheet (VAP) • Removal of the port with electrocautery (VAP) 3. Closure • Suture subcutaneous tissue and skin (VAP) • Wound closure strips

CVC; Central Venous Catheter, VAP; Vascular Access Port. [a] Compilation of the VAP can take place before or after catheter insertion. If compilation takes place after catheter insertion, always check definitive position of the catheter with fluoroscopy.

TABLE 2b Stepwise insertion and removal of tunnelled central venous catheters (CVC)

Post-operative instructions after insertion of tunneled CVC	Post-operative instructions after removal of tunneled CVC
• Paracetamol first 48 hours • Keep insertion site dry for two days • Bathing two weeks after VAP insertion • Refrain from sports for two weeks • Lift small children at buttocks instead of under the armpits	• Paracetamol on indication • Keep insertion site dry for two days • Bathing two weeks after VAP removal and five days after tunneled CVC removal • Refrain from sports for two weeks • Lift small children at buttocks instead of under the armpits

CVC; Central Venous Catheter, VAP; Vascular Access Port.

PERIOPERATIVE COMPLICATIONS

Perioperative complications were observed during 7.1% (i.e., pneumothorax 0.3% and other "minor" complications 6.8%: multiple vein puncture attempts, arterial puncture, cardiac arrhythmias, bleeding/hematoma, tip dislocation, and negative blood return) of the tunneled CVC insertions at our hospital, these have been described in detail in our previous publication. (2) The possible perioperative complications and their treatments are summarized in **Table 3**.

CVC insertion

Malpositioning of the guidewire is a common perioperative complication. (2) If the guidewire needs to be replaced due to damage, but is still located in the vein, the guidewire is first protected by introducing a size-matched intravenous cannula over the guidewire. Tips to prevent a catheter/guidewire malposition during insertion are described in **Table 3**.

In case of catheter damage the catheter is first clamped proximally to prevent the formation of air emboli. If damaged even minimally, the guidewire/catheter are directly removed and replaced in order to prevent damage to the vessel walls and a rare but possible fracture of the catheter or guidewire. If the proximal part of the catheter or guidewire remains in the vein, the cardiothoracic/vascular surgeon or intervention radiologist needs to be consulted to attempt to remove it via an endovascular procedure. (21)

Air emboli can occur during the entire procedure, however, the risk is especially high when the guidewire and dilator are removed from the peel away sheet. In case of air emboli, high flow oxygen with the fraction of inspired oxygen set to 100% is given, this improves the reabsorption of nitrogen gas from the bubble, reducing its size. Durant's maneuver is performed and the patient is positioned in Trendelenburg. This

way, the air remains in the right side of the heart and resolves slowly, thereby preventing cardiopulmonary collapse or even stroke in case of a septal defect. (22)

On very rare occasions, insertion of the dilator and peel-away sheet can result in severe complications. Perforation of the superior vena cava or right atrium and cardiac tamponade have been described. In case of superior vena cava perforation, all inserted devices (i.e. guidewire, dilator and peel-away sheet) are removed (ensure thoracoscopy is available and/or cardiothoracic surgeon is present), a chest drain can be inserted to detect persistent hemorrhage, but in the majority of cases, the bleeding will stop. In case of persistent hemorrhage, a right-sided thoracoscopy or thoracotomy can be performed to locate and stop the bleeding. In case of a suspected cardiac tamponade, the cardiothoracic surgeon is consulted urgently. (23) If the dilator caused the tamponade, it is left in place to prevent major hemorrhage. If the catheter is already in situ, the catheter needs to be removed directly since blood can easily run through the catheter.

CVC removal

During removal, perioperative complications are rare. However, if the catheter cannot be easily removed since it has grown into the tissue, the surgeon can incise the neck scar and remove the proximal part of the catheter through this incision. In very rare cases, the catheter has grown into the vessel, making it impossible to remove it by traction. In these cases a venotomy can be performed or an intervention radiologist can retrieve the part with a snare, but it is also possible to leave the proximal part of the catheter in situ. (4, 24) If the proximal part dislocates, a cardiothoracic surgeon, for intracardiac retrieval, can be consulted.

Guidewire exchange

During guidewire exchange, be aware that the proximal part of the catheter can be pushed into the vein during insertion of the guidewire into the old catheter. When this occurs, the cardiothoracic surgeon or intervention radiologist needs to be consulted.

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TABLE 3a Perioperative central venous catheter (CVC) complications and treatment in alphabetical order

Surgery	Complications	Treatment
CVC insertion (incl. reinsertion over guidewire)	Air embolism	Trendelenburg position, Durant's maneuver, high flow oxygen with fraction of inspired oxygen set to 100%, wait and see.
	Arrhythmias	Check location of CVC tip, pull back if located too deep.
	Arterial puncture	Remove needle and apply pressure.
	Brachial plexus injury	Consult plastic or neurosurgeon.
	Cardiac tamponade	Consult cardiothoracic surgeon, leave dilatator in place if present, remove catheter if present.
	Catheter malposition	Maneuver catheter by rotating and rolling guidewire through your fingers, reinsert if persistent malposition.
	Catheter rupture	Clamp proximal part of catheter, remove and replace. If proximal part of catheter is retained in vessel, consult cardiothoracic surgeon or intervention radiologist.
	Catheter length inadequate	Replace catheter if too short, pull back if too long or replace.
	External jugular vein injury	Pressure.
	Guidewire malposition	Insert cannula over guidewire, pull guidewire back, reinsert while pulling ipsilateral arm down, turning the face up and closing the contralateral subclavian vein, maneuver wire by rotating and rolling guidewire through your fingers.
	Guidewire kink or rupture	Remove and replace. If proximal part of guidewire is retained in vessel, consult cardiothoracic surgeon or intervention radiologist.
	Hematoma	Conservative if no active hemorrhage.
	Hemorrhage	Pressure and optimize coagulation.
	Hemothorax	Remove insertion devices, depending on extensiveness: expectative when minor bleeding, intercostal drain, intervention by thoracoscopy or thoracotomy in case of persistent bleeding.
	Malfunction	Flush with saline while pulling ipsilateral arm down, check port needle and replace if necessary, check location of catheter, reinsert catheter if necessary.
	Mammary gland injury	Conservative.
	Needle/guidewire/catheter luxation	Puncture vein again following steps for primary insertion.
	Pneumothorax	Remove insertion devices, depending on extensiveness: expectative, drain, oxygen and pain killers.
	Phrenic nerve injury	Consult neurosurgeon or neurologist.
	Vessel damage in the cervical region (perforation or dissection)	Remove insertion devices (ensure thoracoscopy and/or cardiothoracic surgeon is available) and pressure. A chest drain can be inserted to detect persistent hemorrhage. Exploration and repair of the vessel.
	Tricuspid valve injury	Consult cardiothoracic surgeon.
	Thoracic duct injury	Depending on extensiveness: mostly conservative, in rare cases intervention by thoracoscopy or thoracotomy.

CVC; Central Venous Catheter.

TABLE 3b Perioperative central venous catheter (CVC) complications and treatment in alphabetical order

Surgery	Complications	Treatment
CVC removal	Catheter grown into tissue	Assess catheter by retaking incision in the neck and remove proximal part of the catheter. Very rare: venotomy or leave proximal part in situ.
	Catheter rupture	Clamp proximal part of catheter and remove. If proximal part of catheter has grown into the vessel, this part can be removed by an intervention radiologist using a snare, if still unsuccessful, it can be left in situ. If the proximal part dislocates to the heart, consult the cardiothoracic surgeon.
	Hematoma	Conservative if no active hemorrhage.
	Hemorrhage	Pressure, coagulation and/or suture over fibrin sheet.
	Remaining cuff or other CVC parts	Remove completely through exit-site if possible. If removal through exit-site is not possible, parents can decide if they want it to be removed through a new incision.

CVC; Central Venous Catheter.

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CHAPTER 3

Satisfaction of paediatric oncology patients, survivors and nurses with the location of their totally implantable venous access port (SPACE-study)

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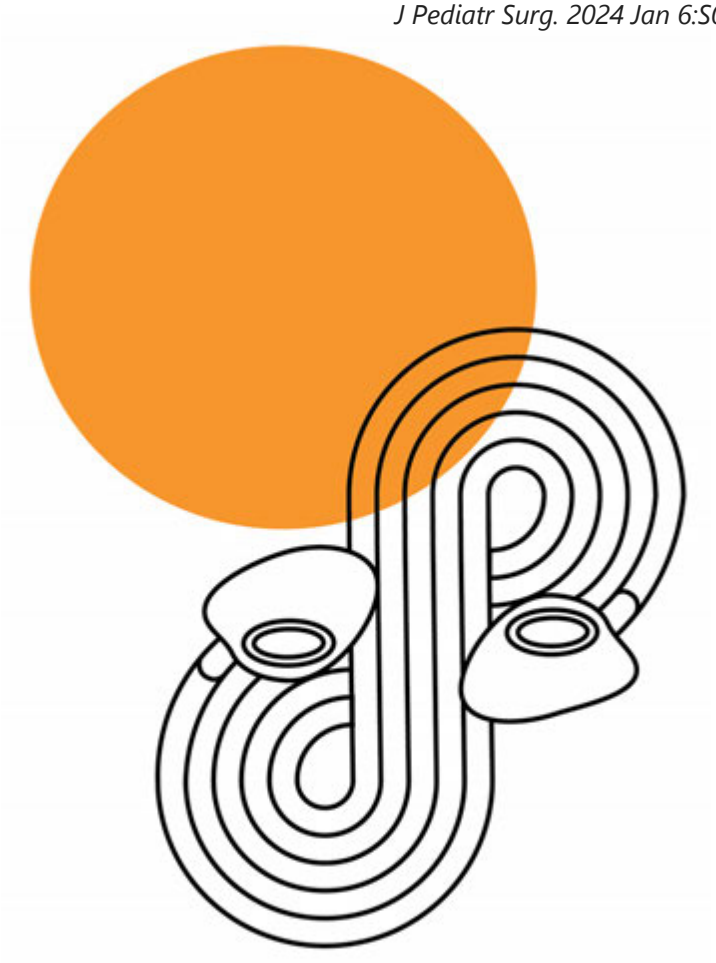


ABSTRACT

Background To compare paediatric oncologic vascular access ports located on the anterior thoracic wall to ports on the lower lateral thoracic wall, in terms of perceived port-related hindrance and scar-quality.

Methods A cross-sectional survey study including paediatric oncology patients (≥8-<19 yrs.), caregivers (in patients <8 yrs.), survivors (>22 yrs. with only anterior ports) and nurses of the Princess Máxima Center, the Netherlands, was performed. The survey consisted of questions regarding satisfaction, hindrance during daily life, and port position preference. For survivors, scar-quality was assessed using the validated Patient and Observer Scar Assessment Scale (POSAS 2.0); a high score (i.e., a displeasing scar) was defined as a score higher than the third quartile of the median for that question.

Results In total, 147 participants were included; 83 patients/caregivers, 31 survivors, and 33 nurses. Overall, 81% was satisfied with the position of their port. Satisfaction, hindrance and complications did not differ between anterior and lower lateral ports. For the anterior position, minimal pressure on the port during daily life was a mentioned reason to prefer this position. For the lower lateral position, less visibility of the scar and easiest access were mentioned. Of all survivors with an anterior port scar, one in five had a displeasing scar and all scars observed were widened. Female patients preferred a lower lateral port, and scar-quality was better for left-sided port scars.

Conclusion The port position should be chosen together with patients/caregivers based on the (dis-)advantages of each position, as identified by this study.

INTRODUCTION

Totally implantable venous access ports (TIVAP) are effective devices used in paediatric oncology patients requiring long-term vascular access during their treatment. The TIVAP is a tunnelled central venous catheter (CVC), mostly inserted in the jugular or subclavian vein, which is attached to a subcutaneous small reservoir, the "port". Whilst in situ, the TIVAP can cause hindrance during activities of daily living; specifically during bathing, showering and playing.(1) After removal, the remaining port scar can have a psychological impact; 11% of childhood cancer survivors reported to be highly impacted by their scar.(2)

When the TIVAP is inserted, there is a choice of port placement positions. The most commonly reported port position is the anterior thoracic wall, above the nipple (in boys and in prepubertal girls) and above the breast tissue in post pubertal girls (see **Figure 1A**). This position is several centimetres caudal to the clavicular bone, i.e., relatively close to the insertion vein.(2) Other port positions such as the axilla, the lower lateral thoracic wall (see **Figure 1B**), or the upper arm have also been studied in terms of various quality of life outcomes, but limited data is available for paediatric patients.(3-10)

In the Netherlands, in the past, the anterior thoracic wall was the preferred position. However, high rates of abnormal port scars of up to 88% were reported in paediatric oncology patients aged two to 21 years old with an anterior thoracic wall port or port scar in case of previous removal.(11) Furthermore, a significant association was found between the wish for a different port scar position and how much the current position affected childhood cancer survivors.(2) The hypothesis is that the cosmetic outcomes of scars at the lower lateral thoracic wall are better; the scar is more hidden and there is less tension on the skin due to breast formation and arm movements.(5, 11) Therefore, since the centralization of the paediatric oncologic care in the

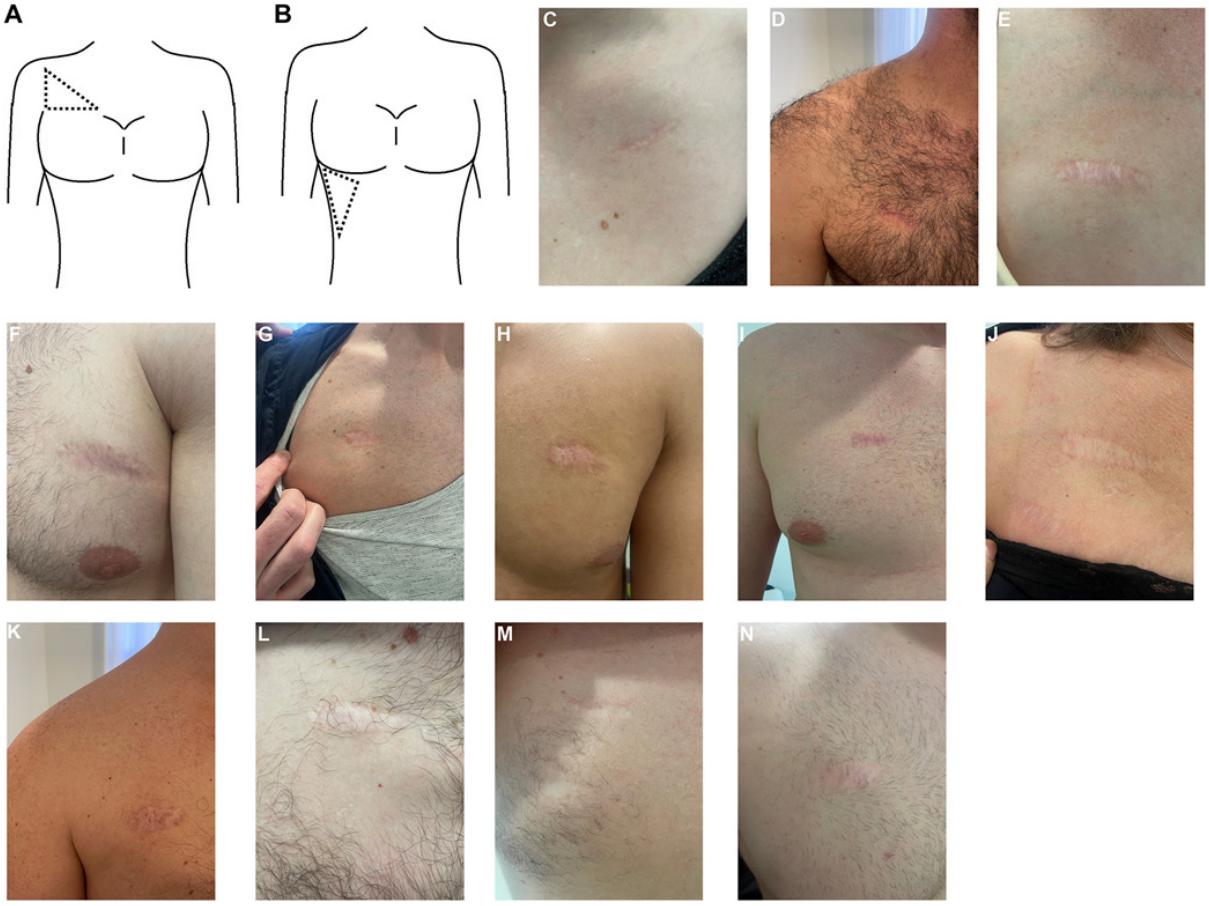
Netherlands in 2018, patients and caregivers are being counselled by the surgeon before TIVAP insertion and are offered, if clinically possible, a choice between inserting the port at the anterior (**Figure 1A**) or the lower lateral thoracic wall (**Figure 1B**) as we will call these positions throughout this article. However, literature on the most ideal port position is still lacking and inconclusive.

Therefore, the aim of this study was to compare satisfaction with the anterior versus the lower lateral thoracic wall port position as reported by patients, caregivers and nurses. Furthermore, the perceived port scar-quality was evaluated in survivors of childhood cancer. The information from this study can be used by health care professionals to inform and advise patients and their caregivers and facilitate the decision on where to locate the port.

METHODS

Recruitment for this cross-sectional study was done from May 2022 until February 2023. Paediatric oncology patients, their caregivers, survivors and nurses of the Princess Máxima Center for paediatric oncology, Utrecht, the Netherlands, were included in this study consecutively. Due to the descriptive nature of the study, no sample size calculation was performed. The goal was to include 140 participants (i.e., at least ≥30 participants per sub-category, we expect that this sample will provide enough informative data to answer our research question): 40 actively treated patients of ≥8-<19 years old, 40 caregivers of actively treated patients of <8 years old, 30 childhood cancer survivors (i.e., treated for a paediatric oncologic malignancy when <19 years old) of >22 years old (i.e., patients who achieved full somatic development, and who have lived with their scar for at least five years), and 30 paediatric oncology nurses. We aimed for a uniform sex distribution in the patient and childhood cancer survivor group to avoid the impact of sex as a confounding factor. Similarly, we aimed for a uniform distribution of port position (anterior versus

Figure 1 TIVAP scar



TIVAP; Totally Implantable Venous Access Port.

TIVAP with the port located at the (A) anterior thoracic wall, or (B) lower lateral thoracic wall. Examples of port scars from childhood cancer survivors; (C) port scar with low computed POSAS score, (D) visible scar because of chest hair, (E) wide scar located on the breast in a female patient, (F) wide scar located on the breast of a male patient, (G) (H) (I) (J) photographs of port scars with the highest computed POSAS scores as reported by the observer, (H) (I) (K) (L) (M) (N) photographs of port scars with the highest computed POSAS scores as reported by the survivors themselves. Photograph (H) shows the port scar in the middle of the picture, below the port scar, on the right side of the breast, a stretch mark is present.

low lateral) among patient (≥8-<19 years old) and caregiver (of patients <8 years old) responder groups to avoid the impact of age as a confounding factor. To achieve this, recruitment for subgroups was stopped when inclusions exceeded the pre-determined number to reach a 1:1 distribution. From that moment on, the researcher searched for the position of the port of eligible patients in the electronic patient files. For each group specific in- and exclusion criteria were defined and described in detail in **Supplemental Table S1**. Written informed consent was obtained from each participant and/or their caregiver. The Medical Ethics Committee NedMec, Utrecht, the Netherlands, waived the need for official approval of this study (file number: 19-130). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline was followed, see **Supplemental File S1**.(12)

Study procedures

Every eligible patient, caregiver or survivor visiting the Princess Máxima Centre at the outpatient clinic during pre-scheduled inclusion days were screened for eligibility and recruited consecutively to avoid selection bias. To avoid information bias, the researcher was primarily (i.e., until the moment that the pre-determined number to reach an equal distribution based on port position and sex was reached as described below) kept unaware about the position of the port during the screening and recruitment process. Nurses were recruited during team meetings at each hospital department (i.e., in- and outpatient departments) or if they took care of an already included patient (i.e., linked nurses). Participants were asked if they wished to participate in the study in person or by letter prior to their hospital visit, give their written informed consent and to subsequently complete the questionnaire. Additionally, for childhood cancer survivors, one observer (C.B.) evaluated the port scar. Photographs of the scars were taken in case the childhood cancer survivors gave their explicit consent, which was registered in the electronic patient files.

The electronic patient files were checked for potential confounders, patient characteristics (sex, age, diagnosis, and date of diagnosis) and TIVAP characteristics (TIVAP history, insertion/removal dates, type, insertion vein, and TIVAP complications). TIVAP complications that were registered were: wound complications (i.e., signs of a local infection such as visible erythema or pus around the TIVAP track, wound dehiscence, or sensitivity loss), dislocations of the port (e.g., port too deep or turned sideways making it difficult to access), and CVC obstruction requiring thrombolysis. These were registered due to their possible relation with the longer CVC track in patients with a lower lateral port. If data could not be obtained from the patient files, participants or health care professionals were contacted to complete the missing information. If the information remained unclear, the data was reported as missing. Data was entered in pseudonymized form from the paper questionnaire forms and electronic patient files in Castor EDC (Castor EDC v2022.4.1.3).

The TIVAP insertion method of our hospital has previously been published.(13) Scar tissue removal during port removal occurred upon the discretion of the surgeon (mostly in case of scars broader than 1cm), and was unfortunately not recorded in the patient files.

Study objectives

The primary objectives were to compare port-related hindrance as reported by patients and their caregivers for anterior versus lower lateral port positions, to observe the scar-quality as reported by survivors with a port scar at the anterior thoracic wall and to compare perceived hindrance as reported by nurses for anterior versus lower lateral port locations. See “questionnaires” and “statistical analysis” paragraphs for definitions and cut-off values.

The secondary objectives were to study overall satisfaction with the port location and the most preferred port location (incl. reason) as reported by patients, caregivers, survivors and nurses. These outcomes were also compared between anterior versus lower lateral port locations.

Questionnaires

Questionnaires were developed for each participant group, as specified in **Supplemental Table S1**. The questionnaire regarding scar quality has been validated for surgery related scars, the additional questions were not validated. (14) The questions in the questionnaire focused on the current port in case of patients on active treatment, and on the first port scar in case of childhood cancer survivors with multiple port scars.

1. Five-point Likert-scales (1-5) were used to answer questions regarding perceived hindrance (1= never, 2= rarely, 3= sometimes, 4= often, 5= very often; a high score was defined as a score of 4 or 5) and overall satisfaction (1= very satisfied, 2= somewhat satisfied, 3= not satisfied and not dissatisfied, 4= somewhat dissatisfied, 5= very dissatisfied; a high score was defined as a score of 4 or 5) when the port was connected and was not connected.
2. The validated Patient and Observer Scar Assessment Scale (POSAS) 2.0 questionnaire was used to evaluate the port scar in terms of symptoms and quality. (14) The POSAS contains two questionnaires, one for the patient and one for the observer. Both contain six items and one overall assessment. The patient scale contains six questions regarding symptoms (pain and itching) and quality (colour, pliability, thickness, and relief). The observers' questionnaire contains six questions regarding scar-quality (i.e., scar vascularity, pigmentation, pliability, thickness, relief, and surface area). Scales of 1-10 are used to measure the different items (1 = as normal skin, 10 = worst scar imaginable).

3. Multiple choice and open questions were used to identify which port location each participant would prefer, including the reason for this. Survivors were asked if they remembered any complications associated with the port, if they treated the scar (e.g., ointments, injections or scar excision surgery) in the past, and what feeling the scar evokes.

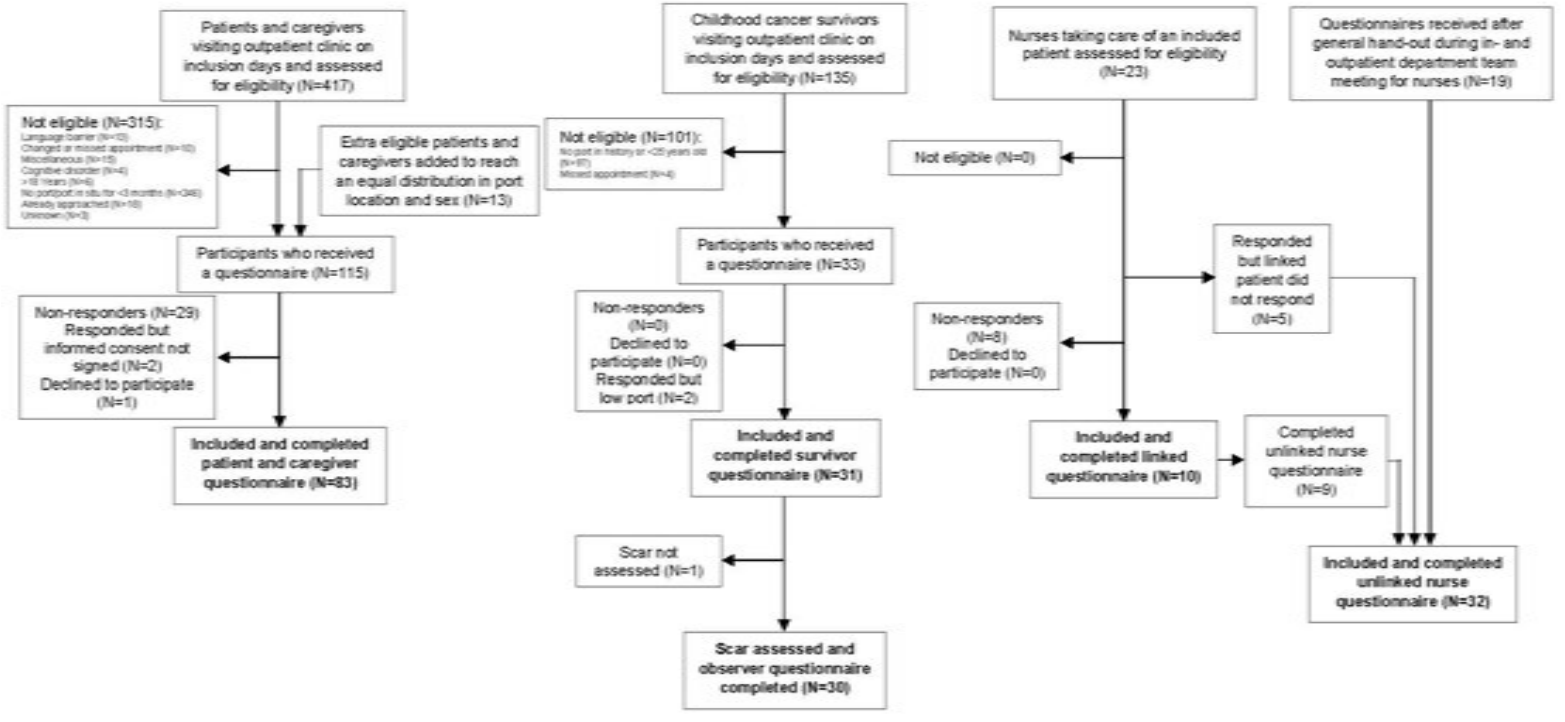
Statistical analysis

Summary statistics were presented for continuous and categorical data (i.e., median, first quartile (Q1), third quartile (Q3), frequencies and percentages). Answers to open-ended questions were grouped by the researcher. The five-point Likert scales were divided in low (score of 1-2), medium (score of 3) or high (score of 4-5), to be clinically more valuable. Since no cut-off values for the POSAS 2.0 have been established yet, a high score (i.e., displeasing scar) will be defined as patients having a score of more than the third quartile (Q3) of the total median for that question. The baseline characteristics and responses to the questionnaires were compared using nonparametric tests (i.e., Chi-square, Fisher's exact test, Mann-Whitney U test, Wilcoxon Signed Rank test) among the following groups: (1) patients with an anterior versus patients with a lower lateral port location, (2) observer versus survivors, and (3) nurses versus their patients. An alpha level of 0.05 was maintained. Data was analysed using IBM SPSS statistics (version 26.0.0.1).(15)

RESULTS

In total, 147 participants were included. The recruitment process has been detailed in **Figure 2**. The baseline characteristics of all participants are described in **Table 1.** An anterior port was in situ in 36 (43%) out of 83 patients on active treatment, a lower lateral port was in situ in 47 (57%) out of 83 patients on active treatment, an equal distribution in baseline characteristics was observed

Figure 2 Recruitment flow-chart



[a] Not eligible due to: language barrier (N=13), changed/missed appointment (N=10), cognitive disorder (N=4), >18 years old (N=6), no port or port in situ for less than three months (N=246), already approached (N=18), miscellaneous (N=15), or unknown (N=3).

[b] Not eligible due to: no port in history or <25 years old (N=97), or changed/missed appointment (N=4).

Table 1a Baseline characteristics

ALL PATICIPANTS (N=147)		**Total**		**Anterior**		**Lower lateral**		**p-value[c]**
Participants, N(%)	Patients total:	83	56.5%	36	53.7%	47	100.0%	0.59
	Caregivers of patients <8yrs	41	27.2%	19	26.9%	22	46.8%	
	Patient ≥8 yrs	42	29.3%	17	26.9%	25	53.2%	
	Survivors	31	21.1%	31	46.3%			
	Nurses total:	33	22.4%					
	Linked	10	6.8%					
	Unlinked	23	15.6%					
PATIENTS (N=83)		**Total**		**Anterior**		**Lower lateral**		**p-value[c]**
Sex, N(%)	Male	46	55.4%	22	61.1%	24	51.1%	0.38
	Female	37	44.6%	14	38.9%	23	48.9%	
Age, median years (Q1-Q3)	During response	8 (4-13)		8 (4-16)		8 (5-12)		0.57
	Port insertion	6 (4-13)		6.5 (3-14)		6 (4-11)		0.78
Dwell time port[a], median days (Q1-Q3)		228 (142-383)		238 (134-492)		224 (156-364)		0.90
Diagnosis, N(%)	Hemato-oncology	28	33.7%	11	30.6%	17	36.2%	0.46
	Lymphoma	11	13.3%	3	8.3%	8	17.0%	
	Neuro-oncology	12	14.5%	5	13.9%	7	14.9%	
	Solid tumour	32	38.6%	17	47.2%	15	31.9%	
Port type[a], N(%)	Baby single lumen	4	4.8%	3	8.3%	1	2.1%	0.05
	Low-profile single lumen	70	84.3%	27	72.2%	44	93.6%	
	Standard single lumen	8	9.6%	6	16.7%	2	4.3%	
	Missing	1	1.2%	1	2.8%	0	0.0%	
Insertion method[a], N(%)	PC	80	96.5%	34	94.4%	46	97.9%	1.00
	Open	2	2.4%	1	2.8%	1	2.1%	
	Missing	1	1.2%	1	2.8%	0	0.0%	
Insertion vein, N(%)	Jugular	71	85.5%	31	86.1%	40	85.1%	0.91
	Subclavian	11	13.3%	5	13.9%	6	12.8%	
	Missing	1	1.2%	0	0.0%	1	2.1%	
Insertion side, N(%)	Left	16	19.3%	7	19.4%	9	19.1%	1.00
	Right	67	80.7%	29	80.6%	38	80.9%	
Port site complications, N(%)	Yes[d]	15	18.1%	9	25.0%	6	12.8%	0.25
	No	68	81.9%	27	75.0%	41	87.2%	
CVC obstruction requiring thrombolysis, N(%)	Yes	14	16.9%	7	19.4%	7	14.9%	0.58
	No	69	83.1%	29	80.6%	40	85.1%	

Table 1b Baseline characteristics

PATIENTS (N=83)		**Total**		**Anterior**		**Lower lateral**		**p-value[c]**
Port replaced previously at same position, N (%)	Yes	7	8.4%	4	11.1%	3	6.4%	0.46
	No	76	91.6%	32	88.9%	44	93.6%	
Number port scars, N (%)	Two	15	18.1%	7	19.4%	8	17.0%	1.00
	One	68	81.9%	29	80.6%	39	83.0%	
History with anterior and lower lateral port insertion, N (%)	Yes	6	7.2%	3	8.3%	3	6.4%	1.00
	No	77	92.8%	33	91.7%	44	93.6%	
SURVIVORS (N=31)		**Total**		**Anterior**		**Lower lateral**		**p-value[c]**
Sex, N (%)	Male	17	54.8%					
	Female	14	45.2%					
Age, median years (Q1-Q3)	During response	30 (26-33)						
	Diagnosis	8 (2-14)						
Diagnosis, N (%)	Hemato-oncology	9	29.0%					
	Lymphoma	9	29.0%					
	Neuro-oncology	0	0%					
	Solid tumour	13	41.9%					
Insertion side, N (%)	Left	10	32.3%					
	Right	21	67.7%					
Port site complications[b], N (%)	Yes[e]	7	22.6%					
	No	15	48.4%					
	Missing	9	29.0%					
Port replaced at same position[b], N (%)	Yes	7	22.6%					
	No	16	51.6%					
	Missing	8	25.8%					
Number of port scars, N (%)	Two	5	16.1%					
	One	26	83.9%					

TIVAP; Totally Implantable Venous Access Port, PC; Percutaneous, US; Ultrasound, CVC; Central Venous Catheter, n.a.; not applicable.

[a] Data on the CVC characteristics of survivors was not available since inserted >16 years ago in other hospitals.

[b] Self-reported by the survivors since no surgery and clinical reports from the past were available.

[c] Fisher-exact and Chi-square test were used for categorical data; Fisher-exact test rather than Chi-square was used when a cell-count was less than five. Mann-Whitney U test was used for continuous data that was not normally distributed.

[d] Erythema (N=12), erythema and pus (N=2), small persisting wound (N=1).

[e] Wound dehiscence (N=2), port too deep to access (N=1), port turned sideways (N=1), sensitivity loss (N=1), infection (N=1), complication but unknown what specifically happened (N=1).

between these two groups (p=0.05-1.00). No difference in complications (i.e., port site related or CVC obstruction) between anterior and lower ports was observed. All survivors included received an anterior port in the past (i.e., before 2018).

The questionnaire responses of patients and their caregivers are described in **Table 2**. Perceived port-related hindrance when the port was not connected was only (very) often experienced by zero to two (0-2%) patients as reported by themselves or by their caregivers. Perceived port-related hindrance when the port was connected was (very) often experienced by eight to 17 (10%-21%) patients as reported by themselves or by their caregivers. Overall, the vast majority (87%) was (very) satisfied with the location of their port. No significant difference in the responses was observed between patients with an anterior versus a lower lateral port location (p=0.43-0.99). Further characteristics of patients with high scores are described in **Supplemental Table S2**.

The questionnaire responses of survivors and the observer are described in **Table 3**. The observer questionnaire was completed for 30 survivor scars by one observer and the survivor questionnaire was completed for 31 scars by 31 survivors. A high computed POSAS score (i.e., a displeasing scar) was reported for six (20%) survivors by the observer and by seven (23%) survivors themselves, three survivors received a high score from both themselves and the observer. The median computed POSAS score describing scar-quality reported by observers was significantly higher than reported by patients themselves (p=0.03). See **Figure 1C** for an example of a scar with a low computed POSAS score as reported by the observer and survivor. Scars on the anterior thoracic wall were particularly visible in patients with chest hair and breast formation, see **Figure 1D, 1E**, and **1F**. High scores for pain and itching were reported by two and three (7% and 10%) survivors, respectively. All scars (100%) were widened. No keloid was observed in any of the scars. Overall, 15 (60%) of 25 survivors

Table 2 Responses of patients and caregivers of patients

	Total (n=83)		**Anterior port (n=36)**		**Lower lateral port (n=47)**		**p-value[b]**
	Median (Q1-Q3)	High score[a], n (%)	Median (Q1-Q3)	High score[a], n (%)	Median (Q1-Q3)	High score[a], n (%)	
Statements concerning hindrance							
(1=never, 2=rarely, 3=sometimes, 4=often, 5=very often)							
Q1. The port bothers me/my child if it is not connected in rest.	1 (1-2)	0 (0.0%)	1 (1-2)	0 (0.0%)	1 (1-2)	0 (0.0%)	0.43
Q2. The port bothers me/my child if it is connected in rest.	2 (1-3)	8 (9.6%)	2 (1-3)	2 (5.6%)	2 (1-3)	6 (12.8%)	0.85
Q3. The port bothers me/my child if it is not connected during activities.	1 (1-2)	1 (1.2%)	1 (1-3)	0 (0%)	1 (1-2)	1 (1.2%)	0.77
Q4. The port bothers me/my child if it is connected during activities.	3 (1-3)	17 (20.5%)	2 (1-3)	7 (19.4%)	3 (1-3)	10 (21.3%)	0.66
Q5. The port bothers me/my child if it is not connected during daily care (washing, clothing).	1 (1-2)	2 (2.4%)	1 (1-2)	2 (5.6%)	1 (1-2)	0 (0.0%)	0.55
Q6. The port bothers me/my child if it is connected during daily care (washing, clothing).	2 (1-3)	16 (19.3%)	2 (1-4)	9 (25.0%)	3 (1-3)	7 (14.9%)	0.99
Overall satisfaction							
(1=very satisfied, 2=somewhat satisfied, 3=not satisfied and not dissatisfied, 4=somewhat dissatisfied, 5=very dissatisfied)							
Q7. Are you satisfied with the location of the port?	1 (1-2)	4 (4.8%)	1 (1-2)	1 (2.8%)	1 (1-2)	3 (6.4%)	0.81

[a] A high score was defined as a score of 4-5 on the five-point Likert scale.
[b] Mann-Whitney U-test.

Table 3a Responses of survivors and observer of survivors

	Median score (Q1-Q3) or n (%)	High score[a], n (%)	Scar category, n (%)	
Observer questionnaire (N=30)				
POSAS score *(1 = normal skin – 10 = worst scar imaginable)*				
Q1. Vascularity	4 (2-5)	3 (10.0%)	Pale	12 (40.0%)
			Pink	3 (10.0%)
			Red	2 (6.7%)
			Purple	2 (6.7%)
			Mix	11 (36.7%)
Q2. Pigmentation	3 (2-4)	4 (13.3%)	Hypo	17 (56.7%)
			Hyper	0 (0.0%)
			Mix	13 (43.3%)
Q3. Thickness	3 (2-4)	1 (3.3%)	Thicker	5 (16.7%)
			Thinner	25 (83.8%)
Q4. Relief	3 (2-4)	2 (6.7%)	More	4 (13.3%)
			Less	21 (70.0%)
			Mix	5 (16.7%)
Q5. Pliability	3 (2-4)	5 (16.7%)	Supple	23 (76.7%)
			Stiff	5 (16.7%)
			Mix	2 (6.7%)
Q6. Surface area	4 (3-6)	5 (16.7%)	Expansion	30 (100.0%)
			Contraction	0 (0.0%)
			Mix	0 (0.0%)
Q7. Overall opinion of the scar	4[b] (2.75-5)	5 (16.7%)		
Computed POSAS score (sum of Q1-Q6) *(6 = normal skin – 60 = worst scar imaginable)*	21.5[c] (15.5-25)	6 (20.0%)		
Survivor questionnaire (N=31)				
POSAS score *(1 = normal skin – 10 = worst scar imaginable)*				
Q1. Is the scar painful?	1 (1-1)	2 (6.5%)		
Q2. Is the scar itching?	1 (1-1)	3 (9.7%)		
Q3. Is the colour of the scar different?	3 (2-6)	3 (9.7%)		
Q4. Is the scar stiffer?	3 (2-6)	4 (12.9%)		
Q5. Is the thickness of the scar different?	4 (1-6)	5 (16.1%)		
Q6. Is the scar irregular?	2 (1-5)	8 (25.8%)		
Q7. Overall opinion of the scar?	4[b] (2-6)	7 (22.6%)		
Computed POSAS score (sum of Q1-Q6) *(6 = normal skin – 60 = worst scar imaginable)*	18[c] (10-24)	7 (22.6%)		

Table 3b Responses of survivors and observer of survivors

	Median score (Q1-Q3) or n (%)	**High score[a], n (%)**
Q8. Are you satisfied with the location of the port?[d] *(1=very satisfied, 2=somewhat satisfied, 3=not satisfied and not dissatisfied, 4=somewhat dissatisfied, 5=very dissatisfied)*	1 (1-3)	2 (8.0%)
Q9. In the past, have you treated the port scar? *(open question, categorized by researcher)*		
No	23 (74.2%)	
Ointment	6 (19.4%)	
Ointment and surgery	1 (3.2%)	
Missing	1 (3.2%)	
Q10. What feeling does the scar evoke in you? *(open question, categorized by researcher)*		
No feeling	14 (45.2%)	
Neutral feelings (e.g., reminder of my past)	8 (25.8%)	
Positive feelings (e.g., proud, strength, victory, cool, wonder, tells my story)	7 (22.6%)	
Negative feelings (e.g., not pretty)	2 (6.5%)	

Definitions as defined by the POSAS scale: vascularity is the presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of plexiglas; pigmentation is brownish coloration of the scar by pigment, plexiglas is applied to the skin with moderate pressure to eliminate the effect of vascularity; thickness is the average distance between the subcutical-dermal border and the epidermal surface of the scar; relief is the extent to which surface irregularities are present (preferably compared with adjacent normal skin); pliability is the suppleness of the scar tested by wrinkling the scar between the thumb and index finger; surface area is the area of the scar in relation to the original wound area.

[a] A high score for the POSAS questions Q1-Q7 and the computed POSAS score was defined as a score of >Q3 of the total median, a high score for Q8 (five-point Likert scale) was defined as a score of 4-5.

[b] No significant difference in the score for Q7 between the observer and survivor (Wilcoxon Signed Rank Test p-value=0.51) was observed.

[c] A significant difference in the computed POSAS score between observer and survivor (Wilcoxon Signed Rank Test p-value=0.03) was observed; the observer reported slightly higher POSAS scores than the survivors.

[d] Six survivors did not respond to question Q8 since they overlooked the question, for this question N=25 responses are shown.

(six survivors did not complete this question) reported that they were (very) satisfied with the location of their port scar. Scar treatments (i.e., ointments and surgery) were reported by seven (23%) survivors. The port scar evoked no particular feelings in 14 (45%) survivors, for eight (26%) survivors it evoked neutral feelings such as "a reminder of the past", for seven (23%) survivors it evoked positive feelings such as "proud", "strength", "victory" and "tells my story, it has shaped me" (23%), and for two (7%) survivors it evoked a negative feeling "not pretty". See **Supplemental Table S2** and **Figure 1** for further characteristics of the survivors with high scores and the photographs of their scars.

The questionnaire responses of nurses are described in **Table 4**. No significant difference in the scores was observed for an anterior versus a lower lateral port location (p=0.07-0.46). No significant differences were observed between the scores given by nurses and their patients or the caregiver of their patients (p=0.08-0.68), see **Supplemental Table S3**.

The preferred port location as reported by all participants has been described in **Supplemental Table S4**. In total, 92 out of 114 (81%) patients, caregivers, and survivors preferred their current port location. A positive, but non-significant, association with preferring the same port location and having a lower lateral port location was observed (OR:1.37, CI95%:0.36-5.15, p=0.74). Of the nurses, 15 (46%) preferred a lower lateral port location, 11 (33%) did not have a preference, and six (18%) preferred an anterior port location.

The difference between the responses reported by patients and caregivers, survivors and the observer on the questions regarding overall satisfaction, which location they would prefer, the overall opinion about the scar and/or the computed POSAS score were compared for various hypothesized factors, see **Supplemental Table S5**. For

Table 4 Responses of nurses

	Anterior port (N=31)		**Lower lateral port (N=32)**		**p-value[d]**
	Median (Q1-Q3)	High score[a], n (%)	Median (Q1-Q3)	High score[a], n (%)	
Statements concerning hindrance					
(1=never, 2=rarely, 3=sometimes, 4=often, 5=very often)					
Q1. It is difficult to insert the needle in the port at this location[b]	2 (2-3)	0 (0.0%)	2 (2-2)	0 (0.0%)	0.46
Q2. The connection wires bother me if a port is inserted at this location	1 (1-2)	1 (3.2%)	1 (1-2)	0 (0.0%)	0.07
Q3. The port bothers me if it is not connected during the daily care of a child[c]	1 (1-1)	0 (0.0%)	1 (1-1)	0 (0.0%)	0.19
Q4. The port bothers me if it is connected during the daily care of a child[c]	1 (1-2)	0 (0.0%)	1 (1-2)	0 (0.0%)	0.16
Overall satisfaction					
(1=very satisfied, 2=somewhat satisfied, 3=not satisfied and not dissatisfied, 4=somewhat dissatisfied, 5=very dissatisfied)					
Q5. Are you satisfied with the location of the port?	2[b] (1-2)	0 (0.0%)	1[b] (1-2)	0 (0.0%)	0.45

In total, 33 nurses participated in this study, one nurse only answered the questions regarding a specific patient (i.e., linked questionnaire), and one nurse answered only the questions regarding a lower later port.

[a] A high score was defined as a score of 4-5.

[b] One participant did not answer Q1, for this question N=30 and N=31 responses are shown for the anterior and lower lateral port, respectively.

[c] One participant did not answer Q3 and Q4, for these questions N=30 and N=31 responses are shown for the anterior and lower lateral port, respectively.

[d] Wilcoxon Signed-Rank test.

patients and caregivers, the preference for a different port location was associated with a higher score for overall satisfaction with the port location ($p<0.01$), and a positive association was found between being female and preferring a lower lateral port position (OR: 2.60, CI95%: 1.04-6.52, $p<0.05$). For survivors, the preference for a different port position was associated with a higher score for overall satisfaction with the port position ($p<0.01$), and a right-sided as compared to a left-sided port resulted in a higher computed POSAS score (i.e., a more displeasing scar) ($p<0.01$). No other significant risk factors were identified.

The reasons for the preference of either an anterior or lower lateral port position are described in **Supplemental Table S6**. The anterior port position was preferred since, during daily life, minimal pressure is put on the port and/or port-needle. The lower lateral position was preferred since the scar is less visible and because of easier access to the port.

DISCUSSION

The aim of this cross-sectional study was to provide information that can be used by health care professionals to inform and advise patients and their caregivers and facilitate the decision on where to locate the port. The vast majority (i.e., 81%) of the participants was satisfied with the position of their port or port scar. Satisfaction of patients, caregivers and nurses did not significantly differ between the anterior and lower lateral port position. Based on the results of this study, we concluded that both port positions should be offered to patients/caregivers, and that the definite position should be chosen together based on the (dis-)advantages of each position, as identified by this study. Recommendations were developed for health care professionals, which are described in **Table 5.**

Table 5 Summary of recommendations

Discuss the possible port positions with your patient and their caregiver and take the following into account for an anterior versus a lower lateral port position:	
Anterior port	1. Scar more visible as compared to a lower lateral scar. 2. Vast majority of the scars will stretch, resulting in high rates of displeasing scars. 3. Less pressure on the port and/or port-needle during daily life as compared to a lower lateral port, but still ask the patient about their sleeping position, sport activities and hobbies, so that you can take the movements made during these activities into account while choosing the most optimal port position. 4. Insert the port into the direction of the axilla (i.e., less visible while wearing clothes, and away from the (future) breast area (also in male patients!) and chest hair area.
Lower lateral port	1. Provides easier access to the port for nurses (i.e., because of less fat disposition and better port fixation), presumably decreasing port connection time, puncturing attempts, and thereby patient distress. 2. Scar less visible as compared to an anterior port scar (i.e., which is specifically preferred by female patients). 3. Hypothesis is that less displeasing/widened scars are observed due to less tension that is put on the skin, future research should investigate this. 5. Patients often report pressure on the port and/or port-needle. Therefore, ask the patient about their sleeping position, sport activities and hobbies, so that you can take the movements made during these activities into account while choosing the most optimal port position. 6. In general, insert the port not too lateral (i.e., so that pressure on the port during daily life is minimized) and insert the port away from the (future) breast area (also in male patients!) and chest hair area.

The computed POSAS score given by the observer was higher than the score given by the survivors themselves. The opposite, however, has previously been described by van der Kar et al.(14) and Connolly et al.(2). Explanations for this difference might be that itching and pain influence the survivor's opinion the most, which was barely reported by the survivors included in this study, and that all scars were widened in this study, which is only a score-item in the observer questionnaire. Furthermore, survivors might have grown into their own deficit, resulting in lower scores as compared to the observers. Observer bias is also presumably present as only one observer assessed the scars in this study, which makes the scoring very subjective. However, when comparing the photographs of the scars with the highest POSAS scores as reported by the observer versus the survivors themselves, no large

difference in scar-quality is observed, see **Figure 1**. At last, right-sided as compared to left-sided port scars were associated with more displeasing scars, which might be explained by more tension that is put on the skin on the right side since the majority of patients are presumably right-handed.

Previous studies have been performed investigating satisfaction of paediatric oncology patients and survivors.(1, 2, 11) Similarly to our results, Ullman et al.(1) reported most difficulties with the CVC during activities and daily care. High rates of abnormal, mostly wide, port scars have also been reported in survivors with anterior ports by Braam et al. (11) and Connolly et al.(2). Braam et al.(11) included patients of which the majority still had a port in situ and reported that 88% of the scars were abnormal, and 81% of the scars had a width larger than 3mm. Itching of the scar was reported more frequently as compared to our study (i.e., 10% versus 31%), which might be explained by the older age of the participants in our study (i.e., survivors of >22 years old versus children of <21 years old). Connolly et al.(2) included adolescent survivors and reported that 75% of the scars had a width larger than 1cm. The median POSAS scores reported by Connolly et al.(2) were consistently lower (i.e., better quality of the scars) than reported in our study. They also reported a low impact of the scar on the quality of life of the survivors, and therefore concluded that a change in the standard port position is not needed. In our study however, the follow-up was longer (i.e., survivors with a median age of 30 years versus 16 years old), which might be a reason for the higher POSAS scores, and further advantages of a lower lateral port as compared to an anterior port were identified. These results in our opinion suggest that a lower lateral port should definitely be offered to patients and caregivers, especially in female patients. Furthermore, upper arm ports might also be promising, as reported in a systematic review including adult literature published by Li et al.(16). The upper arm position has the advantage that it does not have the problem of interference with the breast/bra and cleavage area, and needle insertion

can take place out of the child's sight. However, these ports have not yet been thoroughly studied in children. Future research should further explore this option. Furthermore, future research should focus on the comparison of scar expansion of lower lateral versus anterior scars. It might already be feasible to investigate this in patients on active treatment instead of survivors. A scar assessment in this group was not done during this study since the scars would still change over time. However, in the clinical setting, our experience is that we already observe more expanded scars at the anterior as compared to lower lateral position in patients with a port still in situ.

Strengths of this study are that various perspectives were taken into account (i.e., patients, caregivers, survivors and nurses), that survivors after a long period since diagnosis were included, that scar photographs were taken, and that various risk factors for a displeasing scar were evaluated. Limitations were the cross-sectional design, which does not reflect changes in satisfaction or scar-quality over time, the relatively small sample size per subgroup, selection bias (i.e., very (dis)satisfied people more prone to be selected, participate and respond), confounding factors which we could not identify (e.g., influence of treatment/aplasia on wound healing), observer bias (i.e., subjectivity of one observer, misinterpretation of free-texts answers, change in perspective of the observer after more exposure to different scars), implicit bias since the lower lateral position was introduced more recently, the missing TIVAP history and various TIVAP insertion centres (with probably different techniques) of most survivors, the risk of recall bias in the survivor group, and the vast majority of the survivors was Caucasian, making the results less generalizable for other ethnicities. Specific limitations of the POSAS 2.0 are that the minimal clinically important difference has not been established, and that the improved POSAS 3.0 was not yet available during the start of our study.(14, 17)

To conclude, satisfaction did not differ between the anterior and lower lateral port position. The anterior port scars however, were all widened, which might not be the case for lower lateral port scars, but future research should confirm this hypothesis. The port position should therefore until then, be chosen together with patients and caregivers based on the (dis-)advantages of each position, as identified by this study.

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SUPPLEMENTARY FILES NOT INCLUDED IN THIS THESIS

Supplemental file S1 Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Checklist

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SUPPLEMENTARY TABLES

Supplementary table 1 Overview study design

Participant group	Objective	Inclusion criteria	Exclusion criteria	Group specific outcomes	Overall outcomes
1. Parents of children with paediatric cancer 0-<8 years old (n=40) 2. Children diagnosed with paediatric cancer ≥8-<19 years old (n=40)	A. To compare port-related hindrance between ports inserted at the anterior thoracic wall versus the lateral thoracic wall as reported by paediatric oncology patients or their parents	o Port inserted in Máxima o Port in situ for >3months o Equal distribution of anterior and lateral thoracic wall ports o Equal distribution of male/female participants	Not able to understand the questionnaire or write answers in Dutch	Hindrance in rest, during activities and daily care as reported by parents/patients [Likert-scale]	Overall satisfaction with the port location [Likert-scale] Preferred port location (anterior vs. lateral thoracic wall / right vs. left) Reason for preferred port location
3. Paediatric oncology nurses (n=30)	B. To compare hindrance between ports inserted at the anterior thoracic wall versus the lateral thoracic wall as reported by paediatric oncology nurses.	o Certified paediatric oncology nurse o Experience with connection of ports o Taking care of a patient in group one or two (n=10)[a]		Hindrance during port connection and daily care as reported by nurses [Likert-scale]	
4. Paediatric cancer survivors >22 years old (n=30, 15 male, 15 female)	C. To observe scar-related symptoms and scar-quality as reported by survivors of paediatric oncology who previously received a port at the anterior thoracic wall during their treatment.	o Port in situ when <19 years old at the anterior thoracic wall[b] o No port in situ for >2years (maturation time scars) o Complete remission		Port scar-related symptoms and scar-quality as reported by paediatric cancer survivors [POSAS 2.0]	

[a]Ten nurses who are taking a care of a patient in group one or two will be asked to complete a questionnaire regarding this patient specifically to compare the results given by the patient/parent and the nurse.

[b]All pediatric cancer survivors will have a port at the anterior thorax wall. Therefore, we will have no comparator group for these patients.

Supplementary table 2a Participants with the highest scores to Q7 "Are you satisfied with the location of the port?" for patients and caregivers, Q7 "Overall opinion of the scar?" for survivors and the observer, Q8 "Are you satisfied with the location of the port?" for survivors, and the computed POSAS score for survivors and the observer.

Pt	Group	High score item[a] (score given by survivor+ observer)	Port	Sex	Age	Diagnosis	Yrs since diagnosis	Dwell time days	Port type	Insertion method	Side	Wound specifications	Port replaced	Two scars	Preferred location	Fig
1	Survivor	Q8(4)	A	F	29	ALL	26	n.a.	n.a.	n.a.	R	X	X	No	-	X
2	Survivor	Q7(8)	A	F	40	RMS	24	n.a.	n.a.	n.a.	R	Complication but X	No	No	A	2E
3	Survivor	Computed POSAS(25)	A	F	31	ALL	14	n.a.	n.a.	n.a.	R	Wound dehiscence	Yes	No	A	X
4	Survivor	Computed POSAS(26)	A	M	24	ALL	24	n.a.	n.a.	n.a.	R	No	X	No	A	2N
5	Survivor	Q7(7), Q8(4)	A	F	37	Osteosarcoma	29	n.a.	n.a.	n.a.	R	No	No	No	LL	X
6	Survivor + observer	Q7(7), computed POSAS(28+26)	A	M	30	Ewing	30	n.a.	n.a.	n.a.	R	No	Yes	No	A	2L
7	Survivor	Q7(7), computed POSAS(27)	A	M	24	ALL	20	n.a.	n.a.	n.a.	R	X	Yes	Yes	-	2M
8	Survivor	Q7(8), computed POSAS(33)	A	M	37	PNET	36	n.a.	n.a.	n.a.	R	X	X	No	A	2K

A; Anterior, LL; Lower Lateral, Pt; Patient, POSAS; Patient and Observer Scar Assessment Scale, F; female, M; male, ALL; Acute Lymphoblastic Leukaemia, RMS; Rhabdomyosarcoma, PNET; Primitive Neuro-Ectodermal Tumour, PC; Percutaneous, X; missing

Supplementary table 2b Participants with the highest scores to Q7 "Are you satisfied with the location of the port?" for patients and caregivers, Q7 "Overall opinion of the scar?" for survivors and the observer, Q8 "Are you satisfied with the location of the port?" for survivors, and the computed POSAS score for survivors and the observer.

Pt	Group	High score item[a] (score given by survivor+ observer)	Port	Sex	Age	Diag-nosis	Yrs since diagnosis	Dwell time days	Port type	Insertion method	Side	Wound specifications	Port replaced	Two scars	Preferred location	Fig
9	Observer	Q7(7), computed POSAS(33)	A	M	34	ALL	24	n.a.	n.a.	n.a.	R	No	No	No	LL	2G
10	Observer	Q7(7), computed POSAS(27)	A	F	36	Hodgkin	22	n.a.	n.a.	n.a.	R	Port too deep	Yes	No	LL	2J
11	Observer	Q7(6), computed POSAS(26)	A	M	33	RMS	17	n.a.	n.a.	n.a.	R	No	No	No	A	X
12	Survivor + observer	Q7(7+6), computed POSAS(25+32)	A	M	26	ALL	12	n.a.	n.a.	n.a.	L	No	No	No	LL	2H
13	Survivor + observer	Q7(9+7), computed POSAS(28+29)	A	M	28	Non-hodgkin	18	n.a.	n.a.	n.a.	R	Scar correction	No	No	LL	2I
14	Caregiver of patient	Q7(4)	LL	M	7	Non-hodgkin	n.a.	123	Low-profile	PC	R	No	No	n.a.	A	X
15	Caregiver of patient	Q7(4)	A	F	4	Non-hodgkin	n.a.	227	Standard	PC	R	No	No	n.a.	LL	X
16	Caregiver of patient	Q7(5)	LL	F	6	RMS	n.a.	659	Low-profile	PC	L	No	No	n.a.	LL	X
17	Patient	Q7(5)	LL	F	18	Osteosarcoma	n.a.	430	Low-profile	PC	R	No	No	n.a.	LL	X

A; Anterior, LL; Lower Lateral, Pt; Patient, POSAS; Patient and Observer Scar Assessment Scale, F; female, M; male, ALL; Acute Lymphoblastic Leukaemia, RMS; Rhabdomyosarcoma, PNET; Primitive Neuro-Ectodermal Tumour, PC; Percutaneous, X; missing

Supplementary table 3 Responses of nurses linked to patients

	Nurse (N=10)		**Linked patient (N=10)**		**p-value[b]**
	Median (Q1-Q3)	High score[a], n (%)	Median (Q1-Q3)	High score[a], n (%)	
Statements concerning hindrance					
(1=never, 2=rarely, 3=sometimes, 4=often, 5=very often)					
Q1. The port bothers me if it is not connected during daily care (washing, clothing)[c]	1 (1-1)	0 (0.0%)	1 (1-1.25)	0 (0.0%)	0.32
Q2. The port bothers me if it is connected during daily care (washing, clothing)[c]	1 (1-1.25)	0 (0.0%)	2 (1-3.25)	2 (20.0%)	0.08
Overall satisfaction					
(1=very satisfied, 2=somewhat satisfied, 3=not satisfied and not dissatisfied, 4=somewhat dissatisfied, 5=very dissatisfied)					
Q3. Are you satisfied with the location of the port?	1 (1-2)	0 (0.0%)	1 (1-2.25)	0 (0.0%)	0.68

[a] A high score was defined as a score of 4-5 on the five-point Likert scale.
[b] Wilcoxon Signed-Rank test.
[c] One nurse did not respond to Q1 and Q2, for these questions N=9 responses are shown for the nurses.

Supplementary table 4 Preferred port position

Group	Port location	Preferred port position	N (%)
Patients and caregivers of patient (N=83)	Anterior port in situ (N=36)	Anterior	30 (83.3%)
		Lower lateral	5 (13.9%)
		Missing	1 (2.8%)
	Lower lateral port in situ (N=47)	Anterior	5 (10.6%)
		Lower lateral	41 (87.2%)
		No preference	1 (2.1%)
	History with anterior and lower lateral port (N=6)	Anterior	3 (50.0%)
		Lower lateral	2 (33.3%)
		No preference	1 (16.7%)
Survivors (N=31)	Anterior port in history (N=31)	Anterior	21 (67.7%)
		Lower lateral	8 (25.8%)
		No preference	2 (6.5%)
Nurses (N=33)	n.a.	Anterior	6 (18.2%)
		Lower lateral	15 (45.5%)
		No preference	11 (33.3%)
		Missing	1 (3.0%)

In total 92 (80.7%) patient, caregivers, and survivors (N total=114) preferred the same port location. There is a positive, but non significant, association with choosing the same port location and having a port at the lower lateral thoracic wall (OR 1.37, CI95% 0.36-5.15; p=0.74) for patients and caregivers.

Supplementary table 5a Risk factors

		Patients and caregivers			Survivor							Observer			
		Overall satisfaction with location (Q7)		**Anterior vs. lower lateral**	**Overall satisfaction with location (Q8)**		**Preference different location**	**Overall opinion about scar (Q7)**		**Computed POSAS score**		**Overall opinion about scar (Q7)**		**Computed POSAS score**	
		Median (Q1-Q3)	p-value[a]	p-value[b]	Median (Q1-Q3)	p-value[a]	p-value[b]	Median (Q1-Q3)	p-value[a]	Median (Q1-Q3)	p-value[a]	Median (Q1-Q3)	p-value[a]	Median (Q1-Q3)	p-value[a]
Sex	Female	1 (1-2)	0.27	<0.05*[c]	2 (1-3)	0.93	1.00	4 (2-6)	0.69	15 (10-23)	0.40	3 (2-5)	0.06	15.5 (12-24.5)	0.06
	Male	1 (1-2)			1 (1-3)			5 (2-7)		18 (11-26)		5 (4-6)		24 (19-26)	
Age during response	<8 yrs	1 (1-2)	0.28	1.00	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	≥8 yrs	1 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
	<12 yrs	1 (1-2)	0.47	0.23	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	≥12 yrs	1 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
	<30 yrs	n.a.	n.a.	n.a.	1 (1-3)	0.79	1.00	5 (2-6)	0.52	20 (14-25)	0.13	4 (2-5)	0.35	23 (16-)	0.28
	≥30 yrs	n.a.			2 (1-3)			3 (2-7)		11 (9-22)		5 (3-5)		29 (21-34)	

POSAS; Patient and Observer Scar Assessment Scale, TIVAP; Totally Implantable Venous Access Port. *Significant value

[a] Mann-Whitney U-test or Kruskal-Wallis Test.

[b] Fisher-exact and Chi-square test were used for categorical data; Fisher-exact test rather than Chi-square was used when a cell-count was less than five.

[c] There is a positive association between being female and preferring the lower lateral position (OR: 2.60, CI95%: 1.04-6.52, p<0.05).

Supplementary table 5b Risk factors

		Patients and caregivers			Survivor							Observer			
		Overall satisfaction with location (Q7)		**Anterior vs. lower lateral**	**Overall satisfaction with location (Q8)**		**Preference different location**	**Overall opinion about scar (Q7)**		**Computed POSAS score**		**Overall opinion about scar (Q7)**		**Computed POSAS score**	
		Median (Q1-Q3)	p-value [a]	p-value [b]	Median (Q1-Q3)	p-value [a]	p-value [b]	Median (Q1-Q3)	p-value [a]	Median (Q1-Q3)	p-value [a]	Median (Q1-Q3)	p-value [a]	Median (Q1-Q3)	p-value [a]
Age during port insertion	<12 yrs	1 (1-2)	0.41	0.31	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	≥12 yrs	1 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
Age during diagnosis	<12 yrs	n.a.	n.a.	n.a.	3 (1-3)	0.14	1.00	5 (3-7)	0.26	19 (11-25)	0.39	5 (3-5)	0.93	28 (19-32)	0.82
	≥12 yrs	n.a.			1 (1-2)			2 (1-6)		10 (10-22)		4 (3-5)		24 (21-30)	
Diagnosis	Hemato-oncology	1 (1-2)	0.60	0.62	1 (1-3)	0.62	0.87	5 (2-6)	0.63	23 (12-25)	0.32	5 (3-6)	0.43	24 (19-32)	0.33
	Lymphoma	1 (1-3)			1 (1-3)			3 (2-5)		10 (8-20)		3 (2-7)		16 (11-27)	
	Neuro-oncology	2 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
	Solid tumor	1 (1-2)			3 (1-3)			4 (2-7)		19 (10-23)		4 (3-5)		24 (15.5-25)	

POSAS; Patient and Observer Scar Assessment Scale, TIVAP; Totally Implantable Venous Access Port. *Significant value

[a] Mann-Whitney U-test or Kruskal-Wallis Test.

[b] Fisher-exact and Chi-square test were used for categorical data; Fisher-exact test rather than Chi-square was used when a cell-count was less than five.

Supplementary table 5c Risk factors

		Patients and caregivers			Survivor							Observer			
		Overall satisfaction with location (Q7)		**Anterior vs. lower lateral**	**Overall satisfaction with location (Q8)**		**Preference different location**	**Overall opinion about scar (Q7)**		**Computed POSAS score**		**Overall opinion about scar (Q7)**		**Computed POSAS score**	
		Median (Q1-Q3)	p-value [a]	p-value [b]	Median (Q1-Q3)	p-value [a]	p-value [b]	Median (Q1-Q3)	p-value [a]	Median (Q1-Q3)	p-value [a]	Median (Q1-Q3)	p-value [a]	Median (Q1-Q3)	p-value [a]
Dwell time port	≤1 yrs	1 (1-2)	0.33	0.44	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	>1 yrs	1 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
Port type	Baby and low-profile	1 (1-2)	0.56	0.45	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Standard	2 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
Insertion method	Open	2 (1-2)	0.92	1.00	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Percutaneous	1 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
Insertion side	Right	1 (1-2)	0.43	0.78	2 (1-3)	0.17	0.68	5 (2-7)	0.09	21 (16-25)	<0.01 *	4 (2-5)	0.18	24 (14-26)	0.17
	Left	2 (1-2)			1 (1-3)			3 (1-5)		10 (8-11)		3 (3-4)		19 (16-24)	
Port wound complications	Yes	1 (1-2)	0.31	0.16	1 (1-2)	0.31	0.86	5 (1-6)	0.89	14 (10-21)	0.80	4 (2-5)	0.54	25 (12-25)	0.64
	No	1 (1-2)			1 (1-3)			4 (2-7)		16 (9-25)		5 (3-6)		23 (16-26)	

POSAS; Patient and Observer Scar Assessment Scale, TIVAP; Totally Implantable Venous Access Port. *Significant value

[a] Mann-Whitney U-test or Kruskal-Wallis Test.

[b] Fisher-exact and Chi-square test were used for categorical data; Fisher-exact test rather than Chi-square was used when a cell-count was less than five.

Supplementary table 5d Risk factors

		Patients and caregivers			Survivor							Observer			
		Overall satisfaction with location (Q7)		**Anterior vs. lower lateral**	**Overall satisfaction with location (Q8)**		**Preference different location**	**Overall opinion about scar (Q7)**		**Computed POSAS score**		**Overall opinion about scar (Q7)**		**Computed POSAS score**	
		Median (Q1-Q3)	p-value[a]	p-value[b]	Median (Q1-Q3)	p-value[a]	p-value[b]	Median (Q1-Q3)	p-value[a]	Median (Q1-Q3)	p-value[a]	Median (Q1-Q3)	p-value[a]	Median (Q1-Q3)	p-value[a]
Port replaced	Yes	2 (1-2)	0.59	0.46	1 (1-2)	0.44	0.62	5 (2-7)	0.50	14 (8-27)	0.71	5 (3-6)	0.72	25.5 (14-25)	0.62
	No	1 (1-2)			2 (1-3)			3 (1-7)		17 (10-22)		4 (2-6)		24 (12-26)	
Port scars	One	1 (1-2)	0.10	0.77	2 (1-3)	0.35	1.00	4 (2-6)	0.75	18 (10-24)	0.81	4 (2-5)	0.95	22 (14-25)	0.79
	Two	2 (1-2)			1 (1-2)			5 (2-6)		18 (14-19)		4 (4-4)		24 (24-24)	
History with anterior and lower lateral port	Yes	2 (1-3)	0.44	0.65	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	No	1 (1-2)			n.a.			n.a.		n.a.		n.a.		n.a.	
Preferred location	Same	1 (1-2)	<0.01*	n.a.	1 (1-2)	<0.01*	n.a.	3 (2-5)	0.18	14 (10-21)	0.29	4 (2-5)	0.10	20 (13-25)	0.08
	Different	3 (1-3)			3 (3-3)			5 (3-7)		21 (12-24)		6 (3-7)		25.5 (18-30.5)	

POSAS; Patient and Observer Scar Assessment Scale, TIVAP; Totally Implantable Venous Access Port. *Significant value

[a] Mann-Whitney U-test or Kruskal-Wallis Test.

[b] Fisher-exact and Chi-square test were used for categorical data; Fisher-exact test rather than Chi-square was used when a cell-count was less than five.

Supplementary table 6 Reasons for preference of either an anterior or lower lateral port

	Preferred position, N (% responses)								
	Patients and caregivers[a]		**Nurses**		**Survivors**		**Total**[a]		**Total**[a]
	Anterior (Npt=35, Nres=37)	Lower lateral (Npt=46, Nres=47)	Anterior (N=6)	Lower lateral (N=15)	Anterior (N=21)	Lower lateral (N=8)	Anterior (Npt=62, Nres=64)	Lower lateral (N=69, Nres=70)	(Npt=131, Nres=134)
Main reason for preference *(open question, categorized by researcher)*									
Minimal pressure on port (e.g., during activities, sleeping, or pressure of breast/bra)	14 (37.8%)	6 (12.8%)	1 (16.7)	0 (0.0%)	5 (23.8%)	0 (0.0%)	20 (31.3%)	6 (8.6%)	26 (19.4%)
Scar less visible	0 (0.0%)	13 (27.7%)	0 (0.0%)	0 (0.0%)	2 (9.5%)	7 (87.5%)	2 (3.1%)	20 (28.6%)	22 (16.4%)
Easiest access to port (i.e., fat disposition/port fixation)	0 (0.0%)	1 (2.1%)	3 (50.0)	15 (100.0%)	1 (4.8%)	1 (12.5%)	4 (6.3%)	17 (24.3%)	21 (15.7%)
Less sensitive/pain	3 (8.1%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.7%)	1 (1.4%)	4 (3.0%)
Lifting of a small child easier	2 (5.4%)	2 (4.3%)	1 (16.7)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.7%)	2 (2.9%)	5 (3.7%)
Connection devices covered by clothing	3 (8.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.7%)	0 (0.0%)	3 (2.2%)
Needle insertion out of patients view	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.7%)
No other option due to tumour location	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.7%)
Satisfied/familiar with current position	11 (29.7%)	18 (38.3%)	NA	NA	9 (42.9%)	NA	20 (31.3%)	18 (25.7%)	38 (28.4%)
No reason	3 (8.1%)	5 (10.6%)	1 (16.7)	0 (0.0%)	4 (19.0%)	0 (0.0%)	8 (12.5%)	5 (7.1%)	13 (9.7%)

Npt; number of patients, Nres; number of responses.

[a] Three patients/parents gave two reasons (all answers were counted), two preferred the anterior position, one the lower lateral position.

CHAPTER 4

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

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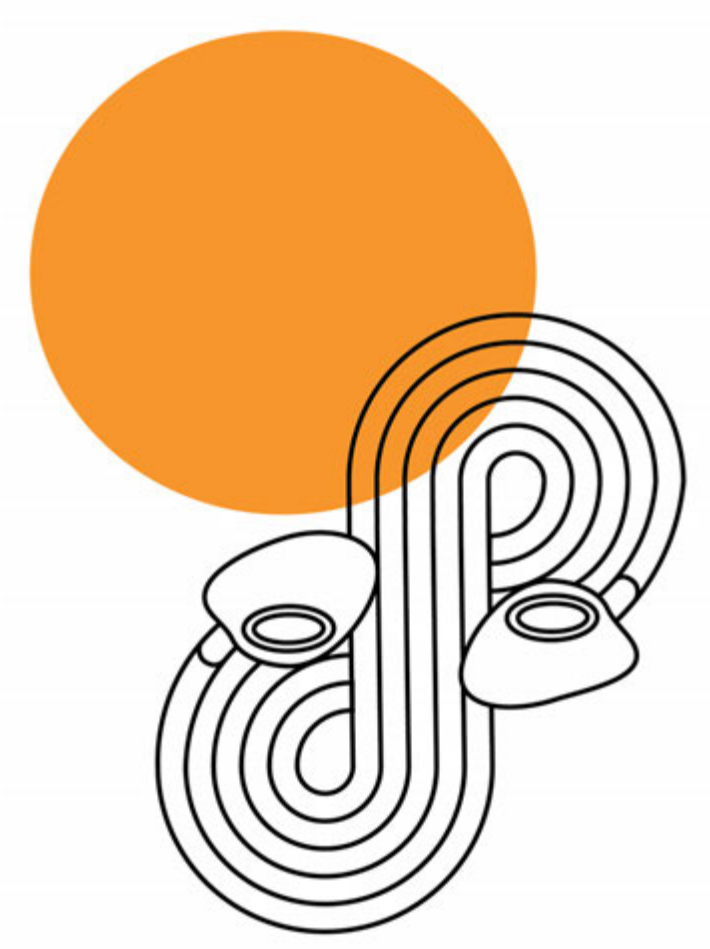


ABSTRACT

Background Central venous access device (CVAD)-related complications are associated with high morbidity rates. This study was performed to underline the importance of CVAD-complication prevention and treatment.

Methods An audit of practice of CVAD-related complications in pediatric oncology patients receiving a CVAD between January 2015 and June 2017 was performed. CVADs included were totally implantable venous access ports (TIVAPs), hickman-broviac® (HB), non-tunneled, and peripherally inserted CVADs.

Results A total of 201 children, with 307 CVADs, were analyzed. The incidence rates per 1,000 CVAD-days for the most common complications were 1.66 for malfunctions, and 1.51 for central line-associated bloodstream infections (CLABSI). Of all CVADs inserted, 37.1% were removed due to complications, of which 45.6% due to CLABSIs. In 42% of the CLABSIs, the CLABSI could be successfully cured with systemic antibiotic treatment only. Of all included patients, 5.0% were admitted to the intensive care unit due to CLABSI. The HB-CVAD compared to the TIVAP was a risk factor for CVAD-related complications, CLABSIs and dislocations in particular.

Conclusions The incidence of CVAD-related complications is high. Research on the prevention and treatment of CVAD-related complications in pediatric oncology patients should be a high priority for all health care professionals.

INTRODUCTION

Central venous access devices (CVADs) are essential in pediatric oncology. Most commonly used CVADs in pediatric oncology are totally implantable venous access ports (TIVAP), and hickman-broviac® (HB) CVADs. (1-3) CVAD-related complications are commonly seen in this patient group and often result in removal of the CVAD, prolonged hospital stays, intensive care unit admission, and death. (1-22) Especially, infections of the CVAD are known to have a high morbidity rate and can result in early removal of the CVAD. (1-22) Previous studies performed on the incidence of CVAD-related complications described little about the severity of CVAD-related complications, the influence of disease severity of the underlying malignancy during the observed central line associated bloodstream infections (CLABSI), the occurrence of relapses and reinfections after treatment for CLABSI, and did not exclude mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBI). (4-22) The aim of this study was to observe the incidence, severity, and outcome of early and late CVAD-related complications in order to identify risk factors for CVAD-related complications, and to evaluate what the focal points in CVAD-related complication prevention and treatment should be. By focusing on these aspects, preventative and treatment strategies for CVAD-related complications in pediatric oncology patients can be developed.

MATERIAL AND METHODS

Patients and study design

A review of published literature on CVAD-related complications and an audit of practice of all patients, 18 years or younger, who received a CVAD at the Princess Máxima Center for Pediatric Oncology (Utrecht, The Netherlands), from January 2015 up to June 2017, was performed. The electronic patient files of these patients were evaluated, and the outcome measurements described below were scored. Exclusion criteria were: age older than 18 years, patients with a primary immunological

disorder, and CVADs inserted in any other hospital than the Princess Máxima Center. Patient/CVAD characteristics scored were age at insertion, gender, diagnosis, CVAD-type, access vein, surgical introduction, CVAD lumen number/diameter, number of CVAD-days, and CVADs per person. The medical ethics committee of the University Medical Center Utrecht (UMCU) declared that official approval by the medical ethics committee was not required.

CVAD insertion and maintenance

The appropriate CVADs were chosen by health care professionals depending on the risks, frequency of use, quality of the veins, and duration/type of treatment (1-3). Peripherally inserted central catheters (PICC), non-tunneled (NT) CVADs, HB-CVADs and TIVAPs were inserted. The HB-CVAD and TIVAP were inserted most commonly since they provide long-term central venous access. Either a specialized PICC-team, pediatric anesthesiologist or surgeon inserted the CVADs. The mode of introduction differed between a (non-) ultrasound-guided percutaneous, open, or rewiring introduction. The maintenance of the CVAD was managed by experienced pediatric oncologic nurses. The maintenance of all CVADs consisted of disinfection of the surrounding skin (chlorhexidine 0.5% in ethanol 70%). The CVAD was flushed with 10 mL sodium chloride (NaCl) (0.9%) before every use and locked with heparin 100 IU/ml after every use and once every four weeks if the CVAD was not used. If the CVAD was disconnected for less than one hour, the CVAD was locked with NaCl 10 mL (0.9%). TIVAPs were filled with 5 mL and all other CVADs were filled with 3 mL heparin or NaCl. Needle-free collectors were used for the collection of blood samples. In case of persistent malfunction, the inability to aspirate or flush the CVAD, alteplase 2 mL (1 mg/mL) was instilled in the CVAD. When there was a suspicion of a CLABSI, at least one blood culture per lumen was collected from the CVAD. Often, empirical systemic antibiotic treatment (SAT) was started. A switch to directed SAT was performed once a pathogen was cultured. If a Staphylococcus aureus, Pseudomonas aeruginosa, or

Candida spp. was cultured, the CVAD was removed immediately, following the protocol of our institution based on the Infectious Diseases Society of America 2009 guideline. (23) In all other cases, treatment response was evaluated after 48 hours of SAT. If there was no significant response after 48 hours (e.g. persistence of fever, chills, hypotension, or persisting positive blood cultures), removal was indicated. If the patient responded well, SAT was continued for one to two weeks, depending on the pathogen.

Definitions and outcome measurements

The primary outcome of this study was the incidence of CVAD-related complications defined per 1,000 CVAD days. The mean CVAD days until complication, the incidence of severe neutropenia during CLABSI, the incidence of intensive care unit admission, the severity of the post-operative complications defined by the Clavien-Dindo classification (**Table 1**) and, when indicated, the reasons for removal were described. (24)

Table 1 Clavien-Dindo classification per CVAD

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

CVAD, Central Venous Access Device

Complications scored due to the surgical procedure were a pneumothorax or hemothorax, confirmed by a chest X-ray. Surgical complications defined as "other" included: failure of puncturing the vein, puncturing an artery, cardiac arrhythmias, hematomas detected by ultrasound, malfunction and dislocation immediately after insertion. Complications scored after the surgical procedure were hematomas, infections (local infections and CLABSIs), malfunctions, thromboses, and mechanical complications (dislocation, breakage/rupture and detachment). Hematomas were scored if the hematoma was detected by visual inspection within 2 cm of the CVAD track or exit-site. Local infections such as phlebitis, exit-site or tunnel-infections were diagnosed by a positive exit-site culture, or erythema, purulent drainage and tenderness within 2 cm of the CVAD track and exit-site.(23) Patients with a bacteremia were classified into patients with a bloodstream infection (BSI), CLABSI, and MBI-LCBI. A BSI was scored in patients with a bacteremia that did not met the CLABSI or MBI-LCBI criteria. CLABSI and MBI-LCBI were defined using the U.S. Centers for Disease Control and Prevention (CDC) criteria (January 2017).(25) CLABSI was scored if the patient met one of the following: (1) the patient had a recognized pathogen cultured from ≥1 blood cultures, or (2) the patient had at least one of the following signs: fever (> 38□C), chills, or hypotension, and the same matching potential contaminant micro-organism had to be cultured from ≥2 blood cultures drawn on separate occasions. A CLABSI could only be scored if the CVAD was in place for >48 hours on the date of the event, if no CLABSI with the same microorganism was scored in the past two weeks (infection relapse time frame), and if the pathogen cultured was not related to an infection at another site. (25) The MBI-LCBI criteria of the CDC (January 2017) were used to exclude bacteremias that were more likely caused by the weakened mucosal barrier of the gut in immunocompromised patients than by CLABSI. (25-27) Malfunction of the CVAD was defined as difficult aspiration of blood, or inadequate flushing of the CVAD lumen. (12) A thrombosis around the CVAD-tip was diagnosed by ultrasound. Mechanical complications were defined as

the detachment of CVAD parts, dislocation of the CVAD diagnosed by an X-thorax or a visible cuff, and rupture of the CVAD parts causing a leakage. Furthermore, the outcomes after CLABSI treatment were analysed, e.g. the incidence of successful SAT, relapses and reinfections. Successful SAT was defined as treatment of CLABSI with SAT only, without further reinfections. A relapse was scored if the same microorganism was cultured within 14 days, with the same CVAD still in situ. A reinfection was scored if (1) a positive blood culture was found with another microorganism during treatment of the initial CLABSI (MBI-LCBI/another infection site excluded), or (2) a CLABSI with the same microorganism was found after 14 days of treatment, and if the blood cultures in the period of 14 days of treatment were negative or not obtained. Additionally, the cultured microorganisms during CVAD-infections, and the risk factors for CVAD-related complications were retrieved. The risk factor analysis was focused on patient- (age at insertion, and diagnosis) and CVAD-characteristics (surgical introduction, site, access vein, CVAD-type, lumen diameter, and lumen number). We chose for an age threshold of two years, since younger patients are more at risk for CVAD-infections. (1) We hypothesized that patients below two years of age, in our hospital, might be more at risk of CVAD-related complications, due to a higher risk of self-removal and more intense chemotherapy (i.e. longer periods of deep aplasia, and more frequent CVAD manipulation) compared to older patients. Surgical introduction, site and access vein were excluded in the multivariant analyses since less than five events were observed in the sub-groups. Since lumen diameter and number corresponded with the CVAD-type, these were also excluded in the multivariate analyses. Disease severity of the underlying malignancy and the associated longer neutropenia episodes have been associated with the incidence of, and removal due to CLABSI. (16, 22, 28) Disease severity was therefore investigated by scoring the presence of severe neutropenia, a neutrophil granulocyte count of less than 100x106 /L, during CLABSI in the HB-CVAD group compared to the TIVAP group.

Statistical analysis

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

RESULTS

Clinical characteristics

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

Of the 307 CVADs inserted, 209 (68.1%) obtained one or more CVAD-related complications. During the study period, a total of 391 CVAD-related complications occurred. Of all CVADs inserted, none obtained Clavien-Dindo grade V after surgery, 10 (3.3%) CVADs eventually obtained grade IV due to CLABSI-related intensive care unit (ICU) admission, 111 (36.2%) CVADs obtained grade III, 63 (20.5%) grade II, 25 (8.1%) grade I, and 98 (31.9%) never obtained any post-operative complications (**Table 1**). (24) Eventually, 114 (37.1%) of the inserted CVADs were removed early due

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

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

NT, Non-Tunneled catheter; PICC, Peripherally Inserted Central Catheter; HB, Hickman-Broviac catheter; TIVAP, Totally Implantable Venous Access Port; CVAD, Central Venous Access Device.

to complications, 11 (3.6%) due to switch of treatment, 74 (24.1%) due to end of treatment, 10 (3.3%) due to death of the patient, 96 (31.3%) were still in place at the end of this study, and two (0.7%) reasons for removal are missing.

Non-infectious CVAD-related complications

The incidence of each CVAD-related complication, their occurrence per 1,000 CVAD days, the mean days until complication and the reasons for removal are summarized in **Table 3**. Malfunction was the most common CVAD-related complication with an incidence rate of 1.66/1,000 CVAD days and appeared after a median of 62 days. Five CVADs were removed due to malfunction.

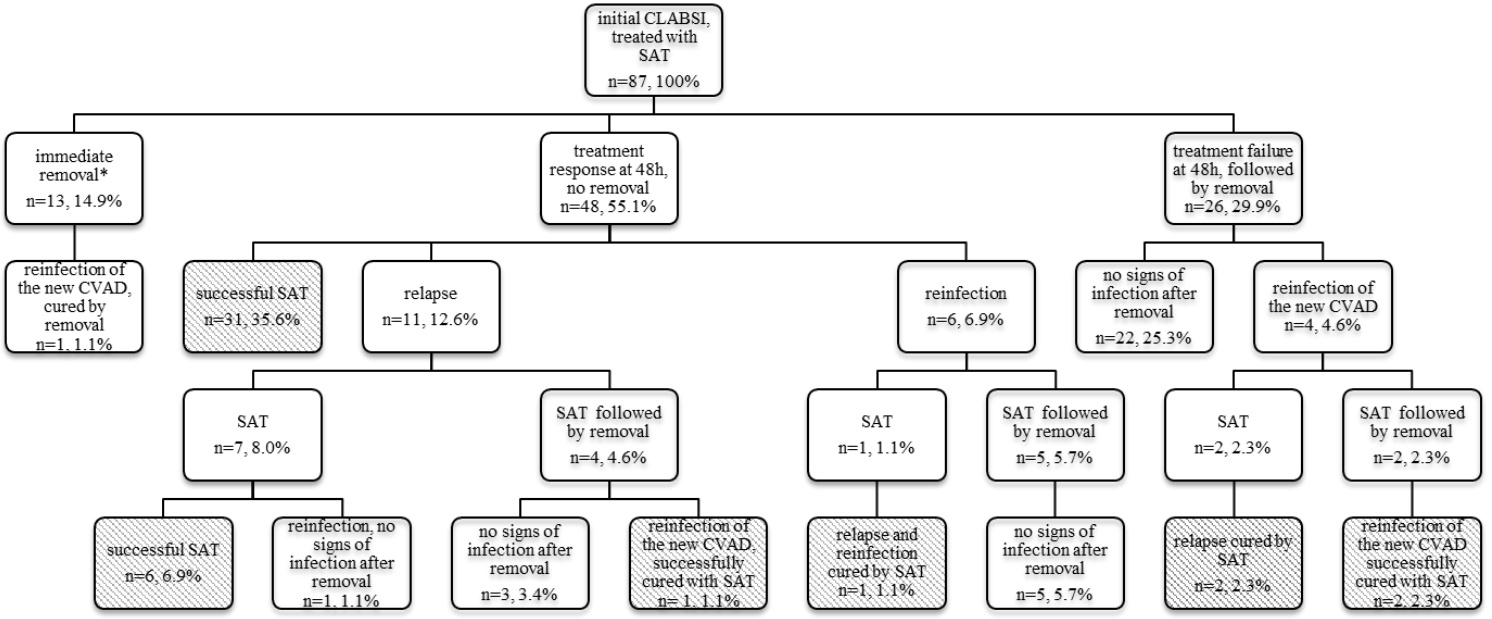
Infectious CVAD-related complications

Local infections had an incidence rate of 0.59/1,000 CVAD days and caused seven early removals of the CVAD. A total of 195 episodes of bacteremia were analyzed, of which 103 (52.8%) were scored as CLABSI, 7 (3.6%) as MBI-LCBI, and 85 (43.6%) as BSI. CLABSI was the second most common CVAD-related complication, with an incidence rate of 1.51/1,000 CVAD-days. CLABSIs appeared after a median of 60 CVAD days. Of all CVADs inserted, 52 (16.9%) were removed due to CLABSIs, 20 (6.5%) due to BSIs, and one (0.3%) due to an MBI-LCBI. In total 10 (5.0%) out of 201 patients were admitted to the ICU due to CLABSI. Microorganisms commonly cultured during CLABSI episodes were: 51 (32.9%) coagulase-negative staphylococci (CoNS), and 22 (14.2%) enterococci. The prevalence of all microorganisms causing CLABSI episodes and local infections is shown in **Table 4**. The treatment outcomes of all initial CLABSIs are described in a flowchart. (**Figure 1**) From the 103 CLABSIs (87 initial CLABSIs, and 16 reinfections) that occurred, 43 (41.7%) were treated successfully with SAT only.

Risk factors for CVAD-related complications

To identify risk factors for all CVAD-related complications, univariate logistic regressions models were estimated. The insertion of a HB-CVAD compared to TIVAP appeared to be a significant risk factor for CLABSI (OR:2.78, CI:1.41-5.47, p=0.005) and dislocations (OR:4.03, CI:1.32-12.33, p=0.02), **Table 5**. No significant difference

Figure 1 CLABSI treatment results



CLABSI, Central Line Associated Blood Stream Infection; SAT, Systemic Antibiotic Treatment; n, number; h = hour

*Following the protocol of our institution, immediate removal is indicated due to CLABSI caused by positive blood cultures with Staphylococcus aureus, Pseudomonas aeruginosa, and Candida spp.

In total 103 CLABSI events are described, initial CLABSIs (n=87), reinfections (n=16), relapses were not scored as a new CLABSI events. Striped blocks are CLABSI events cured successfully with SAT only (n=43). In total, 43/103 (41.7%) of the CLABSIs were successfully treated with SAT.

Table 3a Description of CVAD related complications

	All CVADs[a] (n=307)					
Complications	**Events (n=391) n (%)**	**CVADs (n=307) n (%)**	**Patients (n=201) n (%)**	**Events per 1,000 CVAD days /1,000[b]**	**Days until complication Median (min-max)**	**Removal reason n (%[c])**
Surgical complications:						
▪ Pneumothorax	1 (0.3)	1 (0.3)	1 (0.5)	-	-	0 (0.0)
▪ Hemothorax	0 (0.0)	0 (0.0)	0 (0.0)	-	-	0 (0.0)
▪ Other[d]	23 (5.9)	21 (6.8)	20 (10.0)	-	-	2 (0.7)
Hematoma	32 (8.2)	31 (10.1)	30 (14.9)	0.47	10 (0-409)	0 (0.0)
CLABSI	103 (26.3)	81 (26.4)	60 (29.9)	1.51	60 (1-406)	52 (16.9)
Local Infection	40 (10.2)	39 (12.7)	34 (16.9)	0.59	55 (5-460)	7 (2.3)
Malfunction	113 (28.9)	74 (24.1)	63 (31.3)	1.66	62 (0-547)	5 (1.6)
Thrombosis	9 (2.3)	9 (2.9)	9 (4.5)	0.13	58 (13-440)	4 (1.3)
Mechanical complications:						
▪ Dislocation	23 (5.9)	23 (7.5)	21 (10.4)	0.34	20 (0-412)	16 (5.2)
▪ Breakage/ rupture	14 (3.6)	14 (4.6)	14 (7.0)	0.21	75 (2-320)	4 (1.3)
▪ Detachment	33 (8.4)	29 (9.4)	28 (13.9)	0.49	41 (0-231)	3 (1.0)

CVAD, Central Venous Access Device; CLABSI, Central Line Associated Blood Stream Infection

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

[b] Complication rate per 1,000 CVAD days: total CVAD days = 68,010

[c] Percentage of all CVADs inserted: total n=307

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

Table 3b Description of CVAD related complications

	HB-CVAD (n=123)				TIVAP (n=166)			
	Events (n=190)	**Events per CVAD**	**Events per 1,000 CVAD days**	**Removal reason**	**Events (n=185)**	**Events per CVAD**	**Events per 1,000 CVAD days**	**Removal reason**
Complications	n (%)	Mean	n/1,000[a]	n (%[b])	n (%)	Mean	/1,000[a]	n (%[b])
Surgical complications:								
• Pneumothorax	1 (0.5)	0.01	-	0 (0.0)	0 (0.0)	0.00	-	0 (0.0)
• Hemothorax	0 (0.0)	0.00	-	0 (0.0)	0 (0.0)	0.00	-	0 (0.0)
• Other[c]	11 (5.8)	0.09	-	1 (0.8)	7 (3.8)	0.04	-	0 (0.0)
Hematoma	12 (6.3)	0.10	0.73	0 (0.0)	19 (10.3)	0.11	0.38	0 (0.0)
CLABSI	64 (33.7)	0.52	3.91	34 (27.6)	35 (18.9)	0.21	0.70	17 (10.2)
Local Infection	27 (14.2)	0.22	1.65	4 (3.3)	12 (6.5)	0.07	0.24	3 (1.8)
Malfunction	37 (19.5)	0.30	2.26	2 (1.6)	75 (40.5)	0.45	1.49	3 (1.8)
Thrombosis	5 (2.6)	0.04	0.31	2 (1.6)	3 (1.6)	0.02	0.06	2 (1.2)
Mechanical complications:								
• Dislocation	13 (6.8)	0.11	0.79	11 (8.9)	7 (3.8)	0.04	0.14	3 (1.8)
• Breakage/ rupture	10 (5.3)	0.08	0.61	3 (2.4)	4 (2.2)	0.02	0.08	1 (0.6)
• Detachment	10 (5.3)	0.08	0.61	1 (0.8)	23 (12.4)	0.14	0.46	2 (1.2)

CVAD, Central Venous Access Device; CLABSI, Central Line Associated Blood Stream Infection; HB, Hickman-Broviac®; TIVAP, Totally Implantable Venous Access Port

[a] Complication rate per 1,000 CVAD days: total HB-days = 16,384, total TIVAP- days = 50,336

[b] Percentage of all CVADs inserted: HB-CVAD n=123, TIVAP n=166

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

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

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

CLABSI, Central Line Associated Blood Stream Infection; N.A., Not Applicable; spp., species
CoNS and Enterococci, if cultured from exit sites, were not reported by the clinical microbiology laboratory.
[a] *S. epidermidis* (32), *S. warneri* (1)*, S. haemolyticus* (8), *S. hominis* (6), *S.capitis* (4)
[b] *S.mitis* (9), *S. salivarius (*2), *S. oralis* (1), *S. vestibularis* (1)
[c] *E. faecium* (14), *E. faecalis* (8)
[d] *Micrococcus luteus* (4), *Corynebacterium* spp. (3), *Microbacterium oxydans* (2), *Streptococcus dysgalactiae* (1), *Bacillus* spp. (3), *Clostridium terteus* (1), *Brevibacterium* spp. (1), *Rothia mucilaginosa* (1)
[e] *Escherichia coli* (11), *Klebsiella pneumoniae* (3), *Enterobacter cloacae complex* (3), *Serratia marcescens* (1), *Panthoea* spp. (3) , *Enterobacter asburiae* (1)
[f] *Stenotrophomonas maltophilia* (3), *Acinetobacter* spp. (7), *Chryseobacterium* spp. (1), *Flavobacterium* spp (2), *Moraxella* spp. (3), *Pseudomonas aeruginosa* (2), *Roseomonas mucosa* (1), *Sphingomonas* (1)
[g] *Candida albicans* (5), *Candida lusitaniae* (1)
[h] *Mycobacterium chelonae* (1)

in the number of CLABSIs during severe neutropenia episodes was found between patients with a HB-CVAD and TIVAP (p=0.79). Lumen number (double lumen) and lumen diameter (≥7) were risk factors for CLABSI (OR:3.31, CI:1.68-6.54, p=0.001, and OR:4.31, CI: 2.16-8.64, p<0.001), respectively. Lumen diameter (≥7 Fr) was a risk factor for local infections (OR:2.54, CI:1.07-6.02, p=0.039). Diagnosis (hemato-oncologic diseases) was a risk factor for hematomas (OR:4.93, CI:1.96-12.41, p=0.001). Age (≤2 years) was a risk factor for dislocations (OR:4.69, CI:1.04-21.12, p=0.034). Introduction method (percutaneous vs. open), access vein (jugular vs. subclavian) and introduction

site (right vs. left) were no significant risk factors for CVAD-related complications, results not shown.

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

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

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

CVAD, Central Venous Access Device; HB, Hickman-Broviac; TIVAP, Totally Implantable Venous Access Port; CLABSI, Central Line Associated Blood Stream Infection; CI, Confidence Interval; OR, Odds Ratio; p-value, probability value

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

* Significant values

Table 6 Multivariate analysis

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

CVAD, Central Venous Access Device; HB, Hickman-Broviac; TIVAP, Totally Implantable Venous Access Port; CLABSI, Central Line Associated Bloodstream Infection; CI, Confidence Interval; OR, Odds Ratio; p-value, probability value

* Significant values

DISCUSSION

The incidence of CVAD-related complications in pediatric oncology patients is high. This resulted in frequent dispense of SAT, removal of multiple CVADs, and even intensive care unit (ICU) admission. The most common complications in this study were malfunctions, CLABSIs, and local infections. The incidence of CVAD-related complications in pediatric oncology patients per 1,000 CVAD-days described in literature ranged from 0.8-2.0 for malfunctions, 0.1-1.6 for bloodstream infections related to the CVAD, and 0.1-0.3 for local infections. (4-11) The incidence of less common complications described in literature are comparable to those found in this study. (5-7, 9, 12) The high incidence of CVAD-related complications compared to the literature might be explained by the variety in CVAD-types analyzed, the underlying diseases in the patients observed (e.g. hemato-oncologic or solid malignancies), the non-uniform complication criteria used, and the different CVAD-maintenance protocols used (e.g. CVAD flush/lock protocols). (4-11) Malfunction was the most common complication in this study. Currently in the Netherlands, CVADs are locked with heparin. However, the heparin lock appears to be of limited value in the prevention of malfunction. (29) Preventing malfunction of the CVAD should instead be accomplished by the education of health care providers about the

maintenance of CVADs and by working more protocolized; use more proper flushing policies, needle-free connectors, and no-reflux strategies (e.g. a no-reflux syringe). (29) Future research needs to address the best lock solution for the prevention of CVAD malfunction in this patient population. The high incidence of CLABSIs might be associated with the CVAD-types inserted (i.e. a large number of HB-CVADs), the CVAD-maintenance protocols used (e.g. CVAD flush/lock protocols), or factors related to the underlying malignancy, such as endogenous infections, high-risk chemotherapy, and the supplementation of total parenteral nutrition (TPN). (28) The high incidence might also be explained by the arguable issue of the definition of bloodstream infections related to the CVAD. During the past years, many variations of definitions for bacteremia caused by the CVAD were used in literature. In this study, the CLABSI criteria were used instead of the central line related bloodstream infection (CRBSI) criteria, being the most practical definition considering the lack of peripheral blood cultures and catheter tip cultures in this patient group, which are required for the definition of a CRBSI. Additionally, in clinic, a bacteremia is often being treated as associated to the CVAD, even though the CRBSI criteria are not met. Therefore, we accept a possible overestimation of the incidence rate using the CLABSI criteria. However, it is also possible that the amount of CLABSIs is underestimated, since the BSIs that were not scored as a CLABSI due to an insufficient number of blood cultures, could also have been scored as CLABSIs if more blood cultures were obtained. Other authors scored all positive blood cultures drawn from the CVAD, including bloodstream infections caused by infections located elsewhere in the patient, which can result in an overestimation of CVAD-related infections. (30, 31). To eliminate bacteremias that were the result of the weakened mucosal barrier of the gut in immunocompromised patients, the MBI-LCBIs were excluded in this analysis. Pediatric oncology patients frequently have a weakened mucosal barrier; therefore, physicians are often unsure if the bloodstream infection has originated from the weakened mucosal barrier or the CVAD. These criteria might be useful in

practice to differentiate between CLABSIs and MBI-LCBIs to avoid unnecessary removal of the CVAD. (25-27) SAT was successful in 42% of the CLABSI episodes. This indicates that SAT in combination with clinical observation is an acceptable strategy in case of CLABSI caused by microorganisms other than Candida spp., Pseudomonas aeruginosa, or Staphylococcus aureus. Unfortunately, a great deal of the CLABSI episodes will still result in removal of the CVAD due to continuing symptoms, relapses or reinfections. In the prevention of CLABSIs, the use of lock solutions containing taurolidine, ethanol or citrate appear to be promising, however further research on this subject is needed and strongly recommended. (11, 29, 32-35) Patients diagnosed with hemato-oncologic malignancies were more at risk for CVAD-related complications in general, this might be due to more frequent CVAD-manipulation in this patient group. (1, 7, 9) The insertion of a HB-CVAD appeared to be a significant risk factor for CVAD-related complications in general, dislocations and CLABSIs in particular. Dislocations are probably less common during the use of a TIVAP since it is inserted underneath the skin. Possible explanations for the high incidence of CLABSIs in HB-CVADs are the open access to the bloodstream through the external parts of the HB-CVAD, the frequent occurrence of double lumen HB-CVADs, the higher frequency of TPN supplementation, and the dispense of more high-risk chemotherapy in HB-CVADs. However, no significant difference was found in the incidence of severe neutropenia during CLABSIs in patients with HB-CVADs or TIVAPs. HB-CVADs were also found to be a risk factor for infections in other studies (4, 8, 19-21). Due to the higher risk of CVAD-related complications associated with the HB-CVAD, the insertion of other double lumen CVADs (i.e. double-lumen TIVAP) instead of a HB-CVAD might be considered in the future if a double lumen is indicated. Lumen number and diameter correlated with the CVAD-type inserted, and were therefore also found as significant risk factors. Lumen diameter was a risk factor for local infections. A lumen diameter of ≥7 Fr is associated with the HB-CVAD, which has external parts, and could therefore be more at risk for local infections. Age was

a risk factor for dislocations, probably due to a higher risk of self-removal by these younger patients. (9) Limitations of this study were the retrospective design, the fact that some CVADs were still in situ at the end of the study, and that some patients were treated in a different hospital in the Netherlands or at home for a period of time. Major complications appearing in other institutions were documented in our institution, although it is possible that minor complications are missing since the medical files of other institutions were not reviewed. Additionally, CRBSI is technically the most accurate definition of describing infections related to the CVAD, however, as described above, this definition is not an option in this population. In conclusion, compared to literature we detected a high incidence of CVAD-related complications in pediatric oncology patients. Therefore, CVAD-related complication prevention and treatment is important and could reduce the incidence of CVAD-related complications, SAT dispense, CVAD-removal and ICU admission. We recommend that professionals need to be educated more in CVAD-maintenance, work more protocolized, and perform further research to observe the efficacy of lock solutions (e.g. locks containing taurolidine and citrate) and other double-lumen CVADs (e.g. double-lumen TIVAPs) on the decrease of the most common CVAD-related complications.

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CHAPTER 5

Central venous catheter-associated complications in paediatric patients diagnosed with Hodgkin lymphoma: implications for catheter choice

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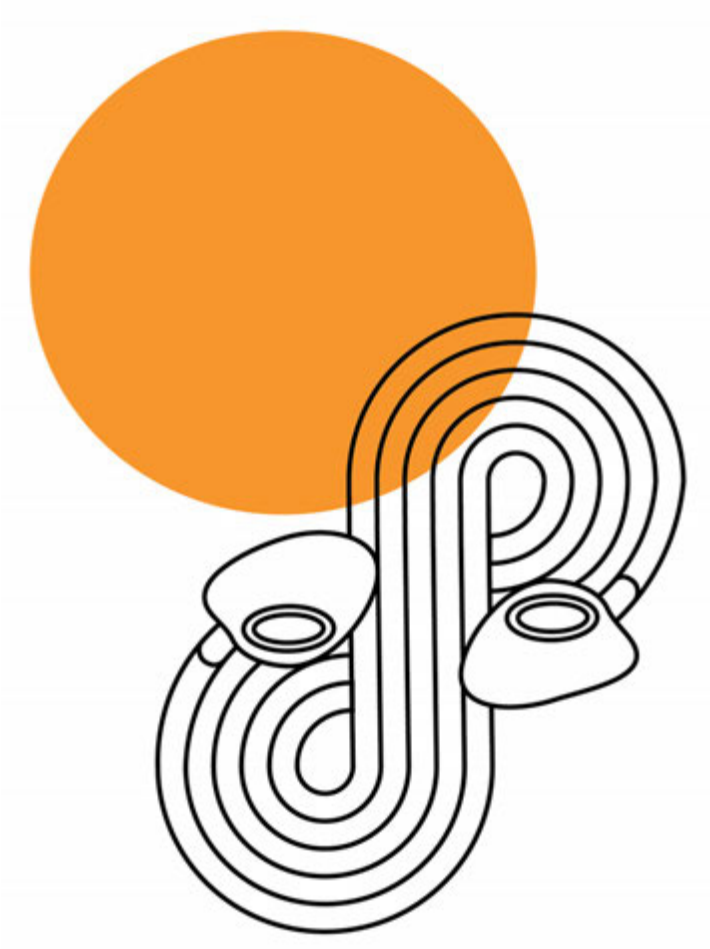


ABSTRACT

Purpose The purpose of this study was to determine the most optimal central venous catheter (CVC) for pediatric patients with Hodgkin lymphoma (HL) in terms of complications.

Methods A retrospective study including patients diagnosed with HL from 2015-2021 at the Princess Máxima Center was performed. Patients were followed from CVC insertion until removal or 06-2021, whichever came first. The primary outcome was the CVC-related complication incidence rate (IR) per 1 000 CVC-days. Furthermore, the incidence rate ratio (IRR) was calculated by comparing complication IRs between peripherally inserted central catheters (PICC) and totally implantable venous access ports (TIVAP). Additionally, risk factors for central venous thrombosis (CVT) were identified.

Results A total of 98 patients were included. The most frequently observed complications were local irritation/infections (18%;IR0.93), malfunctions (15%;IR0.88), and CVC-related CVTs (10%;IR0.52). Single lumen PICCs were associated with a higher risk of complications (49% vs. 26%; IRR5.12, CI95%2.76-9.50), severe complications (19% vs. 7%; IRR11.96, CI95%2.68-53.42), and early removal (18% vs. 7%; IRR9.96, CI95%2.18-45.47). A single lumen PICC, was identified as a risk factor for CVC-related CVT when compared to TIVAPs (12% vs. 7%, IRR6.98, CI9%1.45-33.57).

Conclusion The insertion of a TIVAP rather than a PICC should be recommended for pediatric patients with HL, especially in the presence of CVT-related risk factors. Future trials should evaluate the efficacy and safety of direct oral anticoagulants for the primary prevention of CVT in pediatric patients with a PICC and other CVT-related risk factors

INTRODUCTION

The vast majority of pediatric patients diagnosed with Hodgkin lymphoma (HL) will receive a central venous catheter (CVC) at the start of their treatment. Multiple CVC types are available, but single lumen totally implantable central venous access ports (TIVAP) and peripherally inserted central venous catheters (PICC) are the most frequently used CVCs in this patient group. Insertion of a PICC is still considered favorable in patients with HL since insertion is possible without the need for general anesthesia (which is especially favorable in children with mediastinal masses causing airway problems) and is considered safe because of the relatively short treatment period and larger peripheral vessels of this, usually older, pediatric patient group (1).

In contrast to PICCs, TIVAPs can stay in situ for a longer period and give patients more freedom of movement. However, general anesthesia is needed for insertion, sedation for removal, percutaneous punctures to access the port and a larger scar will remain visible after removal, whereas these disadvantages do not apply to PICCs. On the other hand, higher incidence rates of mechanical failure, CVC-related infections and CVC-related central venous thrombosis (CVT) have been associated with PICCs when compared to other CVC-types in a variety of adult and pediatric patients (i.e. oncology, intensive care unit, total parenteral nutrition) (1-10). However, the incidence of all CVC-related complications for patients with HL specifically has not been described previously.

Based on studies in adults and children, the risk of CVC-related CVTs has been described to be higher in patients with HL, compared to other oncology patients (3, 9). Suggested risk factors that may contribute to this difference are tumor associated inflammation and compression of veins typically occurring in the upper body, the older age of patients and frequent high-dose corticosteroid treatment, which are all known risk factors for thrombosis (1, 3, 11-15). Since pediatric patients with HL might

be at a higher risk of CVC-related CVTs and since the risk of other CVC-related complications per CVC type for this patient group is currently unknown, it is of importance that the most optimal CVC for these children is identified. In this study, we have analyzed all CVC complications and their outcomes.

METHODS

Study design and participants

A retrospective study including all consecutive patients diagnosed with HL, who received a CVC and who were treated in the Princess Máxima Center for pediatric oncology (Utrecht, The Netherlands) from January 2015 until March 2021, was performed. Patients were excluded if their CVC was inserted in any other hospital than the Princess Máxima Center, if they were older than 18 years at CVC insertion, or if they did not give their consent to use their data for scientific research (n=24). Each patient was followed up from first CVC insertion until first CVC removal or June 2021, whichever came first. Patients were treated following the guidelines of the European Network-Pediatric Hodgkin's Lymphoma Study Group (EuroNet-PHL: C1, C2, or LP1) in an outpatient setting. The medical ethics committee of the University Medical Center Utrecht (Utrecht, The Netherlands) waived the need for official approval by the medical ethics committee (File number: 21/723).

Data-collection and definitions

The primary outcome was the incidence rate (IR) per 1 000 CVC-days for all observed CVC-related complications in total and per CVC-type. This aggregated outcome was chosen to give an overview of the overall risk of CVC-related complications for pediatric HL patients. Secondary outcomes were the IRs of each complication type as described below per CVC-type, of early removal due to complications per CVC-type and of CVC-related CVTs per risk factor.

The patient files were assessed retrospectively for the occurrence of the following CVC-related complications: intra-operative complications, central line associated bloodstream infections (CLABSI), local irritation/infection, CVC-related CVT, malfunctions and mechanical complications (dislocations, ruptures and dislodgement). Intra-operative complications were defined as any abnormalities during or directly after CVC insertion (e.g. pneumothorax, arterial puncture, dislocation, bleeding, malfunction). CLABSIs were defined following the Centers for Disease Control and Prevention criteria (16). Local irritation/infections were defined as a positive exit-site culture, erythema, purulent drainage or tenderness within two centimeters of the CVC track. CVTs were scored if their presence was confirmed by the radiology department in the imaging report. Imaging was performed due to the presence of CVT related symptoms or for routine tumor response evaluation. Malfunctions were defined as the inability to flush and/or aspirate requiring the need of thrombolysis or CVC removal. Mechanical complications were defined as the detachment of CVC components, dislocation of the CVC diagnosed by an chest radiograph or a visible cuff, and rupture of the CVC components causing leakage. All complications were thereafter scored following the Clavien-Dindo classification (17). Severe complications were defined as a Clavien-Dindo classification of III or higher. The Clavien-Dindo definitions are described in **Online Resource 1** [Online Resource 1].

Furthermore, to evaluate the presence of CVT-related risk factors, the following data were collected: age, sex, obesity (18), HL type and stage following the Ann-Arbor classification (19, 20), presence of a mediastinal mass (i.e. confirmed by radiologist), smoking, thrombosis or laboratory confirmed thrombophilia in medical (family) history, use of hormonal contraceptives, compression of the veins in the trajectory of the CVC as confirmed by a radiologist at insertion (for the vena cava superior specifically <50% or >50% compression), preference to not insert the CVC under

general anesthesia as evaluated retrospectively by two pediatric lymphoma specialists, pediatric intensive care unit admission from diagnosis until end of study period, (prophylactic) anticoagulant use, signs of infection during CVT diagnosis, >one insertion attempt, CVC type, CVC side and lumen size, CVC use for total parenteral nutrition, and CVC to vein ratio for PICCs specifically. Additionally, the following information was extracted from the patient files: diagnosis date, CVC insertion date, end of treatment date, complication date,

CVC insertion method, CVC insertion vein, reason for CVC removal, complication treatment, hospital/intensive care unit admission due to complications. For CVT events specifically, the severity, symptoms and complications (e.g. pulmonary embolism, CLABSI, vena cava superior syndrome, and post-thrombotic syndrome scored following the modified Villalta score (21)) were collected. If data was not explicitly reported in the patient files, this was reported as missing data.

CVC insertion and maintenance

The vast majority of patients diagnosed with Hodgkin will receive either a PICC or TIVAP at the start of their treatment. A non-tunneled CVC is only inserted for a short period in case of an emergency setting, positive blood cultures or if the insertion of a tunneled CVC is not possible. If a PICC or TIVAP is to be inserted, is determined by the expected treatment duration, lumen needed, presence of a tumor causing airway problems and the wishes of the patient. In case of an expected treatment duration of more than six months, the insertion of a TIVAP is recommended. In patients with a tumor causing airway problems, the insertion of a PICC is preferred to avoid the need for general anesthesia or a TIVAP is inserted after steroid treatment. In all other cases, the (dis)advantages of both CVC types are discussed and the patient is thereafter free of choice. All CVCs were inserted by a specialized vascular access team or a pediatric oncology surgeon. All CVCs were inserted ultrasound-guided, only by exception CVCs were inserted percutaneously based on anatomical land marks. The

insertion vein was chosen based on the availability and quality of the veins (i.e. adequate blood-flow through vein and CVC-to-vein ratio of <45% (22) for PICCs assessed by ultrasound), with a preference for the right jugular vein for the non-PICC CVCs. CVC care was performed by or under supervision of specialized pediatric oncology nurses following international guidelines (23, 24). The CVCs were flushed with NaCl 0.9% before use and locked with heparin 100 international units per milliliter after every use. The locks were replaced once every eight weeks for the TIVAP and once every week for the other CVC types if the CVC was not used.

Statistical analysis

Differences between patients with a SL PICC and TIVAP with respect to baseline characteristics were analyzed using a Fisher Exact or Wilcoxon rank sum test, depending on the variable. The IRs per 1 000 CVC-days were calculated with the number of all CVC-related events observed and total CVC-days (i.e. sum of the days from insertion until the end of follow-up, during in- and outpatient settings). Additionally, the IRs per 1 000 CVC treatment days were calculated with the number of CVC-related events during the treatment period and total CVC-treatment days (i.e. sum of days during in- and outpatient settings from insertion until the end of follow-up or the last day of treatment, whichever came first; in case of a recurrence during insertion of the primary CVC, the days from recurrence diagnosis until the end of follow-up or last day of treatment, whichever came first, were added up to the total sum). This last calculation was performed since the frequency of complications might be higher during the treatment period and some CVCs remained in situ without treatment due to clinical follow-up and delays in the surgical lists.

Incidence rate ratios (IRR) along with their 95% confidence intervals (CI) were computed (1) to compare the IRs per 1 000 CVC-days and CVC-treatment days for all complications between single lumen PICCs and TIVAPs, and (2) to compare the

IRs per 1 000 CVC-days for CVC-related CVT between patients with and without CVT-related risk factors. The second analysis was performed for two different settings: (1) including only single lumen PICCs and TIVAPs (most commonly inserted CVCs) and (2) excluding patients where CVC insertion under general anesthesia was not preferred due to disease severity resulting in the insertion of a PICC instead of a TIVAP (since these patients possibly have a high risk of CVT and TIVAP insertion is not possible (1)). The exact confidence limits for the IRRs were computed based on the polynomial algorithm for person time data (25, 26). The mean CVC to vein ratio for patients with a CVT compared to patients without a CVT was compared using an independent t-test. IBM SPSS Statistics for Windows version 26.0 (IBM Corp, United States of America) was used to perform all statistical analyses (27).

RESULTS

Patient and CVC characteristics

In total 98 patients were included with a median age at diagnosis of 15 years (6-17). Most patients (96%) were diagnosed with classic HL. Compression of the veins due to lymphoma in the CVC tract was observed in 18 (18%) patients. Two patients (2%) received anticoagulants before CVC insertion and kept using it during CVC insertion due to a non-CVC related thrombosis and venous compression (prophylactic dose n=1, therapeutic dose n=1). Additionally, one more patient (1%) received anticoagulants during CVC insertion due to venous compression (prophylactic dose n=1). General anesthesia at diagnosis was not preferred in 14 (14%) patients, resulting in prephase therapy with steroids. In only five (36%) of these patients a PICC instead of a TIVAP was eventually inserted since general anesthesia was still not preferred. [**Table 1**] Baseline characteristics for patients receiving a TIVAP or SL PICC are described separately in **Online Resource 2**. Patients with a SL PICC differed from patients in the TIVAP group in terms of: age at diagnosis, Ann-Arbor stage and CVC-(treatment) days. [**Online Resource 2**]

Table 1a Baseline characteristics

Patient characteristics (N=98)		
Sex, N (%)	Male	50 (51.0)
	Female	48 (49.0)
Age at diagnosis, median (range)		15 (6-17)
Hodgkin type, N (%)	Classic	94 (95.9)
	NLPHL	4 (4.1)
Ann-Arbor staging, N (%)	I	2 (2.0)
	II	43 (43.9)
	III	27 (27.6)
	IV	26 (26.5)
EuroNet-PHL protocol, N (%)	C1	2 (2.0)
	C2	92 (93.9)
	LP1	4 (4.1)
Mediastinal mass, N (%)	No	8 (8.2)
	Yes	90 (91.8)
Obesity at diagnosis[a], N (%)	No	80 (81.6)
	Yes	18 (18.4)
Smoking, N (%)	No	60 (61.2)
	Yes	3 (3.1)
	Passive	6 (6.1)
	Missing	29 (29.6)
Oral anti-conceptive use , N (%)	No	82 (83.7)
	Progesterone	4 (4.1)
	Progesterone and estrogen	12 (12.3)
Thrombophilia, N (%)	No	2 (20)
	Yes	3 (3.1)
	Not tested	93 (94.9)
Thrombotic family history, N (%)	Negative	61 (62.2)
	Positive	5 (5.1)
	Missing	32 (32.7)
Compression veins, N (%)	No	80 (81.6)
	Yes	18 (18.4))
VCS compression, N (%)	No	84 (85.7)
	<50%	10 (10.2)
	>50%	4 (4.1)
Thrombosis before insertion, N (%)	No	97 (99.0)
	Yes	1 (1.0)
Anticoagulant use in period before and at insertion, N (%)	No	96 (98.0)
	Prophylactic	1 (1.0)
	Therapeutic	1 (1.0)
CVC insertion under general anesthesia not preferred[b], N (%)	No	93 (94.9)
	Yes	5 (5.1)
PICU admission, N (%)	No	95 (96.9)
	Yes	3[c] (3.1)

CVCs; Central Venous Catheter, NLPHL; Nodular lymphocyte-predominant Hodgkin lymphoma, PHL; Pediatric Hodgkin Lymphoma, VCS; Vena Cava Superior, TPN; Total Parenteral Nutrition; PICU; Pediatric Intensive Care Unit.

[a] Obesity was scored following: Cole 2000[18]

[b] Based on clinical evaluation by two lymphoma specialists.

[c] PICU admissions due to respiratory or circulatory insufficiency, CVT-related PICU admission registered as "No".

Table 1b Baseline characteristics

CVC characteristics (N=98)		
Days from diagnosis until insertion, median (range)		11 (0-41)
CVC-days, median; sum (range)		143; 19 341 (0-717)
CVC-treatment days, median; sum (range)		118; 11 158 (0-308)
CVC type, N (%)	TIVAP	31 (31.6)
	SL PICC	57 (58.2)
	DL PICC	9 (9.2)
	Non-tunneled	1 (1.0)[a]
Introduction method, N (%)	Ultrasound	96 (98.0)
	Anatomic landmarks	1 (1.0)
	Missing	1 (1.0)
Lumen number, N (%)	Single	88 (89.8)
	Double	9 (9.2)
	Triple	1 (1.0)
Lumen diameter, N (%)	<6.5 Fr	65 (66.3)
	≥6.5 Fr	31 (31.6)
	Missing	2 (2.0)
Insertion vein, N (%)	Jugular	29 (29.6)
	Subclavian	2 (2.0)
	Brachial	39 (39.8)
	Cephalic	1 (1.0)
	Basilica	26 (26.5)
	Femoral	1 (1.0)
Insertion side, N (%)	Right	86 (87.8)
	Left	12 (12.2)
Long-term anticoagulant use during CVC-insertion[b], N (%)	No	95 (96.9)
	Prophylactic	1 (1.0)
	Therapeutic	2 (2.0)
>1 Insertion attempt, N (%)	No	92 (93.9)
	Yes	2 (2.0)
	Missing	4 (4.1)
TPN over CVC, N (%)	TPN[c]	4 (4.1)
	No TPN	94 (95.9)
CVC to vein ratio for PICCs, median (range)		0.27 (0.15-0.33)

CVCs; Central Venous Catheter, TIVAP; Totally Implantable Venous Access Port, PICC; Peripherally Inserted Central Catheter, Fr; French, SL; Single lumen, DL; Double lumen, TPN; Total Parenteral Nutrition.

[a] Inserted during an emergency setting due to an anaphylactic reaction to contrast.

[b] CVCs where thrombolytics were given for only a short period of time due to for example hospitalization or where thrombolytics were given after a CVT was observed are registered as "No". Reasons for anticoagulant use were: not-CVC related thrombosis (n=2) and venous compression (n=1).

[c] Median (range) days of TPN: 4.5 (1-13)

Mainly single lumen CVCs (90%) were inserted; single lumen PICCs (65%) and TIVAPs (35%). The CVCs were in situ for a total of 19 341 CVC-days and 11 158 CVC-treatment days. TIVAPs were in situ for a median of 377 (33-717) days and single lumen PICCs for 105 (0-208) days. Of all CVCs, 12 (12%) were removed due to complications, 75 (77%) due to end of treatment, three (3%) due to the need for another CVC type, one (1%) since the patient was not content with the location, and seven (7%) were still in situ at the end of this study. [**Table 1**]

Complications

A total of 58 complications were observed with an IR of 3.00 per 1 000 CVC-days. In 42% of all CVCs at least one complication was observed. The most frequently observed complications per 1 000 CVC-days were local irritation/infections (18%; IR 0.93), malfunctions (14%; IR 0.88) and CVC-related CVT (10%; IR 0.52). The IRs per 1 000 CVC-treatment days were comparable or higher for all complication types. All complications were observed after a median of 63 (3-378) days. CVC-related CVT was the most frequently observed reason for early CVC removal (50% of CVCs removed early due to complications, 6% of all inserted CVCs). Hospital admission was mainly observed in patients experiencing a CLABSI. One patient was admitted to the intensive care unit due to a combined CVT and CLABSI episode. [**Table 2**]

In total ten CVC-related CVT events were observed, among which eight CVTs were identified due to symptoms and two due to a routine ultrasound and magnetic-resonance imaging for tumor response evaluation. In four patients the CVT resulted in complications; three short-term complications (i.e. vena cava superior syndrome causing chylothorax, pulmonary embolisms, and septic thrombophlebitis) and one long-term complication (i.e. post-thrombotic syndrome; modified Villalta score 4 indicating a moderate post-thrombotic syndrome). The CVTs were diagnosed after a median of 19 (3-374) days after insertion. All CVT events were treated with

Table 2 Incidence of CVC-related complications

Complications	Events, n (%)	CVCs[e], n (% all CVCs)	IR per 1 000 CVC-days	IR per 1 000 CVC-treatment days	Days until complication, median (range)	CVC removal, n (% all CVCs)	Hospital admission days, median (range)
Intra-operative	6 (10.3)	6 (6.1)	NA	NA	NA	1 (1.0)	0 (0-1)
CLABSI	3 (5.2)	3 (3.1)	0.16	0.27	19 (13-99)	1[a] (1.0)	6 (5-10)
Local irritation/infection	18 (31.0)	18 (18.4)	0.93	1.43	66 (30-139)	2 (2.0)	0 (0-5)
CVT	10 (17.2)	10 (10.2)	0.52	0.81	19 (3-374)	6[a] (6.1)	0 (0-28)
Dislocation	2 (3.4)	2 (2.0)	0.10	0.09	4 (3-5)	0 (0.0)	0 (0-0)
Malfunction	17[b] (29.3)	14 (14.3)	0.88	1.43	67 (10-378)	2 (2.0)	0 (0-0)
Rupture	1 (1.4)	1 (1.0)	0.05	0.09	16 (16-16)	1 (1.0)	0 (0-0)
Dislodgement	1 (1.4)	1 (1.0)	0.05	0.09	39 (39-39)	0 (0.0)	0 (0-0)
Total	58 (100.0)	41 (41.8)[c]	3.00	4.75	63 (3-378)	12[d] (12.2)	0 (0-28)

CVCs; Central Venous Catheter, CLABSI; Central Line Associated Bloodstream Infection, CVT; Central Venous Thrombosis, IR; Incidence Rate.

In total, five (8.6%) CVC-related complications were observed after the end of treatment.

[a] One CVC was removed due to a combined CVT and CLABSI episode.

[b] Malfunctions successfully treated with thrombolysis (n=12), unsuccessful thrombolysis resulting in removal (n=2), unsuccessful thrombolysis due to the presence of a CVT for which the CVC was removed (n=1), unsuccessful thrombolysis after which malfunction was treated with pulsatile flushes of regular saline (n=1).

[c] If multiple complications were identified in one CVC, this was counted as one to calculate this percentage. This means that 42.3% of all patients experienced one or more complications during CVC insertion.

[d] Combined CVT and CLABSI episode counted as one in total.

[e] For each complication type, only the first was counted per CVC.

anticoagulants, in six cases the CVC was removed, one patient required a thrombectomy and another required a percutaneous transluminal angioplasty. None of the patients with a CVT received thrombosis prophylaxis before the CVT occurred. In four CVT cases simultaneous clinical signs of infection were present. [**Online Resource 3**]

Complications TIVAP versus single lumen PICC

During CVC-insertion, single lumen PICCs were associated with a significantly higher risk of complications (49% vs. 26%; IRR 5.12, CI95%2.76-9.50) and removal due to complications (18% vs. 7%; IRR 9.96, CI95%2.18-45.47), when compared to TIVAPs during complete CVC insertion. Specifically, a higher risk of local irritation/infections (26% vs. 7%; IRR 14.95, CI95%3.42-65.35) and CVC-related CVTs (12% vs. 7%; IRR 6.98, CI95%1.45-33.57) was associated with the insertion of single lumen PICCs compared to TIVAPs. A Clavien-Dindo grade of I or II was scored for the vast majority of complications. Of all complications, a grade of III or higher was scored in 27.6%. Single lumen PICCs were associated with a significantly higher risk of severe complications, i.e. Clavien-Dindo grade of III or higher, when compared to TIVAPs (19% vs. 7%; IRR 11.96, CI95%2.68-53.42). (**Table 3** and **Online Resource 1**)

During treatment, single lumen PICCs were also associated with a significantly higher risk of complications (IRR 1.97, CI95%1.02-3.80), local irritation/infections in particular (IRR 4.52, CI95%1.02-20.02), and complications with a Clavien-Dindo grade of III or higher (IRR 8.34, CI95%1.09-64.13). (**Table 3** and **Online Resource 1**)

Risk factors for CVC-related CVT

A (single lumen) PICC compared to a TIVAP or other non-PICC CVC were identified as the only significant risk factors for a CVC-related CVT. All other IRRs per CVT-

Table 3 Comparison of CVC-related complication incidence rates between TIVAPs and single lumen PICCs

	TIVAP n=31 12258 CVC days 4193 CVC-treatment days				**Single lumen PICC n=57 6151 CVC days 6033 CVC-treatment days**				**IRR (CI95%)**	
Complications	Events, n (%)	CVCs, n (% all CVCs)	IR per 1 000 CVC days	IR per 1 000 CVC treatment days	Events, n(%)	CVCs, n (% all CVCs)	IR per 1 000 CVC days	IR per 1 000 CVC treatment days	During CVC insertion	During treatment
Intra-operative	2 (14.3)	2 (6.5)	NA	NA	2 (5.6)	2 (3.5)	NA	NA	NA	NA
CLABSI	1 (7.1)	1 (3.2)	0.08	0.24	2 (5.6)	2 (3.5)	0.33	0.33	3.99 (0.36-43.95)	1.39 (0.13-15.33)
Local infection	2 (14.3)	2 (6.5)	0.16	0.48	15 (41.7)	15 (26.3)	2.44	2.15	14.95 (3.42-65.35)	4.52 (1.02-20.02)
CVT	2 (14.3)	2 (6.5)	0.16	0.24	7 (19.24)	7 (12.3)	1.14	1.16	6.98 (1.45-33.57)	4.87 (0.60-39.54)
Malfunction	6 (46.9)	4 (12.9)	0.49	1.19	8 (22.2)	6 (10.5)	1.30	1.33	2.66 (0.92-7.66)	1.11 (0.36-3.40)
Dislocation	0 (0.0)	0 (0.0)	0.00	0.00	1 (2.8)	1 (1.8)	0.16	0.17	Undefined	Undefined
Rupture	0 (0.0)	0 (0.0)	0.00	0.00	1 (2.8)	1 (1.8)	0.16	0.17	Undefined	Undefined
Dislodgement	1 (7.1)	1 (32)	0.08	0.24	0 (0.0)	0 (0.0)	0.00	0.00	Undefined	Undefined
Total	14 (100.0)	8 (25.8)	1.14	2.86	36 (100.0)	28 (49.1)	5.85	5.64	5.12 (2.76-9.50)	1.97 (1.02-3.80)
Clavien-Dindo grade of ≥3	2 (14.3)	2[a] (6.5)	0.16	0.24	12 (33.3)	11[a] (19.3)	1.95	1.99	11.96 (2.68-53.42)	8.34 (1.09-64.13)
Removal due to complications	2 (NA)	2 (6.5)	0.16	0.48	10 (NA)	10 (17.5)	1.63	1.66	9.96 (2.18-45.47)	3.48 (0.76-15.86)

CVCs; Central Venous Catheter, CLABSI; Central Line Associated Bloodstream Infection, CVT; Central Venous Thrombosis, TIVAP; Totally Implantable Venous Access Port, PICC; Peripherally Inserted Central Catheter, IR; Incidence Rate, IRR; Incidence Rate Ratio, CI; Confidence Interval, N; number, NA; Not Applicable.

The events, CVCs, and IR per 1 000 CVC days columns include all CVC-related complications observed. The IR per 1 000 CVC treatment days includes all CVC-related complications observed from CVC insertion until the end of treatment or removal of the first CVC, whichever comes first.

[a] Highest Clavien-Dindo grade per CVC counted.

related risk factor and their associated 95%CI are described in Figure 1 and in more detail in the supporting information. (**Figure 1** and **Online Resource 4**)

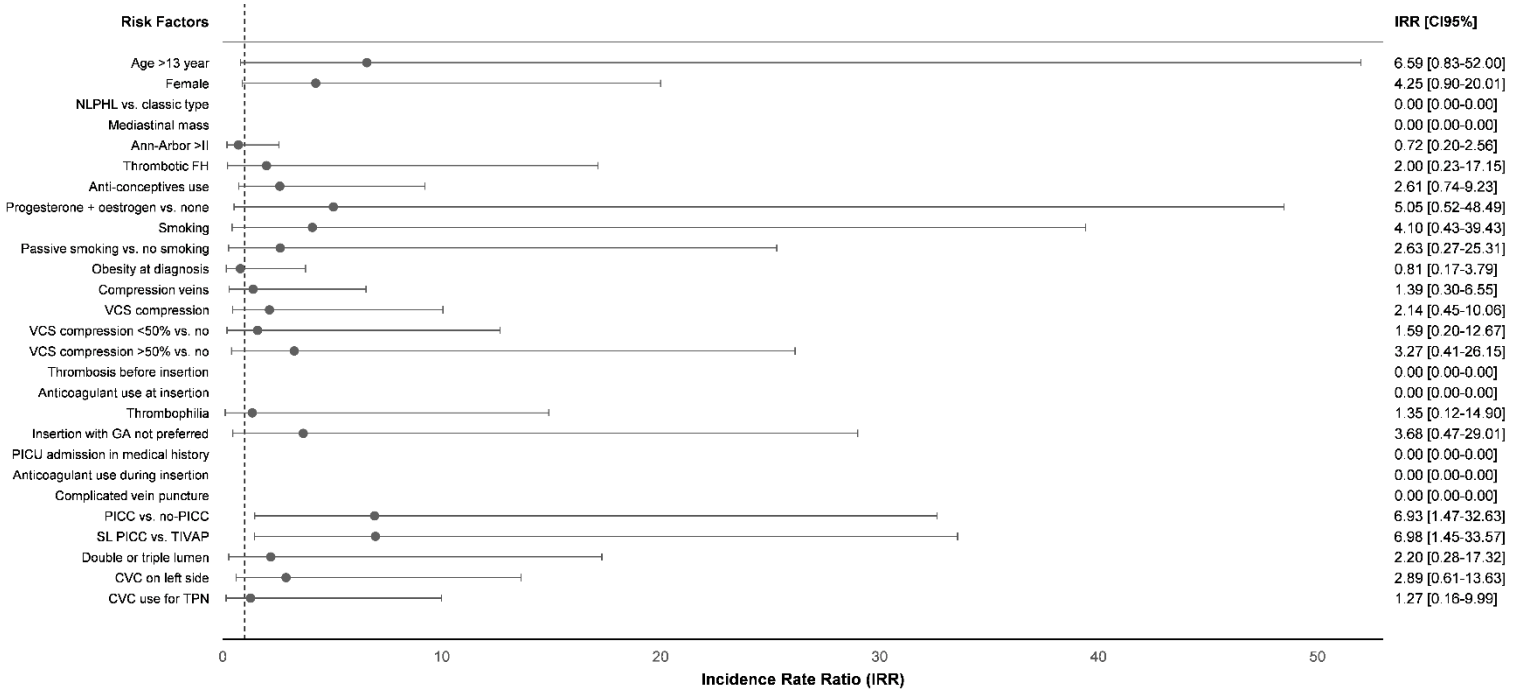
When the analysis was repeated twice including only single lumen PICCs and TIVAPs (n=88) and excluding patients where general anesthesia was not preferred resulting in the insertion of a PICC instead of a TIVAP (n=5), the insertion of a PICC was still identified as a risk factor. For patients with a single lumen PICC or TIVAP only the female sex was additionally identified as a risk factor. (**Online Resource 5 and 6**)

DISCUSSION

In this study, we investigated the incidence of CVC-related complications in patients treated for HL. We found at least one complication in 42% of all patients. Complications were more often observed, more severe, and resulted in more frequent early CVC removal in patients receiving a PICC compared to patients with a TIVAP. One of the most frequent and severe complications was a CVC-related CVT, which occurred in one out of ten patients with HL. The incidence rate of CVC-related CVT in this study was seven times higher for patients with a single lumen PICC compared to patients with a TIVAP.

CVT is a severe complication, as most patients will receive anticoagulant therapy for months and CVC replacement is often necessary. In severe cases, CVT-infections, vena cava superior syndrome, embolisms and long term complications like post-thrombotic syndrome can occur. In this study, a CVC-related CVT incidence of 10% was observed. This incidence falls within the wide range reported for children with cancer in general of 2-50% (28-30). The risk of CVC-related CVTs has been described to be higher in patients with HL compared to other oncology patients, presumably caused by the frequent presence of risk factors for CVT (e.g. vein compression in the upper body, high-dose corticosteroid treatment), as also described in the

Figure 1 Risk factors for CVC-related CVT in pediatric Hodgkin lymphoma patients.



CVC; Central Venous Catheters, CVT; Central Venous Thrombosis, TIVAP; Totally Implantable Venous Access Port, PICC; Peripherally Inserted Central Catheter, FH; Family History, NLPHL; Nodular lymphocyte-predominant Hodgkin lymphoma, TPN; Total Parenteral Nutrition, PICU; Pediatric Intensive Care Unit, SL; Single Lumen, GA; General Anesthesia, VCS; Vena Cava Superior, IRR; Incidence Rate Ratio, CI; Confidence Interval.

Mean CVC to vein ratio (calculated only for patients with a PICC) did not differ between patients with and without a CVC-related CVT (0.25 versus 0.27; CI95% -0.02-0.06).

introduction (1, 3, 9, 11-14, 31). However, the difference between HL and non-HL patients might also be explained by the CVC types included in the previously performed studies, i.e. only 0-3% PICCs (30, 31). Previous studies including lymphoma patients only, reported CVC-related CVT incidences of 7-9% for adults (32) and 3-7% for pediatric patients (1, 14). The low incidence of 3% (definite CVC-related CVT) as reported by Schonning et al. (14) might be explained by the inclusion of mainly patients with a TIVAP and that the other not-definite CVTs reported by the authors might also have been related to the CVC.

The results of this study suggest that single lumen PICCs are associated with much higher complication rates (49% vs. 26%; IRR 5.12), early removal (18% vs. 7%; IRR 9.96) and more severe complications (19% vs. 7%; IRR 11.96) when compared to TIVAPs. The high rate of complications associated with PICCs has also been previously reported in a variety of patient populations (1-9). In this study, the incidence rate of local irritation/infections and CVC-related CVTs specifically, was higher in patients receiving single lumen PICCs compared to TIVAPs (26% vs. 7%; IRR 14.95 and 12% vs. 7%; IRR 6.98, respectively), suggesting that TIVAPs are more suitable for this patient group compared to PICCs in terms of CVC-related complications and the risk of early removal. However, due to the non-randomized retrospective nature of this study, differences in baseline characteristics between patients with a SL PICC and TIVAP were observed. Patients with a SL PICC were slightly older, were more often diagnosed with Ann-Arbor stage I or II, and had their CVC in situ for a shorter (treatment) period compared to patients with a TIVAP. The older age might be explained by the fact that PICC insertion without anesthesia is less preferable in younger patients. This might result in some bias since older age has been described to be associated with a higher incidence of CVT (1). Furthermore, patients with a higher Ann-Arbor stage are more frequently expected to have a longer treatment duration, resulting in the more frequent insertion of a TIVAP in this

group. Higher rates of CVT in children and adults with higher Ann-arbor stage have been previously described, but these results were not significant (11, 15). In this study however, patients with a TIVAP developed less CVTs compared to patients with a PICC. The lower number of CVC-(treatment) days might be explained by the fact that PICCs are removed much sooner after the end of treatment. This can be explained by two reasons: (1) TIVAPs are more often left in situ for the clinical follow-up period compared to PICCs, and (2) the surgical waiting lists for TIVAP removal. Since the risk of some complications might be higher during treatment (i.e. intensive use of CVC), the IRs per 1 000 CVC-treatment days were also calculated, which still showed that the insertion of a SL PICC is associated with a significantly higher risk of (severe) complications and local infections in particular compared to a TIVAP.

The high rate of complications associated with PICCs was also reported previously in adult patients with HL and pediatric oncology patients in general (1, 9-13). Three studies did investigate risk factors for CVT (CVC and non-CVC related) specifically in pediatric patients with lymphoma. Gartrell et al. (1) identified the insertion of a PICC as a risk factor, but noted that this result might be biased since patients unstable for sedation with large mediastinal masses initially received a PICC. Insertion of a PICC as an independent risk factor for CVC-related CVT was not observed by Athale et al. (15) and Schonning et al. (14), however almost all patients included in these studies received a TIVAP. Furthermore, Athale et al. (15) identified the presence of a mediastinal mass as a risk factor. Schonning et al. (14) did not identify any risk factors (1, 14, 15). Previous studies suggested that the device-specific quality of life was lower and costs were higher for oncology patients in general with a PICC compared to a TIVAP (4, 33). Taxbro et al. (33) pointed out that this increase in costs was mainly caused by the costs related to complications.

Based on the complications found in this study together with the current literature, the insertion of a TIVAP rather than a PICC should be advised by physicians in pediatric patients diagnosed with HL, especially in case of CVT-related risk factors. This is in line with the conclusions drawn by Taxbro et al. (6) for oncology patients in general.

If a PICC is preferred, for example since general anesthesia is preferably avoided, the use of prophylactic anticoagulants could be considered, particularly when other risk factors for thrombosis in pediatric oncology patients like, age, sex, thrombophilia and vein compression are present (1). In adult oncology patients with a PICC, the use of direct oral anticoagulants (DOAC) and low-molecular weight heparin for primary CVT prevention resulted in a significant decrease in the incidence of CVT with comparable safety outcomes (34, 35), but the evidence to use primary prophylaxis for patients with cancer and a CVC is still scarce and guidelines therefore do not recommend primary prophylaxis (36). The first results of phase III trials investigating DOACs in children showed that DOACs are at least as efficient and safe as low-molecular weight heparin and vitamin K antagonists for the treatment and secondary prophylaxis of thrombotic events in children with different clinical conditions (37-40). Future trials should be focusing on the use of DOACs as primary prevention for pediatric patients.

This study shows the high risk of CVC-related complications associated with pediatric patients diagnosed with HL receiving a PICC. Strengths are that this study describes a large pediatric HL cohort, that this study investigates all CVC-related complications, that CVC-related complication severity and outcomes were investigated, that multiple CVT-related risk factors were evaluated and that separate analyses were performed excluding patients requiring a PICC instead of a TIVAP since CVC insertion under general anaesthesia was not preferred. Limitations of this study are the

retrospective study design, differences in baseline characteristics between the SL PICC and TIVAP group, and the impossibility to perform a multivariate analysis due to the small patient group.

In conclusion, PICCs were associated with a higher risk of (severe) complications, CVTs specifically, and subsequent CVC removal when compared to TIVAPs. The insertion of a TIVAP rather than a PICC should therefore be advised by physicians in pediatric patients diagnosed with HL, especially in case of CVT-related risk factors. Future trials should evaluate the efficacy and safety of direct oral anticoagulants for the primary prevention of CVT in pediatric patients with a PICC and other CVT-related risk factors.

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SUPPLEMENTARY FILES

Online Resource 1 Clavien-Dindo classification

Grade	Definition	Complications total, n (%)	Complications TIVAPs, n (%)	Complications SL PICCs, n (%)
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions[a]	22 (37.9)	5 (35.7)	14 (38.9)
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.	20 (34.5)	7 (50.0)	10 (27.8)
Grade III	Requiring surgical, endoscopic or radiological intervention	15 (25.9)	2 (14.3)	11 (30.6)
IIIa	Intervention not under general anesthesia	12 (20.7)	0 (0.0)	10 (27.8)
IIIb	Intervention under general anesthesia	3 (5.2)	2 (14.3)	1 (2.8)
Grade IV	Life-threatening complication (including CNS complications)* requiring ICU-management	1 (1.7)	0 (0.0)	1 (2.8)
IVa	Single organ dysfunction	1 (1.7)	0 (0.0)	1 (2.8)
IVb	Multi organ dysfunction	0 (0.0)	0 (0.0)	0 (0.0)
Grade V	Death	0 (0.0)	0 (0.0)	0 (0.0)
Total		58 (100.0)	14 (100.0)	36 (100.0)

TIVAP; Totally Implantable Venous Access Port, PICC; Peripherally Inserted Central Catheter, SL; Single Lumen, CNS; Central Nervous System, ICU; Intensive Care Unit.

[a]Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy.

Online Resource 2a Risk factor analysis for CVC-related CVT in pediatric Hodgkin lymphoma patients

			Patients without CVT events		Patients with CVT events		CVC-days	Incidence rate (IR) per 1 000 CVC-days	Comparison IRs or means
			N	%	N	%	N		IRR (CI95%)
Patient related risk factors	Age at insertion	≤13 years	33	97.1	1	2.9	9725	0.10	1
		>13 years	55	85.9	9	14.1	13283	0.68	6.59 (0.83-52.00)
	Sex	Male	48	96.0	2	4.0	11852	0.17	1
		Female	40	83.3	8	16.7	11156	0.72	4.25 (0.90-20.01)
	Hodgkin type	Classic	84	89.4	10	10.6	22692	0.44	1
		NLPHL	4	100.0	0	0.0	316	0.00	Undefined
	Mediastinal mass	No	8	100.0	0	0.0	1255	0.00	1
		Yes	80	88.9	10	11.1	21753	0.46	Undefined
	Ann-Arbor classification	≤II	41	91.1	4	8.9	7472	0.54	1
		>II	47	88.7	6	11.3	15536	0.39	0.72 (0.20-2.56)
	Thrombotic FH	Negative	56	91.8	5	8.2	14036	0.36	1
		Positive	4	80.0	1	20.0	1401	0.71	2.00 (0.23-17.15)
	Anti-conceptives	No	77	92.8	6	7.2	18319	0.33	1
		Yes	11	73.3	4	26.7	4689	0.85	2.61 (0.74-9.23)
	Anti-conceptive type	Progesterone	3	75.0	1	25.0	3360	0.30	1
		Progesterone + estrogen	9	75.0	3	25.0	1998	1.50	5.05 (0.52-48.49)
	Smoking	No	57	95.0	3	5.0	14015	0.21	1
		Yes	2	66.7	1	33.3	1139	0.88	4.10 (0.43-39.43)
		Passive smoking	5	83.3	1	16.7	1774	0.56	2.63 (0.27-25.31)
	Obesity at diagnosis	No	72	90.0	8	10.0	17554	0.46	1
		Yes	16	88.9	2	11.1	5454	0.37	0.81 (0.17-3.79)
	Compression veins	No	72	90.0	8	10.0	19502	0.41	1
		Yes	16	88.9	2	11.1	3506	0.57	1.39 (0.30-6.55)
	VCS compression	No	76	90.5	8	9.5	20597	0.39	1
		Yes	12	85.7	2	14.3	2411	0.83	2.14 (0.45-10.06)
		<50%	9	90.0	1	10.0	1624	0.61	1.59 (0.20-12.67)
		>50%	3	75.0	1	25.0	787	1.27	3.27 (0.41-26.15)

CVC; Central Venous Catheters, CVT; Central Venous Thrombosis, TIVAP; Totally Implantable Venous Access Port, FH; Family History, NLPHL; Nodular lymphocyte-predominant Hodgkin lymphoma, TPN; Total Parenteral Nutrition, PICC; Peripherally Inserted Central Catheter, IR; Incidence Rate

Online Resource 2b Risk factor analysis for CVC-related CVT in pediatric Hodgkin lymphoma patients

			Patients without CVT events		**Patients with CVT events**		**CVC-days**	**Incidence rate (IR) per 1 000 CVC-days**	**Comparison IRs or means**
			N	%	N	%	N		IRR (CI95%)
Patient related risk factors	Thrombosis before insertion	No	87	89.7	10	10.3	23008	0.43	1
		Yes	1	100.0	0	0.0	0	0.00	Undefined
	Anticoagulant use at insertion	No	86	89.6	10	10.4	22846	0.44	1
		Yes	2	100.0	0	0.0	162	0.00	Undefined
	Thrombophilia	No	1	50.0	1	50.0	321	3.12	1
		Yes	1	33.3	2	66.7	475	4.21	1.35 (0.12-14.90)
	Insertion with GA not preferred	No	84	90.3	9	9.7	22333	0.40	1
		Yes	4	80.0	1	20.0	675	1.48	3.68 (0.47-29.01)
	PICU admission in history	No	85	89.5	10	10.5	22652	0.44	1
		Yes	3	100.0	0	0.0	356	0.00	Undefined
CVC related risk factors	Long-term anticoagulant use during CVC-insertion	No	85	89.5	10	10.5	19061	0.52	1
		Yes	3	100.0	0	0.0	280	0.00	Undefined
	Complicated vein puncture	No	82	89.1	10	10.9	18654	0.54	1
		Yes	2	100.0	0	0.0	211	0.00	Undefined
	CVC type	No-PICC	30	93.8	2	6.3	12263	0.16	1
		PICC	58	87.9	8	12.1	7078	1.13	6.93 (1.47-32.63)*
	CVC type	TIVAP	29	93.5	2	6.5	12258	0.16	1
		Single lumen PICC	50	87.7	7	12.3	6151	1.14	6.98 (1.45-33.57)*
	CVC lumen number	Single	79	89.8	9	10.2	18409	0.49	1
		>Single	9	90.0	1	10.0	932	1.07	2.20 (0.28-17.32)
	CVC side	Right	78	90.7	8	9.3	17803	0.45	1
		Left	10	83.3	2	16.7	1538	1.30	2.89 (0.61-13.63)
	CVC use for TPN	No	85	90.4	9	9.6	17780	0.51	1
		Yes	3	75.0	1	25.0	1561	0.64	1.27 (0.16-9.99)
			Mean	SD	Mean	SD			(CI95%)
	CVC to vein ratio		0.27	0.05	0.25	0.06			(-0.02-0.06)

CVC; Central Venous Catheters, CVT; Central Venous Thrombosis, TIVAP; Totally Implantable Venous Access Port, FH; Family History, NLPHL; Nodular lymphocyte-predominant Hodgkin lymphoma, TPN; Total Parenteral Nutrition, PICC; Peripherally Inserted Central Catheter, IR; Incidence Rate

Online Resource 3 Risk factor analysis for CVC-related CVT in pediatric Hodgkin lymphoma patients only including SL PICC and TIVAP (N=88)

			Incidence rate (IR) per 1 000 CVC-days	**Comparison IRs or means**
				IRR (CI95%)
Patient related risk factors	Age at insertion	≤13 years	0.10	1
		>13 years	0.66	6.27 (0.78-50.11)
	Sex	Male	0.09	1
		Female	0.76	8.46 (1.06-67.64)*
	Ann-Arbor classification	≤II	0.59	1
		>II	0.33	0.57 (0.15-2.11)
	Thrombotic family history	Negative	0.38	1
		Positive	0.00	Undefined
	Anti-conceptives	No	0.29	1
		Yes	0.87	2.98 (0.80-11.11)
	Anti-conceptive type	Progesterone	0.30	1
		Progesterone + estrogen	1.57	5.29 (0.55-50.81)
	Smoking	No	0.22	1
		Yes	0.88	3.92 (0.41-37.65)
		Passive smoking	0.64	2.88 (0.30-27.65)
	Obesity at diagnosis	No	0.42	1
		Yes	0.40	0.96 (0.20-4.63)
	Compression veins	No	0.37	1
		Yes	0.64	1.71 (0.35-8.21)
	VCS compression	No	0.36	1
		Yes	0.93	2.60 (0.54-12.49)
		<50%	0.73	2.04 (0.25-16.60)
		>50%	1.27	3.56 (0.44-28.90)
	Thrombophilia	No	0.00	1
		Yes	4.21	Undefined
	Insertion with GA not preferred	No	0.38	1
		Yes	1.48	3.90 (0.49-31.19)
CVC related risk factors	CVC type	TIVAP	0.16	1
		Single lumen PICC	1.14	6.98 (1.45-33.57)*
	CVC side	Right	0.47	1
		Left	0.65	1.38 (0.17-11.04)
	CVC use for TPN	No	0.47	1
		Yes	0.64	1.35 (0.17-10.79)
	CVC to vein ratio	NA	NA	(-0.03-0.04)

CVC; Central Venous Catheter, CVT; Central Venous Thrombosis, TIVAP; Totally Implantable Venous Access Port, GA; General Anesthesia, TPN; Total Parenteral Nutrition, PICC; Peripherally Inserted Central Catheter, IR; Incidence Rate, IRR; Incidence Rate Ratio, VCS; Vena Cava Superior, SD; Standard Deviation, CI; Confidence Interval. *Significant values

Online Resource 4 Risk factor analysis for CVC-related CVT in pediatric Hodgkin lymphoma patients only including SL PICC and TIVAP and excluding patients where general anesthesia was not preferred (N=83)

			Incidence rate (IR) per 1 000 CVC-days	**Comparison IRs or means**
				IRR (CI95%)
Patient related risk factors	Age at insertion	≤13 years	0.11	1
		>13 years	0.59	5.42 (0.67-44.01)
	Sex	Male	0.09	1
		Female	0.69	7.54 (0.93-61.31)
	Ann-Arbor classification	≤II	0.49	1
		>II	0.33	0.68 (0.16-2.85)
	Anti-conceptives	No	0.24	1
		Yes	0.87	3.58 (0.90-14.32)
	Anti-conceptive type	Progesterone	0.30	1
		Progesterone + estrogen	1.57	5.29 (0.55-50.81)
	Smoking	No	0.23	1
		Yes	0.88	3.76 (0.39-36.17)
		Passive smoking	0.64	2.76 (0.29-26.56)
	Obesity at diagnosis	No	0.37	1
		Yes	0.40	1.08 (0.22-5.34)
	Compression veins	No	0.36	1
		Yes	0.56	1.03 (0.13-8.40)
	VCS compression	No	0.36	1
		Yes	0.57	1.57 (0.19-12.75)
		<50%	0.73	2.01 (0.25-16.37)
		>50%	0.00	Undefined
CVC related risk factors	CVC type	TIVAP	0.16	1
		Single lumen PICC	1.07	6.59 (1.33-32.63)*
	CVC side	Right	0.43	1
		Left	0.65	1.53 (0.19-12.40)
	CVC use for TPN	No	0.43	1
		Yes	0.64	1.49 (0.18-12.11)
	CVC to vein ratio, mean (SD)	NA	NA	(-0.05-0.03)

CVC; Central Venous Catheter, CVT; Central Venous Thrombosis, TIVAP; Totally Implantable Venous Access Port, TPN; Total Parenteral Nutrition, PICC; Peripherally Inserted Central Catheter, IR; Incidence Rate, IRR; Incidence Rate Ratio, VCS; Vena Cava Superior, SD; Standard Deviation, CI; Confidence Interval. *Significant values

PART II

CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING PREVENTION

CHAPTER 6

Prophylactic antibiotics for preventing gram-positive infections associated with long-term central venous catheters in adults and children receiving treatment for cancer

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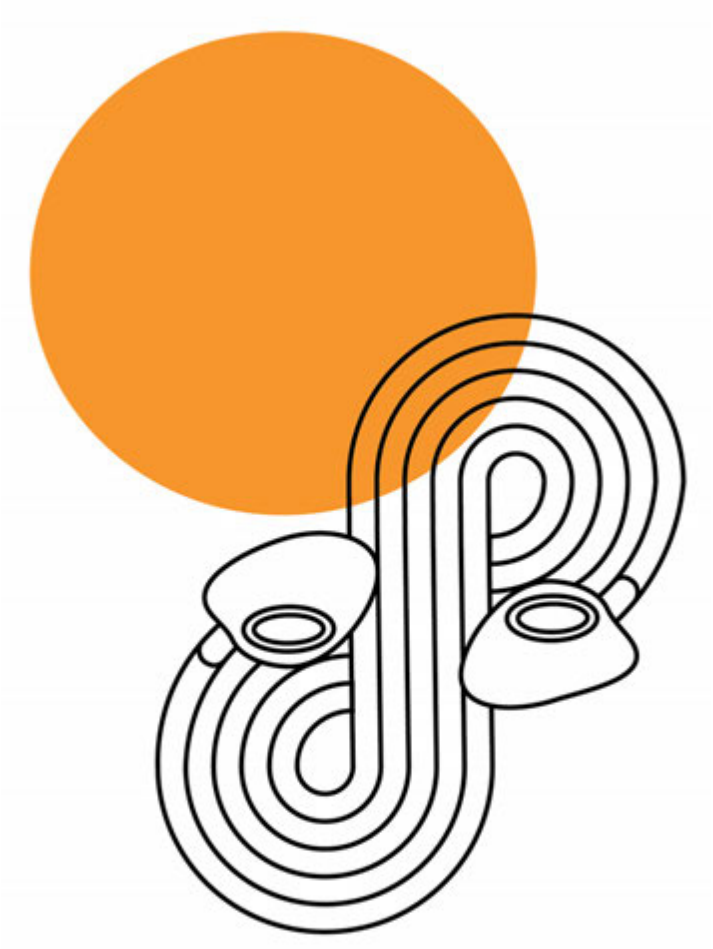


ABSTRACT

Background This is an updated version of a Cochrane Review last published in 2013. Long-term central venous catheters (CVCs), including tunnelled CVCs (TCVCs) and totally implanted devices or ports (TIDs), are increasingly used when treating people with cancer. Despite international guidelines on sterile insertion and appropriate CVC maintenance and use, infections remain a common complication. These infections are mainly caused by gram-positive bacteria. Antimicrobial prevention strategies aimed at these micro-organisms could potentially decrease the majority of CVC-related infections. The aim of this review was to evaluate the efficacy of prophylactic antibiotics for the prevention of gram-positive infections in people with cancer who have long-term CVCs.

Objectives To assess the effects of administering antibiotics prior to the insertion of long-term CVCs or as a flush/lock solution, or both during long- term CVC access to prevent gram-positive CVC-related infections in adults and children receiving treatment for cancer.

Search methods The search for this updated review was conducted on 19 November 2020. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE via Ovid and Embase via Ovid. We searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform portal for additional articles.

Selection criteria We included randomised controlled trials (RCTs) that compared either the administration of prophylactic antibiotics prior to long-term CVC insertion versus no administration of antibiotics, or the use of an antibiotic versus a non-antibiotic flush/lock solution in long-term CVCs, in adults and children receiving treatment for cancer.

Data collection and analysis We used standard methodological procedures expected by Cochrane. Two authors independently selected studies, classified them and extracted data onto a predesigned data collection form. The outcomes of

interest were gram-positive catheter-related infection events and total number of CVCs and CVC days. We pooled the data using a random-effects model for meta-analyses. We used the GRADE approach to assess the certainty of the evidence.

Main results For this update, we identified 310 potentially relevant studies and screened them for eligibility. We included one additional RCT with 404 participants. The original review included 11 RCTs with a total of 840 people with cancer (adults and children). In total this review included 12 RCTs with 1244 participants.

Antibiotics prior to insertion of the CVC Six trials compared the use of antibiotics (vancomycin, teicoplanin, ceftazidime or cefazolin) versus no antibiotics given before the insertion of a long-term CVC. One study did not observe any CVC-related infection events in either group was not included in the quantitative analysis as it was not possible to calculate a risk ratio. Administering an antibiotic prior to insertion of the CVC may not reduce gram-positive CVC- related infections (pooled risk ratio 0.67, confidence interval (CI) 95% 0.32 to 1.43; control versus intervention group risk 10.4% versus 7.3% of the participants; 5 studies, 648 participants; moderate-certainty evidence). We sought adverse event data, but these were not described by the authors. The overall risk of bias was deemed low.

Antibiotics as a flushing or locking solution Six trials compared a combined antibiotic (vancomycin, amikacin or taurolidine) and heparin solution with a heparin-only solution for flushing or locking the long-term CVC after use. One study did not observe any CVC-related sepsis events (CRS) and was not included in this study in the quantitative analysis as it was not possible to calculate a risk ratio. Flushing and locking long-term CVCs with a combined antibiotic and heparin solution likely reduced the risk of gram-positive CVC-related infections compared to a heparin-only solution (pooled rate ratio 0.47, CI 95% 0.26 to 0.85; control versus intervention group rate ratio 0.66 versus 0.27 per 1000 CVC-days; 5 studies, 443 participants; moderate-certainty evidence). One trial reported a higher incidence of occlusions and participants in one trial reported an unpleasant taste after flushing associated

with a combined antibiotic and heparin solution. The overall risk of bias was deemed low.

Authors' conclusions Since the last version of this review, we included one additional study. There was no observed benefit of administering antibiotics before the insertion of long-term CVCs to prevent gram-positive CVC-related infections. Flushing or locking long-term CVCs with an antibiotic solution likely reduces gram-positive CVC-related infections experienced in people at risk of neutropenia through chemotherapy or disease. However, a limitation of this review is heterogeneity between the studies for both outcomes. Insufficient data were available to evaluate if the conclusions apply equally for different CVC types and for adults versus children. It must be noted that the use of an antibiotic flush/ lock solution may increase microbial antibiotic resistance, therefore it should be reserved for high-risk people or if the baseline CVC- related infection rates are high. Further research is needed to identify high-risk groups most likely to benefit from these antibiotic flush/ lock solution.

This review is published as a Cochrane Review in the Cochrane Database of Systematic Reviews 2021, Issue 10. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms. The Cochrane Database Database of Systematic Reviews should be consulted for the most recent version of this review.

BACKGROUND

Description of the condition

This review is an update of a Cochrane Review last published in 2013 (van de Wetering 2013).

People undergoing treatment for cancer need adequate venous access because of the frequent blood draws and administration of chemotherapy, intravenous fluids, blood products and other medications. To limit the discomfort of short-term venous access, long-term central venous catheters (CVCs), including tunnelled central venous catheters (TCVCs) and totally implanted devices or ports (TIDs), are used in more than two thirds of the children and adults undergoing chemotherapy (Groeger 1993; Ingram 1991; Simon 2006). However, the use of long-term CVCs is limited by the risk of blood clot formation and infection. The risk of CVC- related infections ranges from 1.4 infections per 1000 catheter days (Bagnall-Reeb 2004; Press 1984; Schinabeck 2003) to 2.2 infections per 1000 catheter days (Groeger 1993; Sarper 2006). The duration of antimicrobial therapy to treat these infections mostly ranges from seven to 21 days. Success rates of 60% to 91% are reported, although often the device has to be removed (Bagnall-Reeb 2004). Approximately one third of all people with cancer experience an episode of infection while having a long- term CVC in place. Seventy per cent of the organisms that are cultured are gram-positive organisms, mainly coagulase- negative staphylococci, Staphylococcus aureus and enterococci. Other organisms include gram-negative organisms (15%), mainly Escherichia coli, fungal organisms (8%) (for example Candida species) and anaerobic organisms (7%) (O'Grady 2002).

The adherence to and colonisation of CVCs with micro-organisms is facilitated by the formation of a very thin biofilm inside the catheterlumen. This process is influenced by several factors, such as the production of fibro glycocalyx (extracellular slime)

by bacteria. In addition, the host reaction to the CVC results in the formation of a thrombin sleeve rich in clotting factors such as fibronectin, fibrinogen and fibrin, which contributes to the formation of the biofilm (Bagnall-Reeb 2004; Darouiche 1999). This means that adequate antibiotic treatment may only lead to the resolution of the CVC infection in certain cases (e.g. infections caused by less pathogenic coagulase-negative staphylococci), whereas in other cases (e.g. infections caused by *Pseudomonas*, *S aureus* or fungi) this will be much more difficult, leading to removal of the CVC (Simon 2006).

The organisms responsible for CVC colonisations and infections come from different sources. These are: the skin, the catheter hub, the CVC prior to insertion, hematogenous seeding (infections originating outside the catheter can reach the CVC via the bloodstream) and contamination of the intravenous fluids given to the person (e.g. intravenous total parenteral nutrition) (Hachem 2002). Early CVC-related infections (infections that develop within 45 days after placement of the catheter) are mostly caused by organisms from the skin insertion site. This is the time period during which many manipulations of the CVC are necessary due to the intensity of the chemotherapy. After 45 days, the catheter hub becomes a far more important source of infection (Abbas 2004; Shaul 1998). International guidelines have been developed to prevent CVC-related infections (CPAC 1990; O'Grady 2002). These include guidelines for CVC insertion, maintenance and care. The clinical care management bundle published by Schiffer 2013 (including hand hygiene, barrier precautions for insertion, chlorhexidine skin antisepsis, optimal catheter site selection and assessment of CVC necessity) sets the standard for CVC care.

Description of the intervention

Systemic antibiotics may be given intravenously before the insertion of the CVC in an attempt to reduce early infections; however, in the original versions of this review we found no evidence to support the use of prophylactic antibiotics in this way (van de Wetering 2007; van de Wetering 2013).

Standard maintenance of long-term CVCs includes flushing the CVC with saline after usage and closing the CVC with a lock solution to remain in the CVC until the next use. There are conflicting data about the relative value of adding prophylactic heparin to saline lock solutions (López-Briz 2018; SchiHer 2013); however, heparinised saline is still commonly used. Adding an antibiotic to the flush solution may prevent biofilm formation and eliminate bacteria introduced into the CVC via the skin or during CVC access, from any source. Antibiotics that have activity against gram-positive organisms and which have been evaluated for this purpose include vancomycin, taurolidine, teicoplanin and minocycline.

How the intervention might work

People with cancer are at an increased risk of infections due to the immunosuppressive effects of chemotherapy or their disease (e.g. haematological malignancies), or both. Administering prophylactic antibiotics may reduce the likelihood that gram- positive bacteria, introduced at the time of CVC insertion or following access, will thrive and lead to a CVC-related infection.

Why it is important to do this review

This review is an update of a Cochrane Review originally published in 2003 then updated in 2007 and 2013 (see other published versions of this review), in which we found evidence of moderate-certainty to support adding an antibiotic with activity against gram- positive organisms to the standard flush or lock solution,

and no evidence to support the use of systemic antibiotics prior to long-term CVC insertion. There remains uncertainty as to whether antibiotic prophylaxis is of benefit to adults and children at a high risk of CVC-related infections. By updating this review and incorporating new evidence, we hoped to clarify the role of prophylactic antibiotics to prevent gram-positive infections in long- term CVCs.

OBJECTIVES

To assess the effects of administering antibiotics prior to the insertion of long-term CVCs or as a flush/lock solution, or both during long-term CVC access to prevent gram-positive CVC-related infections in adults and children receiving treatment for cancer.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trials (RCTs) that compare the administration of antibiotics to no administration of antibiotics prior to the insertion of long-term central venous catheters (CVCs) to reduce gram-positive infections related to the CVC.
2. RCTs that compare an antibiotic flush/lock solution with a standard non-antibiotic solution to reduce gram-positive infections related to the CVC.
3. RCTs that combine the first two comparisons.

Types of participants

We included trials in adults and children with newly inserted long- term CVCs (tunnelled CVCs (TCVCs) or totally implantable devices (TIDs)) to facilitate chemotherapy.

Types of interventions

1. Intravenous antibiotics for gram-positive organisms, e.g. vancomycin, taurolidine, teicoplanin and minocycline, administered before long-term CVC insertion.
2. An antibiotic solution administered as a CVC flush/lock solution during long-term CVC use.

Types of outcome measures

We investigated the following gram-positive CVC-related infections and adverse events related to the interventions.

Primary outcomes

We defined CVC-related infections as follows.

- CVC-related sepsis (CRS). Many CRS definitions are used throughout the literature; most studies used the catheter- related bloodstream infection (CRBSI) or central-line associated bloodstream infection (CLABSI) definition (CDC CLABSI Criteria; Mermel 2009; O'Grady 2002). Some authors registered all bloodstream infections (BSI), defined as infection-related symptoms and a positive blood culture.
- Local infections, i.e. exit-site infections (positive exit site culture, cellulitis or pus around the exit site) or tunnel infections (cellulitis overlying the tunnel tract).

If studies reported CRBSI/CLABSI and proxy outcomes, we preferentially used the CRBSI/CLABSI data in our meta-analyses.

Secondary outcomes

We investigated adverse events related to the interventions.

Search methods for identification of studies

Electronic searches

The original review's search was run in July 2001 (Medline and Embase 1966 to 2000, and Central: Issue 4, 2000). We ran subsequent searches on 6 September 2006, 28 June 2013 and 17 September 2013. For this updated review, we searched the following databases on 19 November 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 11), in the Cochrane Library;
- MEDLINE via Ovid (June 2013 to week 1 November 2020);
- Embase via Ovid (June 2013 to week 46 2020).

The search strategies are outlined in **Appendix 1**; **Appendix 2**; and **Appendix 3**.

Searching other resources

For the initial review, we hand searched the following conference proceedings: International Society for Paediatric Oncology (SIOP) (1995 to 2005), Multinational Association of Supportive Care in Cancer (MASCC) (1995 to 2005), American Society of Clinical Oncology (ASCO) (1995 to 2005), Interscience Conference of Antimicrobial agents and Chemotherapy (ICAAC) (1995 to 2005). We did not obtain any extra information from the conference proceedings. For this updated review, we did not hand search conference proceedings.

To identify any additional articles, we searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform). Additionally, we hand searched reference lists of included studies and other related publications.

Data collection and analysis

For this version of the review, we updated the methods. Please see differences between protocol and review.

Selection of studies

We independently identified and classified the eligible studies. For the first original review (published in Issue 3, 2003; updated version published in 2007), Marianne van der Wetering (MvdW) and Job van Woensel (JvW) performed this; Theresa Lawrie (TAL) and MvdW undertook this for the updated version of 2013. For this current update, MvdW and Ceder van den Bosch (CvdB) identified and classified the eligible studies.

Data extraction and management

We extracted data on to a predesigned data extraction and collection form (gram-positive CVC-related infection events and total number of participants/CVCs). In addition, we recorded the following information for each study, where possible:

- study location, accrual dates;
- participant inclusion and exclusion criteria;
- type of long-term CVCs used, site, technique and timing of insertion;
- type of intervention(s), dose and timing of administration;
- methods of randomisation and allocation concealment;
- baseline characteristics of participants including age, type of cancer and previous chemotherapy;
- types of outcomes; and
- adverse events.

Assessment of risk of bias in included studies

We assessed the included studies using the Cochrane Risk of Bias version 1.0 tool (RoB 1) according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). As in the original review, we also assessed the methodological quality (quality of randomisation, blinding and analysis) according to the van Tulder criteria (van Tulder 1997). We contacted the authors for additional information, where necessary, and resolved disagreements between review authors by discussion.

Measures of treatment effect

For the studies assessing the efficacy of prophylactic antibiotics prior to CVC insertion, dichotomous data were required. We presented these results as pooled risk ratios with 95% confidence intervals (CIs). We did not present these results as pooled rate ratios per 1000 CVC-days because only one of the included studies reported CVC-days. For studies assessing the efficacy of antibiotic flush/lock solutions, we used the generic inverse variance to calculate the pooled rate ratios per 1000 CVC-days and their 95% CIs.

Unit of analysis issues

All review outcomes required randomisation at the level of CVCs or participants if only one CVC was inserted per person.

Dealing with missing data

We contacted trial authors in cases of missing data. If data were not available, we only analysed the available data.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We considered heterogeneity to be substantial if I^2 was 50% or more.

Assessment of reporting biases

If no trial protocol was accessible or the outcomes described in the method section differed from the outcomes described in the result section, we suspected a high risk of reporting bias. Where 10 or more trials contributed to the meta-analysis, we planned to visually assess the risk of publication bias using funnel plots.

Data synthesis

We grouped the studies according to the interventions evaluated and analysed these groups separately, as follows:

1. studies of intravenous antibiotic prophylaxis prior to insertion of the long-term CVC versus placebo or no antibiotics;
2. studies of antibiotic flush or lock solutions versus standard flush or lock solutions following long-term CVC insertion.

We pooled data in the meta-analyses using RevMan 2020. Where the results for CVC-related infections also described gram-negative infections, we included the gram-positive data only. We used the random-effects model for all meta-analyses due to substantial heterogeneity between studies with regard to design, interventions and populations.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses, where possible. Potential reasons for

heterogeneity included the age of participants (adults versus children), antibiotic types (vancomycin versus others) and CVC types.

Sensitivity analysis

We performed sensitivity analyses where there was a high risk of bias associated with the quality of one of the included studies.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using the GRADE approach (Schünemann 2013). This takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Schünemann 2020). We created a summary of findings table based on the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2020) and using the GRADEPro Guideline Development Tool (GRADEpro GDT). We used the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). For each study limitation we downgraded the evidence from 'high' certainty by one level for serious concerns, or by two levels for very serious concerns. We scored the certainty of evidence as very low, low, moderate or high.

RESULTS

Description of studies

We included 12 studies in total in this review; six evaluated the efficacy of antibiotic administration prior to central venous catheter (CVC) insertion, and six evaluated the efficacy of antibiotic lock/flush solutions for the prevention of CVC-related infections (**Characteristics of included studies**).

Results of the search

In the original 2007 review (search from 1966 to 2006), we identified the abstracts of 40 potentially relevant studies and on screening excluded 20 of these. Of the remaining 20 studies, we classified 11 studies as excluded and nine as included.
In the 2013 updated review (search from 2006 to 2013), we identified an additional 16 records for classification. Of these 16 records, we classified 11 studies (12 citations) as excluded and two (four citations) as included.

For the current updated review, we found 336 potentially relevant studies through database searches. After de-duplication, 310 studies remained. After using the Cochrane RCT Classifier machine learning tool and title and abstract screening, we identified three potentially relevant records for classification. We excluded two records after full-text screening due to the inclusion of only non- tunnelled CVCs (Gudiol 2020), and one ongoing study (van den Bosch 2017). We contacted the authors of one study to check if they included participants who did not have newly-inserted CVCs. The authors replied that participants with metastatic solid cancer (57% of all included participants) already had a CVC before inclusion, therefore we excluded this article (Longo 2017). After searching the trial registries, we identified two potentially relevant studies; one was still ongoing (Chambrier 2014), and we included the other one after full-text screening (Karanlik 2011). We contacted the authors of the included Karanlik 2011 study to check if children were included, but we did not receive a reply.

Thus, for this updated review we included one additional study. (Karanlik 2011; **Figure 1**; **Characteristics of included studies; Characteristics of excluded studies**; **Characteristics of ongoing studies**).

Included studies

The 12 studies enrolled 1244 participants in total. Five studies were conducted in adults (N = 352) (Di Carlo 2011; Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995), four studies in children (N = 344) (Handrup 2013; Henrickson 2000; RackoH 1995; Schwartz 1990), two studies enrolled both (N = 144) (Barriga1997; Daghistani 1996), and for one study (N = 404) it was not clear if children were also included in the trial (Karanlik 2011). Nine trials included participants with solid tumours and haematological malignancies, two trials included participants with haematological malignancies only (Lim 1993; Ljungman 1997), and one trial included participants with solid tumours only (Di Carlo 2011). We only included studies observing newly-inserted CVCs, except for the study by Henrickson 2000, which also enrolled an unspecified number of children with tunnelled central venous catheters (TCVCs) already in situ. Most studies evaluated infections in TCVCs, three studies used totally implantable devices (TIDs) (Di Carlo 2011; Handrup 2013; Karanlik 2011). The Handrup 2013 study used both TCVCs and TIDs.

Six studies evaluated the administration of antibiotics prior to central venous catheter (CVC) insertion. The antibiotics used in these studies were as follows:

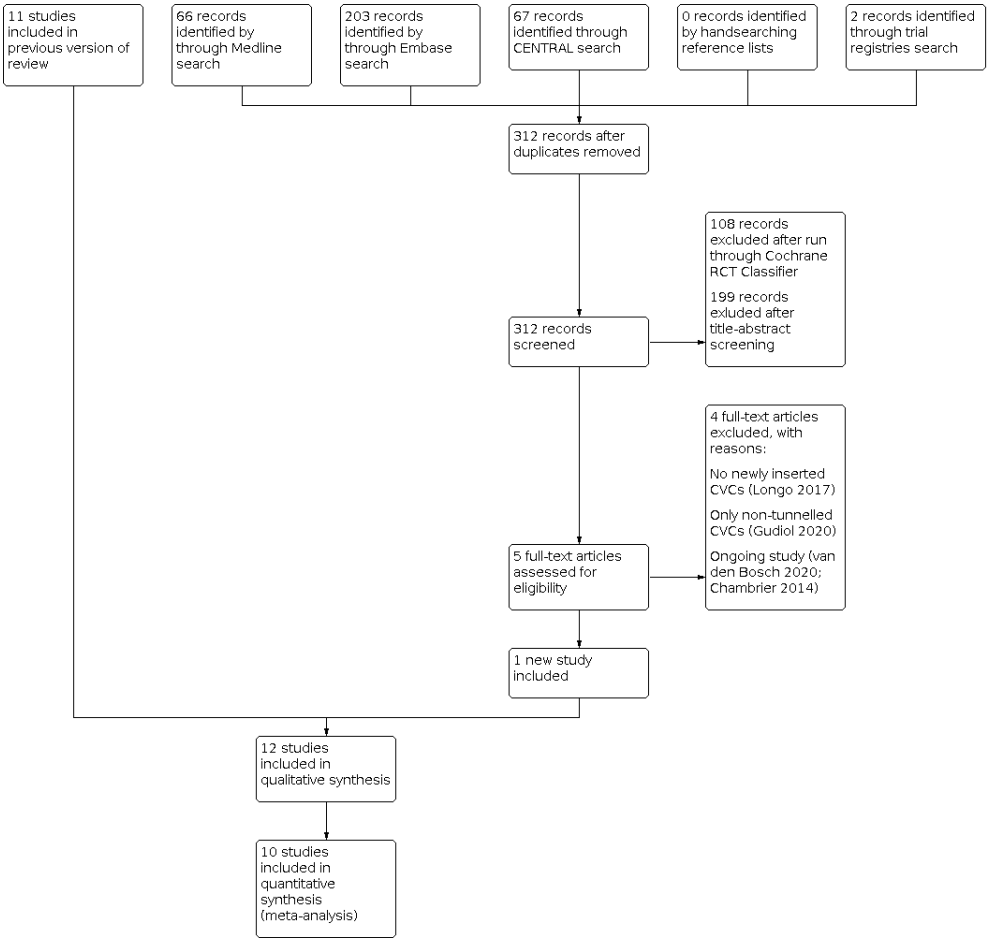
- vancomycin (Ranson 1990; Vassilomaniakis 1995);
- teicoplanin (Lim 1993; Ljungman 1997);
- ceftazidime (Di Carlo 2011);
- cefazolin (Karanlik 2011).

Six studies evaluated flushing or locking the CVC with a combination of an antibiotic and heparin. Antibiotics used in these studies were as follows:

- vancomycin (Barriga 1997; Rackoff 1995; Schwartz 1990);
- vancomycin (+/- ciprofloxacin) (Henrickson 2000);

- vancomycin and amikacin (Daghistani 1996);
- taurolidine (Handrup 2013).

Figure 1 Updated Search Flow Diagram



Most studies evaluated and reported CVC-related infections overthe lifespan of the CVC. Four studies reported early CVC-related infections, occurring within 21 to 30 days of insertion (Di Carlo 2011; Karanlik 2011; Ljungman 1997; Ranson 1990). Seven studies reported a catheter related sepsis (CRS) completely or partially defined following the central line associated bloodstream infection (CLABSI) or catheter related bloodstream infection (CRBSI) criteria (Handrup

2013; Henrickson 2000; Lim 1993; Ljungman 1997; Rackoff 1995; Schwartz 1990; Vassilomaniakis 1995). A minority defined a CRS as a positive blood culture and clinical symptoms (Barriga 1997; Daghistani 1996), another study used a definition for CRS mainly depending on the response to treatment (Ranson 1990). Two studies reported local infections (Di Carlo 2011; Karanlik 2011).

Excluded studies

We excluded 26 studies for the following reasons (11 for the original review, 11 for the first updated review and 4 for the current updated review; see **Characteristics of excluded studies**).

- Participants were ill neonates and not people with cancer (two studies: Garland 2005; Ocete 1998).
- Non-tunnelled CVCs were used (seven studies: Carratala 1999; Chatzinikolaou 2003b; Gudiol 2020; Hanna 2004; Jaeger 2005; Raad 1998; Schierholz 2010).
- Studies were not RCTs (seven studies: Al Sibai 1987; Chatzinikolaou 2003a; Dawson 2000; Fourcade 2001; Rubie 1995; Scaife 2010; Simon 2008);
- RCT did not evaluate newly-inserted CVCs (four studies: Akyuz 2012; Dumichen 2012; Ferreira Chacon 2011; Longo 2017).
- RCT did not evaluate prophylactic antibiotics (four studies: Abdelkefi 2005; Chambers 2005; Hitz 2012; Raad 2005);

Ongoing studies

We identified two ongoing RCTs without preliminary results (Chambrier 2014; van den Bosch 2017; see **Characteristics of ongoing studies**).

Risk of bias in included studies

Methodology assessment following the van Tudler 1997 criteria

The methodology, evaluated following the van Tulder 1997 criteria, of the included studies was mostly of a reasonable quality. However, sample sizes were relatively small and ranged from 27 (Vassilomaniakis 1995) to 404 participants (Karanlik 2011). All studies described the eligibility criteria sufficiently and included adults, children or both, who were at risk of neutropenia due to their disease or chemotherapy. Most studies excluded participants already receiving antibiotics, except those used orally for selective gut decontamination (that is, the use of oral antibiotics before a neutropenic episode is expected in which the potentially pathogenic aerobic organisms are eliminated without affecting the non-pathogenic anaerobic organisms). All studies evaluated participants with newly-inserted CVCs; however, Henrickson 2000 also included an unspecified number of participants with CVCs already in situ. In Vassilomaniakis 1995, randomisation was initially performed but all participants were later included in the experimental group; therefore we only used the first part of the study in our analyses. Further details regarding the methodological quality assessment can be found in the additional tables: **Table 1, Table 2** and **Table 3**.

Risk of bias assessment using the Cochrane RoB 1 tool

Using the Cochrane RoB 1 tool, we deemed the overall risk of bias of the trials to be low. The trials mainly scored an unclear or high risk of bias since the methods of allocation and randomisation were not described, a non-blinded study design was used, and since not all studies included all randomised participants in the final analyses. The details of the risk of bias assessment for each domain are described below and in the Characteristics of included studies table; a summary is provided in **Figure 2** and **Figure 3**.

Allocation

Only three studies clearly described their method of randomisation (Daghistani 1996; Handrup 2013; Karanlik 2011). Seven studies did not specify their method of allocation concealment, so we assessed these as having an unclear risk of bias for this domain (Di Carlo 2011; Handrup 2013; Lim 1993; Ljungman 1997; Rackoff 1995; Schwartz 1990; Vassilomaniakis 1995).

Blinding

Six trials were open-label studies, where neither the investigator nor the participant were blinded (Di Carlo 2011; Handrup 2013; Lim 1993; Ljungman 1997; Rackoff 1995; Vassilomaniakis 1995). We therefore judged these to have a high risk of bias for this domain. We judged the other six studies to have a low risk of bias (Barriga 1997; Daghistani 1996; Henrickson 2000; Karanlik 2011; Ranson 1990; Schwartz 1990).

Incomplete outcome data

Three trials did not include all randomised participants in the analyses, so we considered them to have a high risk of attrition bias (Daghistani 1996; Karanlik 2011; Ranson 1990). We did not observe any missing data in the other included studies, so gave them a low risk of bias for this domain.

Selective reporting

There was no suspicion of selective reporting in the included studies, since all studies reported the preplanned outcomes and described the outcomes in their method section.

Figure 2 Risk of bias summary: review author's judgements about each risk of bias item for each included study.

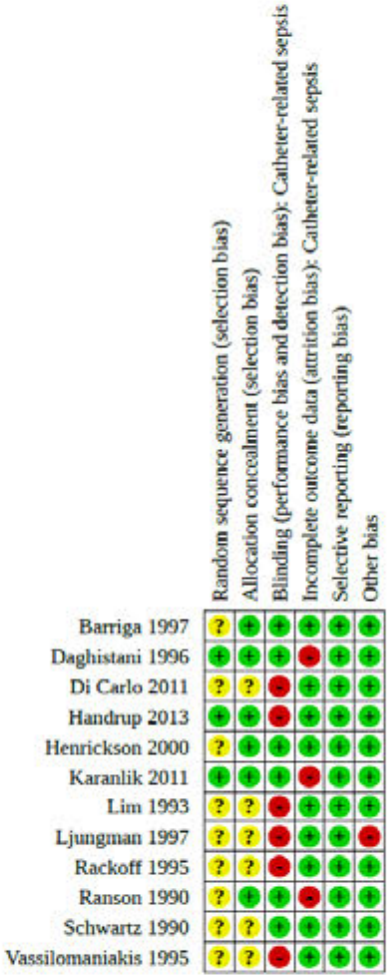
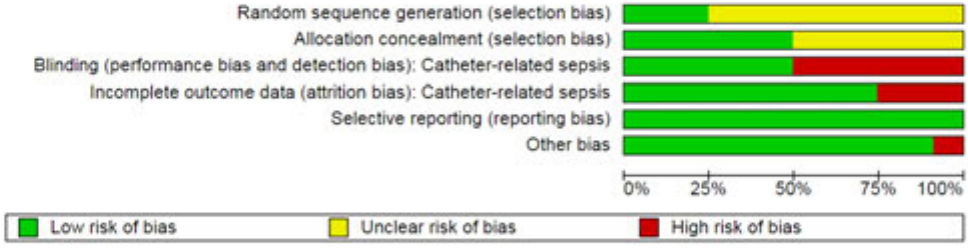


Figure 3 Risk of bias graph for overall judgements about each risk of bias item.



Other potential sources of bias

In Ljungman 1997, open randomisation was performed and the study was stopped after an interim analysis (N = 65) since the pre-set efficacy estimation could not be met. We considered this study to be at a high risk of bias and therefore performed sensitivity analyses with and without these data. We did not identify any other potential sources of bias in the remaining studies.

Effects of interventions

We have included the key outcomes for both comparisons in **Summary of findings 1**.

Antibiotic administration prior to long-term central venous catheter (CVC) insertion

We included six studies: two used vancomycin, two used teicoplanin, one used ceJazidime, and one used cefazolin prophylaxis versus a placebo or no antibiotic administration. All six studies were conducted in adults (Di Carlo 2011; Karanlik 2011; Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995). One study, with 108 participants, did not observe any CVC-related infection events in either group (Di Carlo 2011); we could not include this study in the quantitative analysis since it was not possible to calculate a risk ratio for it. The impact of this study on the pooled risk ratio would presumably be minimal. There was no difference in the risk of CVC-related infections between the prophylactic antibiotic and control groups for the other five studies (pooled risk ratio 0.67, CI 95% 0.32 to 1.43; control versus intervention group risk 10.4% versus 7.3%; P = 0.30, IO = 55%; 648 adults; moderate-certainty evidence; **Analysis 1.1**). There were no differences between the antibiotic subgroups (test for subgroup differences P = 0.83). In the sensitivity analysis, we removed a study that was at a high risk of bias (Ljungman

1997), which made little difference to the overall effect (pooled RR 0.52, 95% CI 0.24 to 1.12; P = 0.09, I^2 = 40%; 583 adults). None of the studies reported the occurrence of adverse events.

Antibiotic versus non-antibiotic flush/lock solution

We included six studies in this meta-analysis; most studies were performed in children (Barriga 1997; Daghistani 1996; Handrup 2013; Henrickson 2000; Rackoff 1995; Schwartz 1990). The majority of studies used a combined vancomycin and heparin solution; one study used a vancomycin, amikacin and heparin solution (Daghistani 1996), and another used a combined taurolidine and heparin solution (Handrup 2013). One study, with 45 participants, did not observe any CRS events in the intervention group during 4.792 CVC-days (i.e. the sum of days from the start until the end of follow-up during which a CVC is in situ). We could not include this study in the quantitative analysis since it was not possible to calculate a risk ratio. Six CRS events in the comparator group were observed during 6.303 CVC days (Schwartz 1990). The impact of this study on the pooled rate ratio would presumably be minimal.

A combined antibiotic and heparin solution was associated with fewer CRS events than a heparin-only solution (pooled rate ratio 0.47, CI 95% 0.26 to 0.85; control versus intervention group risk ratio 0.66 versus 0.27 per 1000 CVC-days; P = 0.01, I^2 = 0%; 443 participants; moderate-certainty evidence; **Analysis 2.1**).

When we excluded the studies which enrolled both adults and children (Barriga 1997; Daghistani 1996), and restricted our analyses to children only (N = 355), the pooled rate ratio was similar to the overall result (pooled rate ratio 0.45, 95% CI 0.19 to 1.04).

Summary of findings 1 Summary of findings table

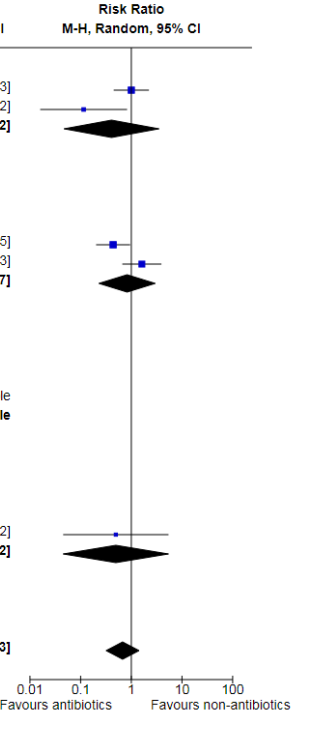
Patient or population: adults and children diagnosed with an oncologic disease with a newly-inserted long-term CVC who were at risk of neutropenia due to chemotherapy or disease
Setting: inpatient and outpatient
Intervention: prophylactic antibiotics (prior to long-term CVC insertion or as lock/flush solutions)
Comparison: no antibiotic administration

Outcomes	Anticipated absolute effects*		Relative effect (95% CI)	N of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk control groups	Absolute effect prophylactic antibiotics (95% CI)				
Antibiotics prior to long-term CVC insertion versus control: catheter-related infections	104 per 1000 participants	71 per 1000 (30 to 164) participants	Risk ratio 0.67 (0.32 to 1.43)	648 (5 RCTs)	⊕⊕⊕⊖ MODERATE[a]	Data inconsistent across studies; I2 = 55%; P= 0.30.
Antibiotic versus heparin only lock/flush solution: catheter-related infections	0.66 per 1000 CVC-days	0.27 per 1000 (0.16 to 0.43) CVC-days	Rate ratio 0.47 (0.26 to 0.85)	443 (5 RCTs)	⊕⊕⊕⊖ MODERATE[b]	Data consistent across included studies; I2 = 0%; P= 0.01.
Antibiotic versus heparin only lock/flush solution: adverse events	See comment	See comment	Not estimable	300 (3 RCTs)	⊕⊕⊖⊖ LOW[b,c]	An unpleasant taste was described by the majority of the participants included in the taurolidine/citrate group by one study. One study reported a significant lower incidence of occlusions associated with the vancomycin/ ciprofloxacin /heparin group compared to the heparin-only group.

CI: confidence interval; RCT: randomised controlled trial; CVC: central venous catheter.
*The basis for the assumed risk is the mean control group risk across studies. The absolute effect (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a] We downgraded the evidence by one level due to substantial heterogeneity between the studies (I^2 > 50% and confidence intervals were not overlapping).
[b] We downgraded the evidence since the sample was clinically heterogeneous.
[c] We downgraded the evidence due to imprecision since only a few studies described the incidence of adverse events.

Analysis 1.1 Comparison 1: Antibiotics versus non-antibiotics prior to long-term CVC insertion, Outcome 1: CVC-related infections

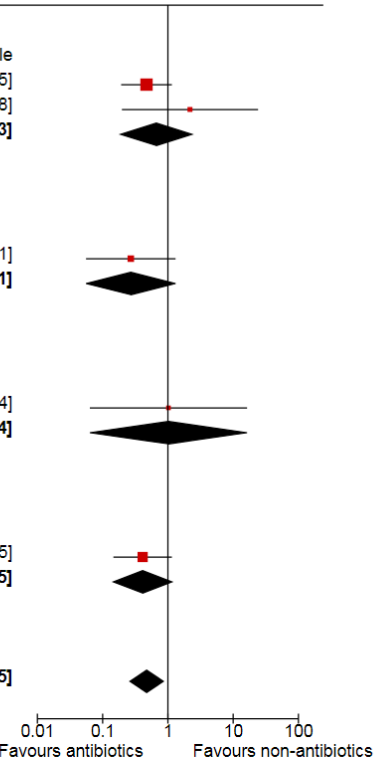
Study or Subgroup	Antibiotics prior to long-term CVC insertion Events	Total	Non-antibiotics prior to long-term CVC insertion Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Vancomycin						
Ranson 1990 (1)	9	36	9	36	27.6%	1.00 [0.45 , 2.23]
Vassilomaniakis 1995 (1)	1	16	6	11	10.6%	0.11 [0.02 , 0.82]
Subtotal (95% CI)		**52**		**47**	**38.2%**	**0.41 [0.05 , 3.52]**
Total events:	10		15			
Heterogeneity: Tau² = 1.90; Chi² = 4.23, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.1.2 Teicoplanin						
Lim 1993 (2)	7	40	16	40	28.2%	0.44 [0.20 , 0.95]
Ljungman 1997 (2)	10	33	6	32	25.7%	1.62 [0.67 , 3.93]
Subtotal (95% CI)		**73**		**72**	**53.9%**	**0.83 [0.23 , 2.97]**
Total events:	17		22			
Heterogeneity: Tau² = 0.67; Chi² = 4.74, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.1.3 Ceftazadime						
Di Carlo 2011 (3)	0	54	0	54		Not estimable
Subtotal (95% CI)		**54**		**54**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.4 Cefazolin						
Karanlik 2011 (4)	1	203	2	201	7.9%	0.50 [0.05 , 5.42]
Subtotal (95% CI)		**203**		**201**	**7.9%**	**0.50 [0.05 , 5.42]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**382**		**374**	**100.0%**	**0.67 [0.32 , 1.43]**
Total events:	28		39			
Heterogeneity: Tau² = 0.37; Chi² = 8.96, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%						



Footnotes
(1) adults; vancomycin
(2) adults; teicoplanin
(3) adults; ceftazidime
(4) cefazolin

Analysis 2.1 Comparison 2: Antibiotic versus non-antibiotic flush/lock solutions, Outcome 1: CVC-related infections

Study or Subgroup	log[Rate Ratio]	SE	Antibiotic flush/lock solutions Total	Non-antibiotic flush/lock solutions Total	Weight	Rate Ratio IV, Random, 95% CI
2.1.1 Vancomycin						
Schwartz 1990 (1)	0	0	21	24		Not estimable
Barriga 1997	-0.755	0.4565	39	44	43.2%	0.47 [0.19 , 1.15]
Rackoff 1995	0.7793	1.2256	28	27	6.0%	2.18 [0.20 , 24.08]
Subtotal (95% CI)			**88**	**95**	**49.2%**	**0.66 [0.19 , 2.33]**
Heterogeneity: Tau² = 0.32; Chi² = 1.38, df = 1 (P = 0.24); I² = 27%						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.1.2 Vancomycin (+/- ciprofloxacin)						
Henrickson 2000	-1.3093	0.8058	35	80	13.9%	0.27 [0.06 , 1.31]
Subtotal (95% CI)			**35**	**80**	**13.9%**	**0.27 [0.06 , 1.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
2.1.3 Vancomycin and amikacin						
Daghistani 1996	0.0198	1.4152	28	33	4.5%	1.02 [0.06 , 16.34]
Subtotal (95% CI)			**28**	**33**	**4.5%**	**1.02 [0.06 , 16.34]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
2.1.4 Taurolidine						
Handrup 2013	-0.8916	0.5262	64	65	32.5%	0.41 [0.15 , 1.15]
Subtotal (95% CI)			**64**	**65**	**32.5%**	**0.41 [0.15 , 1.15]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.69 (P = 0.09)						
Total (95% CI)			**215**	**273**	**100.0%**	**0.47 [0.26 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 2.41, df = 4 (P = 0.66); I² = 0%						
Test for overall effect: Z = 2.50 (P = 0.01)						
Test for subgroup differences: Chi² = 1.13, df = 3 (P = 0.77), I² = 0%						



Footnotes

(1) Schwartz 1990 observed zero events in the antibiotic and six events in the non-antibiotic flush/lock solution group. Due to zero events in one of the groups, a risk ratio could not be calculated.

Henrickson 2000 included some participants with existing CVCs; we performed a sensitivity analysis by excluding this study from the analysis and the results remained largely the same as the overall finding (pooled rate ratio 0.52, 95% CI 0.27 to 0.97).

Schwartz 1990 reported that 8 out of 21 (vancomycin and heparin group) versus 7 out of 24 (heparin-only group) participants experienced occlusions requiring urokinase; they reported no other adverse events. Henrickson 2000 observed the occurrence of 3.99 (heparin-only group) versus 3.47 (heparin and vancomycin group) and 1.75 (heparin, vancomycin and ciprofloxacin) occlusions per 1000 CVC-days (P = 0.37 and P < 0.01, respectively); no other adverse events occurred. Handrup 2013 reported that the majority of participants in the taurolidine and citrate group described an unpleasant taste when the CVC was flushed. Other authors did not describe the possible occurrence of adverse events.

DISCUSSION

Summary of main results

Administering antibiotics prior to the insertion of long-term CVCs did not reduce the risk of subsequent CVC-related infections. An antibiotic flush/lock solution combined with heparin, however, probably halved the risk of subsequent CVC-related infections in people with cancer with long-term CVCs. Only mild adverse events associated with prophylactic antibiotic administration were reported. The strength of this review is that it provides an up-to-date overview of the efficacy of antibiotic prophylaxis for the prevention of CVC-related infections, a very serious and frequently observed problem in this vulnerable group. The certainty of the evidence was deemed moderate for both outcomes due to the limitations described in detail below. (**Summary of findings 1**)

Overall completeness and applicability of evidence

Clinical heterogeneity between the included studies was observed. In this review, we included studies that enrolled adults, children, or both. However, children and adults can differ greatly regarding their primary risk of CVC-related infections due to several factors, e.g. CVC type inserted, CVC duration, intensity of chemotherapy (de Jonge 2005). As the first meta-analysis included studies comprising mainly adults (**Analysis 1.1**), it is possible that the results of this meta-analysis are not generalizable to children. Similarly, the second meta-analysis (**Analysis 2.1**) included studies that were mainly conducted in children. Therefore, it is possible that the associated evidence, which indicates a beneficial effect of antibiotic flush/lock solutions, may not be generalizable to adults.

Furthermore, we included studies evaluating the risk of CVC-related infections in TIDs and TCVCs. However, TIDs might be associated with a lower risk of CVC-related infections. Unfortunately, we did not identify enough studies to perform subgroup analyses for these groups to draw separate conclusions about the eHicacy of prophylactic antibiotic use in people with either a TID or TCVC. One included study evaluated both participants with either TCVCs or TIDs (Handrup 2013), and two studies evaluated participants with TIDs only (Di Carlo 2011; Karanlik 2011). In Handrup 2013, which comprised mainly TIDs, long-term CVC-related infection rates in the control group were comparable to those reported in the TCVC studies. However, no early CVC-related infections occurred in the 108 participants who were included in the Di Carlo 2011 study, and only three early gram-positive CVC-related infections occurred in the Karanlik 2011 study's 404 participants.

Moreover, different antibiotic types were used in the included studies. These antibiotics possibly differ in terms of their efficacy against gram-positive CVC-

related infections. Most antibiotic types were only investigated by one or two studies, so it was not possible to perform proper subgroup analyses. Therefore, we were not able to conclude which antibiotic type might be the most appropriate for the prevention of gram-positive bloodstream infections in people with cancer.

The included studies authors' used different definitions for CRS. Some definitions included all positive blood cultures in participants with clinical symptoms of an infection (Barriga 1997; Daghistani 1996). This might result in the inclusion of non-CVC- related infections, resulting in questionable applicability of the evidence. Moreover, although the risk of infections is considered to be highest during the first 45 to 100 days after placement (Abbas 2004; Salzman 1995), few of the included studies defined or evaluated early CVC-related infections.

It should be noted that baseline infection rates might differ between institutions and that these should always be assessed before the introduction of antibiotic prophylaxis.

Quality of the evidence

Overall, we consider the evidence for the administration of antibiotics prior to CVC insertion to be of moderate-certainty. We downgraded the evidence due to the substantial high heterogeneity of the results (**Analysis 1.1**, caused by differences in the population (adults versus pediatrics, TIDs versus TCVCs), intervention (different antibiotic types, doses, frequency of administration), and outcome (CVC-related infection definitions) observed (**Summary of findings 1**).

We consider the evidence for the use of antibiotic flush/lock solutions to be of moderate-certainty. We downgraded the evidence due to clinical heterogeneity

caused by the factors as described above. Unfortunately, adverse events were not described by the majority of the studies and clinical heterogeneity was suspected, resulting in the quality of the evidence being assessed as low with regard to the incidence of adverse events (**Summary of findings 1**).

We deemed the overall risk of bias for all the included studies to be low. However, the trials frequently scored an unclear or high risk of bias for two of the domains (allocation and blinding). The majority of the studies did not describe their allocation or randomisation method, or both, possibly explained by the inclusion of a large number of studies performed before the year 2000. Additionally, in a majority of the included studies, the outcome assessors were not blinded. A blinded study is preferred since the evaluation of the positive blood cultures (i.e. CVC-related or related to another infection source) might be susceptible for bias if a non-blinded study design was used.

Potential biases in the review process

We attempted to reduce bias in this review by excluding studies in which long-term CVCs were already in situ. CVCs that were in situ prior to enrolment were likely to be pre-colonised with bacteria. Including such studies may have led to spurious findings, higher rates of CVC-related infections, and would have introduced another variable by which to adjust the results.

Some included studies reported culture-negative, gram-negative and gram-positive CVC-related infections (for example: Barriga 1997; Handrup 2013; Henrickson 2000; Karanlik 2011). In these instances, we only used the gram-positive data. It must be noted that the antibiotic group in Handrup 2013 and Henrickson 2000 also experienced lower rates of gram-negative CRS. Had we

included these data, the rate ratio would probably have more strongly favoured the antibiotic group in **Analysis 2.1**.

Like Snaterse 2010, we did not differentiate between flush and lock solutions in our meta-analyses as we considered them to have the same effect on the catheter lumen. Similarly, as also stated above, we combined the results of studies using various antibiotics with activity against gram-positive organisms into one meta-analysis.

Agreements and disagreements with other studies or reviews

The original review found weak evidence in favour of antibiotic flush or lock solutions and no evidence to support systemic antibiotics. There remains no demonstrable benefit from prophylactic intravenous antibiotics before long-term CVC insertion. However, evidence from our updated meta-analysis supports a beneficial effect of an antibiotic solution for flushing or locking long-term CVCs. In a 2010 review, Snaterse 2010 pointed out that the lack of specificity in the outcomes measured in many of the included studies may have led to an overestimation of the effect. Other reviews and meta-analyses all support a possible beneficial effect of an antibiotic and heparin flush or lock solution but conclude that the evidence is weak (Liu 2013; Liu 2014; Norris 2017; Sun 2020). We agree that more evidence is needed.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review, we have included one additional study. Flushing or locking long-term central venous catheters (CVCs) with an antibiotic solution appears to reduce gram-positive CVC-related infections experienced in people at risk of neutropenia through chemotherapy or disease. Due to

insufficient data it is not clear whether this applies equally to tunnelled CVCs and totally implantable devices, or equally to adults and children. The use of an antibiotic and heparin flush/lock solution may be of value in people who are at high risk and where baseline CVC infection rates are high. However, routine antibiotic administration, irrespective of risk, is likely to increase microbial resistance.

Implications for research

Although some of the included studies stratified risk groups (for example, neutropenic and non-neutropenic), none analysed these separately due to insufficient numbers. A large randomised controlled trial to investigate the role of prophylactic antibiotic lock solutions and to identify high-risk groups that are most likely to benefit from antibiotic prophylaxis is needed.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We expanded the types of studies to include lock solutions as well as flush solutions.
- Ceder van den Bosch joined as an author for the updated review in 2021 due to her contributions described in the Contributions of authors section.
- We extracted information about adverse events from the articles, as described in the included studies.
- We assessed the included studies with the Cochrane Risk of Bias version 1.0 tool ((RoB 1), in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).
- For studies investigating the efficacy of antibiotic flush/lock solutions, we assessed outcomes as rate ratios per 1000 CVC-days instead of risk ratios. We performed a new meta-analysis (including a new forest plot). This was done due to a high variety of CVC insertion days between participants.

- We updated the summary of findings table following the GRADE approach (Schünemann 2013).

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SUPPLEMENTARY FILES

Characteristics of included studies Ordered by study ID

Barriaga 1997

Study characteristics		
Methods	Double-blind randomisation; inclusion period: May 1991 to February 1994	
Participants	Adults and children with various malignancies, mainly leukaemia, with only single lumen external TCVCs (N = 83)	
Interventions	Vancomycin 25 ug/ml and heparin 25 units/ml flush versus heparin-only flush 25 units/ml	
Outcomes	CRS defined as ≥ 1 positive blood culture obtained from the CVC or peripheral.	
Notes	A difference was stated in neutropenia and non-neutropenia episodes.	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Low risk	Blind randomisation to one of four colour-coded ampoules by pharmacy
Blinding (performance bias and detection bias) Catheter-related sepsis	Low risk	Double-blinded
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	All participants included in the analyses and no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Daghistani 1996

Study characteristics		
Methods	Double-blind randomisation; inclusion period: April 1992 to October 1993	
Participants	Adults and children < 22 years oldwith various malignancies, mainly leukaemia receiving TCVCs (N=61)	
Interventions	Vancomycin 25 ug/ml, amikacin 25 ug/ml andheparin 100 units/ml flush versus heparin-only 100 units/Ml flush	
Outcomes	CRS defined as a febrile episode or ≥ one central and peripheral positive blood culture, or both.	
Notes	The only study in which amikacin was added.	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random order was used. Three participants were randomised in an unblinded fashion, but these outcomes were separately described so the risk of bias was scored low.
Allocation concealment (selection bias)	Low risk	Participants were assigned to either A or B by a computer-generated random order, unblinding was performed at the conclusion of the study.
Blinding (performance bias and detection bias) Catheter-related sepsis	Low risk	Double-blinded
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	Not all participants were included in the analyses.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Di Carlo 2011

Study characteristics		
Methods	Open-label randomisation; consecutive allocation by sealed envelopes; inclusion period: January 2004 to December 2008	
Participants	Adults with various malignancies, mainly colon tumours, receiving a TID (N = 108)	
Interventions	Ceftazidime 1 g intravenous 10 min before skin incision versus no antibiotics	
Outcomes	Local infections (superficial and deep) defined as temperature of > 37.5°C, white blood cell count of > 10 x 10/L, and one or more of: pain, swelling, redness, or heat	
Notes	Outcomes assessed for 30 days after insertion.	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sealed envelopes were used but method of random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation by sealed envelopes opened 30 minutes before surgery, but unclear if the researchers developed and monitored the allocation process to preserve concealment.
Blinding (performance bias and detection bias) Catheter-related sepsis	High risk	No blinding
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	All participants included in the analyses and no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the re- sults section.
Other bias	Low risk	No other source of bias identified.

Handrup 2013

Study characteristics	
Methods	Open-label randomisation; computer generated randomisation code in blocks of 20; inclusion period: April 2008 to December 2010
Participants	Children with various malignancies, 49% haematological and 51% solid tumours, receiving 129 TCVCs; 113 TIDs and 16 external CVCs (N = 112)
Interventions	Taurolidine 1.35%, sodium citrate 4% and heparin 100 units/ml lock versus heparin 100 units/ml lock
Outcomes	• CRS defined as growth of microbes from a blood sample drawn from a CVC ≥ 2 hours before microbial growth was detected in a blood sample obtained from a peripheral vein OR if peripheral cultures were not obtained/negative: (1) a recognised pathogen cultured from ≥ one blood cultures; or (2) a common skin contaminant cultured from ≥ two blood cultures, both drawn at separate occasions. In both cases, the cultured organism must not be related to pathogens identified at other infection sites • Adverse events
Notes	Followed up (CVCs in situ) from 12 to 1176 days Type of CVC was a risk factor for CRS (TIDs were less likely to get infected than external CVCs)

Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code 1:1 in randomisation blocks of 20
Allocation concealment (selection bias)	Low risk	Allocation concealment method not described.
Blinding (performance bias and detection bias) Catheter-related sepsis	High risk	No blinding
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	One participant was excluded from the analysis since he/she dropped out on participant request after 1 day; this was judged as justifiable, no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Henrickson 2000

Study characteristics	
Methods	Double-blind randomisation; stratified for risk groups; inclusion period: October 1993 to May 1997
Participants	Children with acute lymphatic leukaemia (4%), solid tumours (40%) or requiring bone marrow transplantation, or both, receiving 153 external TCVCs (N = 126)
Interventions	Vancomycin 25 ug/ml and heparin 100 units/ml flush (N = 28) (+ ciprofloxacin 2 ug/ml N = 34) versus heparin-only flush 100 units/ml
Outcomes	CRS defined as positive blood specimens obtained from the TCVC immediately before beginning antibiotic therapy, whereas blood specimens obtained from a peripheral vessel are culture-negative, or the concentration of bacteria isolated from the TCVC is ≥ 10 times greater than the concentration of one bacterium isolated from a simultaneously sampled peripheral vessel.
Notes	

Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation with 1:1 assignment and balanced between risk groups, but method of random sequence generation not described.
Allocation concealment (selection bias)	Low risk	Blind randomisation by trial pharmacy
Blinding (performance bias and detection bias) Catheter-related sepsis	Low risk	Double-blinded
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	One participant died before receiving the first lock and was not included in the analysis, but this was judged as justifiable; no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Karanlik 2011

Study characteristics		
Methods	Double-blind randomisation; inclusion period: September 2008 to December 2009	
Participants	People with cancer with different malignancies receiving TIDs (N = 404)	
Interventions	Cefazolin (1 g) versus sterile saline intravenously	
Outcomes	Local infections defined following the Centers for Disease Control and Prevention Guidelines for Surgical Site Infections (SSI) (Mangram 1999).	
Notes		
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	20-block randomisation by a computer-generated code, by a nurse who also prepared the sealed antibiotic or placebo syringes.
Allocation concealment (selection bias)	Low risk	Randomisation by trial nurse, who was unaware of the research in progress and was never involved in surgery, data collection or participant follow-up.
Blinding (performance bias and detection bias) Catheter-related sepsis	Low risk	Participant and surgeon who inserted the CVC and followed up the participants were blinded.
Incomplete outcome data (attrition bias) Catheter-related sepsis	High risk	10 Participants who were not available for all follow-up evaluations were contacted by telephone, 5 participants had second surgical procedures immediately after obtaining radiographs postoperatively because of malposition. None of these participants developed wound infections, but all were excluded from the analysis.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Lim 1993

Study characteristics		
Methods	Randomisation, probably open-label; method of randomisation not described; inclusion period:May 1989 to July 1990	
Participants	Adults with haematological malignancies receiving double lumen external TCVCs (N = 88) Baseline characteristics reported without a significant difference between the groups	
Interventions	Teicoplanin 400 mg before CVC insertion versus no antibiotics	
Outcomes	CRS defined as positive blood cultures from the CVC or similar isolates from the peripheral veins in the presence of clinical symptoms related to an infection, or both.	
Notes	All episodes of CVC related infections occurred in people who were neutropenic.	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described.
Blinding (performance bias and detection bias) Catheter-related sepsis	High risk	No blinding
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	All participants included in the analyses and no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Ljungman 1997

Study characteristics		
Methods	Randomisation, probably open-label; method of randomisation not described; study dates not described	
Participants	Adults with lymphoma, leukaemia or requiring bone marrow transplantation, or both, receiving TCVCs (N = 66)	
Interventions	Teicoplanin 300 to 500 mg (depending on weight) prior to insertion and 24 hrs after insertion versus no antibiotics	
Outcomes	CRS defined as ≥ 1 positive blood culture with recognised pathogens OR ≥ 2 positive blood cultures with common commensals from separate sites.	
Notes	At interim analysis, the preset efficacy could not be met; therefore the study was stopped.	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described.
Blinding (performance bias and detection bias) Catheter-related sepsis	High risk	No blinding
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	One participant was lost to follow-up and was not included in the analysis, but this was judged as justifiable; no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	High risk	The study was stopped after an interim analysis since the preset efficacy estimation could not be met with the maximum estimated inclusion of 220 participants.

Rackoff 1995

Study characteristics		
Methods	Double-blind randomisation; inclusion period: September 1991 to June 1992	
Participants	Children with various malignancies receiving cuffed external TCVCs (N = 55) Analysis was of the data from the children with cancer only. Total group consisted of 63 participants, of whom 8 received total parenteral nutrition for bowel disorders.	
Interventions	Vancomycin 25 ug/ml, and heparin 100 units/ml flush versus heparin-only 100 units/ml flush	
Outcomes	CRS defined as blood specimen obtained from a peripheral vein which had < 10% of the number of colonies compared to a specimen obtained from a CVC, with low colony count cultures excluded.	
Notes		
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described.
Blinding (performance bias and detection bias) Catheter-related sepsis	High risk	No blinding
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	All participants included in the analyses and no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Ranson 1990

Study characteristics		
Methods	Double-blind randomisation; study dates not described	
Participants	Adults, divided into two groups (1) people diagnosed with acute leukaemia or undergoing bone marrow transplantation, (2) people with all other malignancies, receiving a total of 72 TCVCs (N = 98)	
Interventions	Vancomycin 500 mg (prior to insertion and aJer positioning of the CVC) intravenously versus 0.9% saline (prior to insertion and aJer positioning of the CVC) intravenously	
Outcomes	CVC-related infections in the first 30 days defined as: (1) coagulase-negative staphylococci bacteraemia, defined as fever with positive cultures with coagulase-negative staphylococci resolving after an- tibiotic therapy or CVC removal, (2) vancomycin-responsive fever defined, as fever with negative cul- tures resolved on institution of vancomycin or CVC removal and (3) tunnel/exit-site infection, defined as tunnel/exit-site infection requiring removal or antibiotic therapy, or more than one of these.	
Notes		
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Low risk	Randomisation and drug reconstitution performed by pharmacy.
Blinding (performance bias and detection bias) Catheter-related sepsis	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) Catheter-related sepsis	High risk	Not all randomised participants were included in the analyses.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Schwartz 1990

Study characteristics		
Methods	Double-blind randomisation; inclusion period: May 1987 to October 1988	
Participants	Children with various malignancies receiving 53 TCVCs (N = 45)	
Interventions	Vancomycin 25 ug/ml and heparin 100 units/ml flush versus heparin only 100 units/ml flush	
Outcomes	CRS defined as a specimen obtained from a peripheral vein with < 10% of the number isolated from a blood specimen drawn through the TCVC without evidence of an exit-site infection due to the same organism.	
Notes	Statistics on the number of children not CVCs Quantitative blood cultures	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described.
Blinding (performance bias and detection bias) Catheter-related sepsis	Low risk	Double-blinded
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	All participants included in the analyses and no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

Vassilomaniakis 1995

Study characteristics		
Methods	Randomisation; randomisation by cards in closed envelopes; study dates not described	
Participants	Adults with various malignancies, mainly solid receiving 46 double lumen external TCVCs (N = 40)	
Interventions	Vancomycin 500 mg (1 h prior to insertion, 6 and 12 h afterwards) versus no antibiotics	
Outcomes	CRS defined as similar isolates cultured from the CVC as peripheral in a febrile participant.	
Notes	Only initially randomised	
Risk of bias		
Bias	**Author's judgements**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation by cards in sealed envelopes, but unclear if the researchers developed and monitored the allocation process to preserve concealment.
Blinding (performance bias and detection bias) Catheter-related sepsis	High risk	No blinding
Incomplete outcome data (attrition bias) Catheter-related sepsis	Low risk	All participants included in the analyses and no missing data.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods were also the outcomes described in the results section.
Other bias	Low risk	No other source of bias identified.

CRS;catheter-related sepsis, TCVC;tunnelled central venous catheter, CVC;central venous catheter, TID;totally implantable device

Characteristics of excluded studies Ordered by study ID

Study	Reason for exclusion
Abdelkefi 2005	Ineligible intervention: low-dose heparin prophylaxis not antibiotic prophylaxis to reduce non-tun- nelled CVC-related infections in haemato-oncological disease.
Akyuz 2012	Ineligible population: study did not specifically include people with newly-inserted TCVCs
Al Sibai 1987	Ineligible study design: the antibiotic use and duration were at the discretion of the attending physician, and the results were retrospectively analysed.
Carratala 1999	Ineligible population: participants with non-tunnelled catheters were included.
Chambers 2005	Ineligible intervention: sustained release chlorhexidine dressings (not antibiotics) versus standard dressings for TCVCs in neutropenic people.
Chatzinikolaou 2003a	Ineligible study design: prospective cohort study.
Chatzinikolaou 2003b	Ineligible population and intervention: participants with non-tunnelled catheters with a short dwell time and impregnated catheters were used as intervention.
Dawson 2000	Ineligible study design: no randomisation performed and intervention period was compared to pre-intervention period.
Dumichen 2012	Ineligible intervention: the lock solution was not used immediately after TCVC insertion in most participants (given up to 2 months after insertion in some cases).
Ferreira Chacon 2011	Ineligible population: participants with not newly inserted TCVCs.
Fourcade 2001	Ineligible study design and ineligible population: not an RCT, comparison with historical control and participants with non-tunnelled catheters.
Garland 2005	Ineligible population: concerns neonates with non-tunnelled catheters.
Gudiol 2020	Ineligible population: people with a non-tunnelled CVC, and due to the inclusion of people without a newly-inserted CVC.
Hanna 2004	Ineligible population: participants with non-tunnelled catheters and not newly-inserted tunnelled catheters.
Hitz 2012	Ineligible intervention: TCVCs coated with a thrombogenic coating versus no coating.
Jaeger 2005	Ineligible population and intervention: participants with non-tunnelled catheters, chlorhexi- dine/sulphadiazine impregnated CVCs versus standard CVCs.
Longo 2017	Ineligible population: participants most likely did not receive newly inserted CVCs, the authors were contacted and verified that not all patients received newly inserted CVCs.
Ocete 1998	Ineligible study design and population: not blinded study design, only newborns were included re- ceiving parenteral nutrition and no tunnelled catheters were used.
Raad 1998	Ineligible study design and population: cross-over study, participants with non-tunnelled catheters, participants with melanoma on interleukin-2 treatment and therefore very specific and at a high risk of infection.
Raad 2005	Ineligible intervention: dalbavancin versus vancomycin for the treatment of adults with CRBSIs.
Rubie 1995	Ineligible study design: this study was not randomised and the results were retrospectively analysed.
Scaife 2010	Ineligible study design: retrospective study
Schierholz 2010	Ineligible intervention and population: participants with non-tunnelled antibiotic-releasing CVCs.
Simon 2008	Ineligible study design: a prospective cohort study.

CRS; catheter-related sepsis, BMT; bone marrow transplant, TCVC; tunnelled central venous catheter, TPN; total parenteral nutrition, CVC; central venous catheter, TID; totally implantable device, CRBSI; catheter-related blood stream infection, RCT; randomised controlled trial.

Characteristics of ongoing studies Ordered by study ID

Chambrier 2014

Study characteristics	
Study name	Primary Prevention of Infections Related to Chambers Implantable Catheter by a Taurolodine Lock in Patients With Cancer Receiving Parenteral Nutrition
Methods	Randomised triple-blinded
Participants	People with solid cancer with a totally implantable device and receiving parenteral nutrition (n = 70)
Interventions	Taurolidine 1.35% and citrate 4.0% versus saline lock solution
Outcomes	*CVC related infections
Starting date	01-2015
Contact information	Cécile Chambrier, cecile.chambrier@chu-lyon.fr
Notes	Recruitment status unknown

van den Bosch 2017

Study characteristics	
Study name	CATERPILLAR-study
Methods	Randomised; outcome assessors blinded; inclusion period: ongoing since October 2020
Participants	Children with cancer with various malignancies receiving a TID or external tunnelled CVC (N = 462)
Interventions	Taurolidine 1.35%, citrate 4.0%, and heparin 100 units/ml versus heparin 100 units/ml lock solutions
Outcomes	CRS defined as either one recognized pathogen or >1 common commensals cultured in a participant with clinical symptoms and no other source of infection. Excluding mucosal-barrier injury lab- oratory confirmed bloodstream infections.
Starting date	27-10-2020
Contact information	van den Bosch, MD PhD-Candidate C.H.vandenBosch-4@prinsesmaximacentrum.nl
Notes	

CVC; central venous catheter

Comparison 1 Antibiotics versus non-antibiotics prior to long-term CVC insertion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 CVC-related infections				
1.1.1 Vancomycin	6	756	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.43]
1.1.2 Teicoplanin	2	99	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.05, 3.52]
1.1.3 Ceftazadime	2	145	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.23, 2.97]
1.1.4 Cefazolin	1	108	Risk Ratio (M-H, Random, 95% CI)	Not estimable

CVC; central venous catheter

Comparison 2 Antibiotics versus non-antibiotics prior to long-term CVC insertion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 CVC-related infections				
2.1.1 Vancomycin	6	488	Rate Ratio (IV, Random, 95% CI)	0.47 [0.26, 0.85]
2.1.2 Vancomycin (+/- ciprofloxacin)	3	183	Rate Ratio (IV, Random, 95% CI)	0.66 [0.19, 2.33]
2.1.3 Vancomycin and amikacin	1	115	Rate Ratio (IV, Random, 95% CI)	0.27 [0.06, 1.31]
2.1.4 Taurolidine	1	61	Rate Ratio (IV, Random, 95% CI)	1.02 [0.06, 16.34]

CVC; central venous catheter

Table 1a Criteria for the assessment of methodological quality of included studies (van Tudler 1997)

Item ID	Description	Implementation
Participant selection		
a	Were the eligibility criteria specified?	Participant inclusion/exclusion criteria must have been described appropriately according to the reviewer.
b1	Was a method of randomisation applied?	A random (unpredictable) allocation must have been applied.
b2	Was the treatment allocation concealed?	Allocation should have been performed by an independent person not responsible for determining eligibility for inclusion.
c	Were the groups similar at baseline with regard to the most important prognostic indicators?	Groups must be similar at baseline with regard to at least three of the four prognostic indicators of age sex duration of symptoms and value of main outcome measures.
Intervention		
d1	Was the experimental intervention explicitly described?	Adequate description of the experimental intervention so that treatment can be replicated
d2	Was the control intervention explicitly described?	Adequate description of the control intervention so that treatmentcan be replicated
e	Were co-interventions avoided orsimilar for all groups?	Co-interventions should either have been avoided in the trial de-sign or be similar in the 2 groups.
f	Was the participant blinded for the intervention?	Adequate information about blinding must have been provided.
Outcome measurement		
g	Was the outcome assessor blindedto the intervention?	Adequate information about blinding must have been provided.
h	Were the outcome measures relevant?	At least one of the following outcome measures must be included: catheter-related sepsis, exit infections, tunnel infections and time to first infection.
i	Were complications described?	Any adverse events should be noted.
j	Was the dropout loss to follow updescribed and acceptable?	Included people who did not complete the follow up period or werenot included in the analysis should be described; if the percentage of dropouts is less than 20% a '+' is scored.
k	Was a follow-up measurement per-formed?	Outcome assessment after randomisation
l	Was the timing of the outcomesimilar for all groups?	Timing of outcome assessment should have started from the moment of treatment allocation and be identical for all intervention groups and all important outcome measures.

Table 1b Criteria for the assessment of methodological quality of included studies (van Tudler 1997)

Item ID	Description	Implementation
Statistics		
m	Was the sample size described foreach group?	Sample size should have been presented for each group at randomisation and for the most important outcome measures.
n	Did the analysis include an intention-to-treat analysis?	For all randomised people the most important moments of effectmeasurement should have been reported.
o	Were point estimates and measures of variability presented forthe primary outcome measures?	For continuous data mean, median, standard deviation with 95 %confidence interval should be presented. For nominal and ordinaloutcomes the number of people to whom the outcome measure applies and the total number of people must be presented.

Table 2 Internal validity scores for van Tudler 1997 methodological quality criteria (items b1, b2, c, e, f, g, j, l, n)

Reference	b1	b2	c	e	f	g	j	l	n
Karanlik 2011	+	+	+	+	+	+	+	+	-
Vassilomaniakis 1995	+	-	+	+	-	-	+	+	+
Ranson 1990	+	+	+	+	+	+?	+	+	+?
Lim 1993	+	-	+	+	-	+?	+	+	+
Barriga 1997	+	+	+	+	+	+	+	+	+
Rackoff 1995	+	+	+	+	+	+	+	+	+
Schwartz 1990	+	+	+	+	+	+	+	+	+
Henrickson 2000	+	+	+	+	+	+	+	+	+
Daghistani 1996	+	+	+	+	+	+?	+	+	+
Ljungman 1997	+	-	-	-	-	-	+	+	+
Di Carlo 2011	+	+	+	+	-	-	+	+	?
Handrup 2013	+	-	+	+	-	-	+	+	+

Table 3 External validity scores for van Tudler 1997 methodological quality criteria (items a, d1, d2, h, i, k, m, o)

Reference	a	d1	d2	h	i	k	m	o
Karanlik 2011	+	+	+	+	-	+	+	+
Vassilomaniakis 1995	+	+	+	+?	-	+	+	+
Ranson 1990	+	+	+	+?	-	+	+	+
Lim 1993	+	+	+	+	-	+	+	-
Barriga 1997	+	+	+	+	-	+	+	+
Rackoff 1995	+	+	+	+	-	+	+	+
Schwartz 1990	+	+	+	+	-	+	-	+
Henrickson 2000	+	+	+	+	-	+	+	+
Daghistani 1996	+	+	+	+	-	+	+	+
Ljungman 1997	+	+	+	+	-	+	+	+
Di Carlo 2011	+	+	+	+	-	+	+	+
Handrup 2013	+	+	+	+	-	+	+	+

Appendix 1 Search strategy for CENTRAL

#1 MeSH descriptor: [Neoplasms] explode all trees
#2 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or oncolog* or leukemia* or leukaemia* or lymphoma*
or metasta* or bone marrow transplant*)
#3 #1 or #2
#4 MeSH descriptor: [Catheters] explode all trees
#5 MeSH descriptor: [Catheterization] explode all trees
#6 MeSH descriptor: [Catheter-Related Infections] this term only
#7 (catheter* or central venous line* or central venous device* or CVC* or TCVC*)
#8 #4 or #5 or #6 or #7
#9 MeSH descriptor: [Antibiotic Prophylaxis] this term only
#10 MeSH descriptor: [Anti-Infective Agents] explode all trees
#11 MeSH descriptor: [Gram-Positive Bacterial Infections] explode all trees and with qualifiers: [Drug therapy - DT]
#12 antibiotic*
#13 #9 or #10 or #11 or #12
#14 #3 and #8 and #13

Appendix 2 Search strategy for MEDLINE

MEDLINE Ovid
1 exp Neoplasms/
2 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or oncolog* or leukemia* or leukaemia* or lymphoma* or metasta* or bone marrow transplant*).mp.
3 1 or 2
4 exp Catheters/
5 Catheter-Related Infections/
6 exp Catheterization/
7 (catheter* or central venous line* or central venous device* or CVC* or TCVC*).mp.
8 4 or 5 or 6 or 7
9 Antibiotic Prophylaxis/
10 exp Anti-Infective Agents/
11 exp Gram-Positive Bacterial Infections/dt [Drug Therapy]
12 antibiotic*.mp.
13 9 or 10 or 11 or 12
14 randomised controlled trial.pt.
15 controlled clinical trial.pt.
16 randomized.ab.
17 placebo.ab.
18 clinical trials as topic.sh.
19 randomly.ab.
20 trial.ti.
21 14 or 15 or 16 or 17 or 18 or 19 or 20
22 3 and 8 and 13 and 21
23 exp animals/ not humans.sh.
24 22 not 23
Key: mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt = publication type
ab = abstract
sh = subject heading
ti = title

Appendix 3 Search strategy for EMBASE

EMBASE Ovid
1 exp neoplasm/
2 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or oncolog* or leukemia* or leukaemia* or lymphoma* or metasta* or bone marrow transplant*).mp.
3 1 or 2
4 exp catheter/
5 catheter infection/
6 catheterization/
7 (catheter* or central venous line* or central venous device* or CVC* or TCVC*).mp.
8 4 or 5 or 6 or 7
9 antibiotic prophylaxis/ 10 exp antiinfective agent/
11 Gram positive infection/dt [Drug Therapy]
12 antibiotic*.mp.
13 9 or 10 or 11 or 12
14 crossover procedure/
15 double-blind procedure/
16 randomised controlled trial/
17 single-blind procedure/
18 random*.mp.
19 factorial*.mp.
20 (crossover* or cross over* or cross-over*).mp.
21 placebo*.mp.
22 (double* adj blind*).mp.
23 (singl* adj blind*).mp.
24 assign*.mp.
25 allocat*.mp.
26 volunteer*.mp.
27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 3 and 8 and 13 and 27
29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
30 28 not 29
key: mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

CHAPTER 7

The efficacy of taurolidine containing lock solutions for the prevention of central-venous-catheter-related bloodstream infections: a systematic review and meta-analysis

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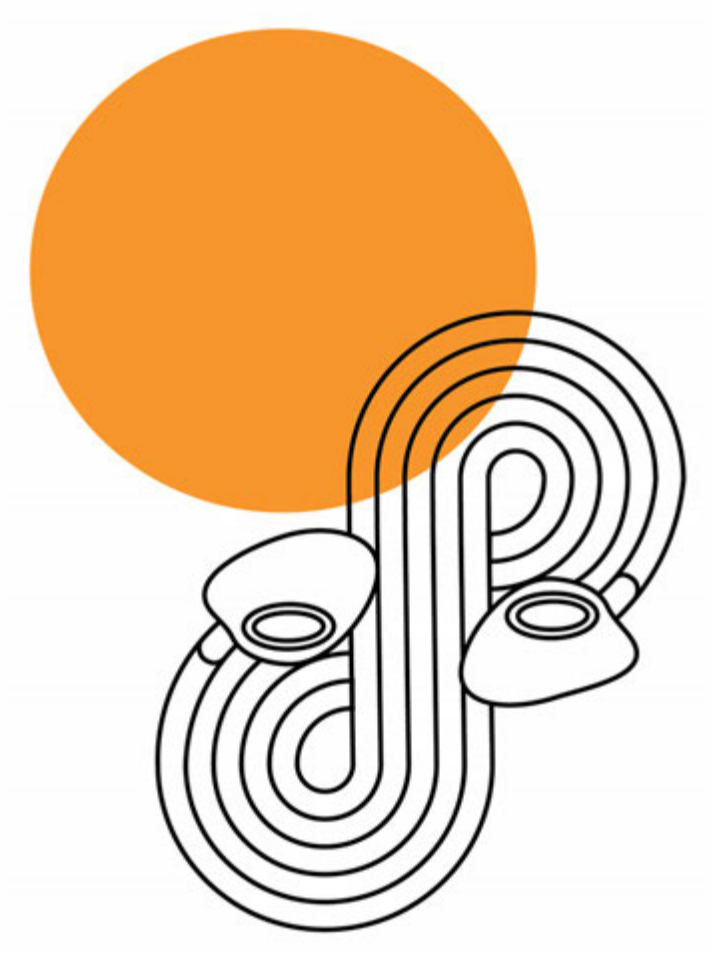


ABSTRACT

Background The incidence of central venous catheter (CVC)-related bloodstream infections is high in patients requiring a long-term CVC. Therefore, infection prevention is of the utmost importance.

Aim To provide an updated overview of randomized controlled trials (RCT) comparing the efficacy of taurolidine containing lock solutions (TL) to other lock solutions for the prevention of CVC-related bloodstream infections in all patients populations.

Methods On 15 February 2021, PubMed, Embase and The Cochrane Library were searched for RCTs comparing the efficacy of TLs for the prevention of CVC-related bloodstream infections with other lock solutions. Exclusion criteria were non-RCTs, studies describing <10 patients and studies using TLs as treatment. Risk of bias was evaluated using the Cochrane Risk of Bias 2 tool. A random effects model was used to pool individual study incidence rate ratios (IRR). Subgroup analyses were performed based on the following factors: CVC indication, comparator lock and bacterial isolates cultured.

Findings A total of 14 articles were included in the qualitative synthesis describing 1219 haemodialysis, total parenteral nutrition and oncology patients. The pooled IRR estimated for all patient groups together (nine studies; 918 patients) was 0.30 (CI95% 0.19-0.46), favouring the TLs. Adverse events (ten studies; 867 patients) were mild and scarce. The quality of the evidence was limited due to a high risk of bias and indirectness of evidence.

Conclusion The use of TLs might be promising for the prevention of CVC-related bloodstream infections. Large scale RCTs are needed to draw firm conclusions on the efficacy of TLs.

INTRODUCTION

Central venous catheters (CVC) are essential for patients requiring long-term central venous access. CVCs however, are associated with high rates of CVC-related bloodstream infections, which mainly depend on the patient group observed and CVC type inserted. (10, 21, 22) CVC-related bloodstream infections often result in hospital admissions for the administration of intravenous antibiotics, postponement of treatment for primary disease, early CVC removal, or intensive care unit admissions due to severe sepsis. (11) Prevention of CVC-related bloodstream infections is therefore of the utmost importance. (23, 24)

The use of prophylactic antimicrobial lock solutions with or without the addition of an anticoagulant have been suggested as a method for the prevention of CVC-related bloodstream infections by preventing biofilm formation, killing bacteria and/or the inhibition of bacterial growth. However, the efficacy of these antimicrobial lock solutions is still under debate. Currently, in many hospitals, heparin-only lock solutions (HL) are used to maintain CVC patency. Heparin locks however, do not have antimicrobial properties and the current available evidence even suggests that the use of regular saline locks might be as effective as heparin locks to maintain CVC patency. (25-27) The results of a consensus meeting held in 2016 report that a lock solution containing taurolidine and/or citrate appears to be the most promising lock solution for the prevention of CVC-related bloodstream infections. (27) Taurolidine and citrate have both antimicrobial, anti-biofilm and anticoagulant properties without reported antimicrobial resistance. (27, 28) Taurolidine causes a chemical reaction with the bacterial cell wall, endotoxins and exotoxins, resulting in irreversible damage to the bacteria and inhibition of bacterial pathogenicity and surface adhesion of bacteria. (15, 29-31)

Currently, it is not yet clear how effective taurolidine containing lock solutions (TL) are for the prevention of CVC-related bloodstream infections and which patient populations are most likely to benefit from this lock solution. (27) Previous meta-analyses have been performed on this topic. (32-37) However, the majority of these meta-analyses did not include studies performed in all different patient groups. The most recent systematic review and meta-analysis including randomized controlled trials (RCT) investigating the efficacy of TLs in all patient populations was published in 2014. (33) Liu 2014 included three RCTs and observed a possible beneficial effect of TLs for the prevention of CVC-related bloodstream infections. They concluded that further RCTs need to be performed to confirm the results. (33) We identified eleven additional articles that were published since then or were not included by Liu 2014. Therefore, this systematic review and meta-analysis was conducted to give an updated overview of all the available evidence and draw more robust conclusions concerning the efficacy of TLs for the prevention of CVC-related bloodstream infections in several patient populations.

METHODS

Search strategy and selection process

A systematic search in PubMed, The Cochrane Library and Embase was performed on 15 February 2021. All databases were searched from inception to 15 February 2021. Search strings were developed with the assistance of a medical librarian and contained terms and synonyms for taurolidine and infections. [**Appendix 1**] The systematic screening was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines of 2009. (38) After removal of the duplicates, a title/abstract and full-text screening was performed independently by two authors (C.B. and B.J.) using pre-defined in- and exclusion criteria. All original RCTs comparing the efficacy of TLs with any other lock solution for the prevention of CVC-related bloodstream infections in all patient populations

were included. Exclusion criteria were non-RCTs, studies describing <10 patients and studies using TLs as treatment instead of prevention. The search was finalized by hand searches and snowballing. Disagreements were resolved by discussion. [**Figure 1**]

Data collection process

Data from each study was extracted and double checked by two authors (C.B. and B.J.). Our primary outcome was the pooled incidence rate ratio (IRR) comparing the efficacy of TLs to non-antibiotic lock solutions in terms of the incidence rates (IR) of CVC-related bloodstream infections per 1000 CVC-days. CVC-related bloodstream infection events were scored following the definitions stated in the original article, but must at least include a positive bloodculture in a patient with a CVC in situ.

Secondary outcomes were the incidence of adverse events (i.e. side-effects reported during lock replacement) and malfunction events (i.e. inability to flush and/or aspirate, thrombosis, administration of thrombolytics). Other data collected: first author, year of publication, study design, patient characteristics (number of patients included, CVC indication, age, in- or outpatient setting during CVC use, previous infections, and the administration of antibiotic prophylaxis), CVC characteristics (number of CVCs inserted, newly inserted CVCs, type, dwell time), lock characteristics (type, dose, frequency, method of removal), and CVC-related bloodstream infection characteristics (number of events following the definition reported in the article, CVC-related bloodstream infection definition and number of Gram-positive and Gram-negative bacterial isolates cultured). In case of missing or unclear data, the authors were contacted by email. If no reaction was obtained, the data was reported as missing.

Risk of bias and applicability

The risk of bias per study was evaluated and double checked by two authors (C.B. and B.J.) using the Risk of Bias (RoB) 2.0 tool for randomized controlled trials. (39) Additionally, the applicability of the included studies was assessed per PICOS (Population, Intervention, Comparator, Outcomes, and Setting) domain. Each domain was assessed for low (+), high (-), or moderate (+/-) applicability concerns. (40)

Synthesis methods

The incidence rate ratio (IRR) along with the 95% confidence interval (CI) was used to compare the IRs of CVC-related bloodstream infections per 1000 CVC-days between the two study groups. If the IRR was not given, the IRR was estimated based on the total number of events and CVC-days reported. The exact confidence limit for the IRRs were computed based on the polynomial algorithm for person time data. (41, 42)

RCTs comparing TLs with other non-antibiotic locks were used in the meta-analyses using IRRs along with their 95%CIs. Additional meta-analyses were planned focusing on (1) the indication for CVC insertion (total parenteral nutrition (TPN), haemodialysis, oncology treatment), (2) the bacterial isolates cultured, (3) age per indication for CVC insertion (pediatrics and adults), and (4) the comparator lock used (i.e. HL, saline, citrate). A meta-analysis was performed if ≥3 studies could be included. Sensitivity analyses were performed excluding studies where (1) antibiotic prophylaxis use was reported by the authors, (2) citrate locks (CL) (since citrate also has anti-biofilm properties) were used as a comparator, (3) non-tunneled CVCs were included, and (4) only high risk patients (i.e. history of ≥1 CVC-related bloodstream infections) were included in one or both groups. A random effects model was employed to pool the IRR in order to estimate an overall IRR and its 95%CI. An overall test on heterogeneity between the studies was performed for each meta-analysis (I^2).

The heterogeneity was considered "serious" if the I^2 was >50% and "very serious" if the I^2 was >80%. Cochrane Review Manager Version 5.4 was used for the statistical analysis. (43)

Reporting bias and quality of evidence assessment

To assess the presence of reporting bias, a funnel plot was used, where the estimate of the reported effect size was plotted against a measure of precision (standard error of log rate ratio). The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach for all outcomes and subgroup analyses performed. (40)

RESULTS

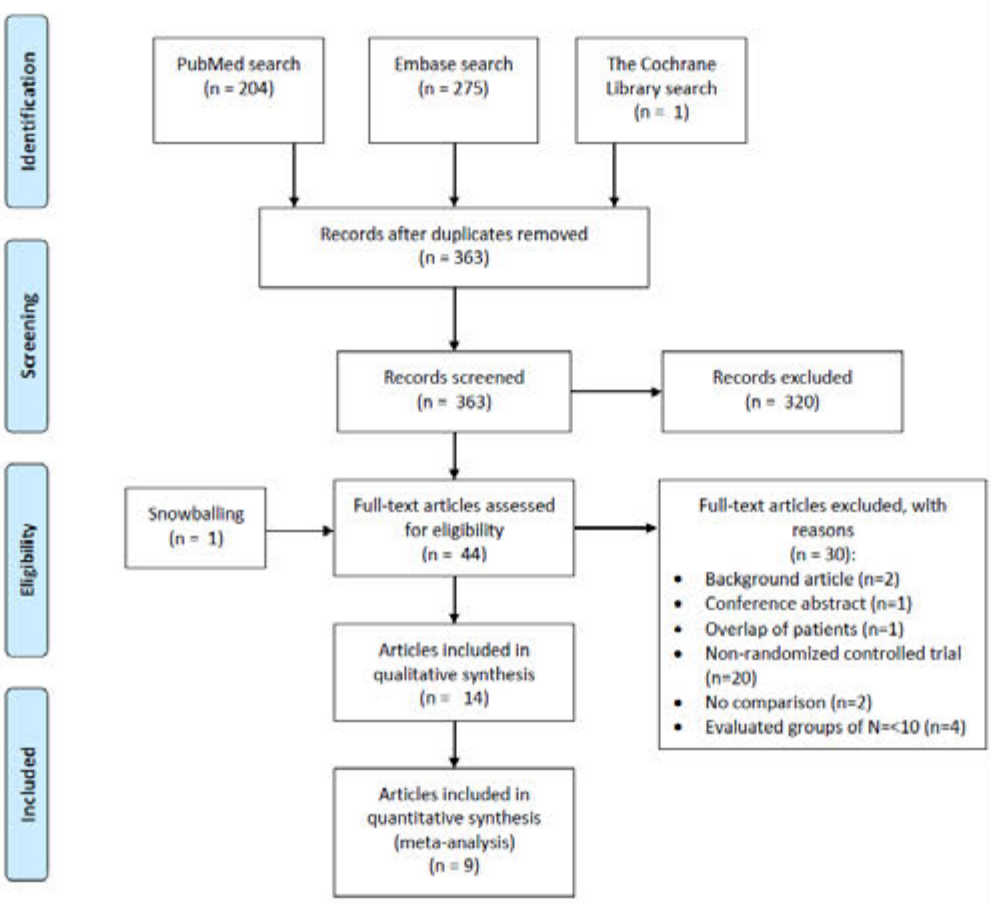
Study selection process

A total of 480 articles were identified from PubMed (n=204), Embase (n=275) and The Cochrane Library (n=1). After duplicate removal, 363 articles were included for the title and abstract screening. Three conflicts were observed afterwards, which were resolved by discussion. A total of 44 articles were eventually included in the full-text screening, of which one article was added after snowballing. Thirty articles were excluded after full-text screening. (44-73) Fourteen articles (1219 patients) were included in the qualitative synthesis, nine (918 patients) of these articles were included in the quantitative synthesis. (74-87) [**Figure 1**]

Study characteristics

Of the 14 included articles, five (36%) had a blinded study design, of which four had a double-blinded design. (78, 83-86) Two (14%) non-blinded studies used an assessor-masked design to avoid bias. (79, 81) The 14 included articles described patients receiving haemodialysis (n=5, 36%) or TPN (n=4, 29%), oncology patients (n=4, 29%), or a combination of these (n=1, 7%). The majority, described patients

Figure 1 PRISMA flow diagram



with tunneled CVCs and/or vascular access ports (VAP) (n=12, 86%). A small number of articles discussed also or only patients with non-tunneled CVCs (n=6, 43%).

During three (21%) studies the use of prophylactic antibiotics during the study period was reported; cotrimoxazole for the prevention of *Pneumocystis jirovecii* pneumonia (Dumichen 2012), nasal mupirocin ointment before CVC insertion for the prevention of *Staphylococcus aureus* infections (Winnicki 2017), and systemic antibiotic prophylaxis not further specified (Gudiol 2020). (76, 78, 85)

Most studies compared TLs with or without the addition of heparin and/or citrate to regular saline or heparin locks (n=12, 86%), and one study used CLs as a comparator. Another study used gentamicin locks as a comparator, this study was therefore not included in the meta-analyses. [**Table 1**]

Risk of bias and applicability

A "moderate" to "high" risk of bias was observed in a majority of the studies, mainly due to open-labelled study designs, inappropriate definitions of CVC-related bloodstream infections and/or confounding factors [**Figure 2**].

The applicability per evaluated domain was scored as "moderate" or "high" concerns for some studies, since patients with previous CVC-related bloodstream infections or not newly inserted CVCs were included, the comparator lock was not described, and/or the CVC-related infection definition was inappropriate [**Figure 2**].

Results of individual studies

Many studies observed an IRR per 1000 CVC-days of less than 1.00, suggesting a beneficial effect associated with the TLs compared to other lock solutions for the prevention of CVC-related bloodstream infections. Two studies reported an IRR of more than 1.00, both with p-values of >0.05. (77, 78) For four (28.6%) studies, the IRR could not be estimated since in one of the groups no events occured. (74, 80, 84, 87) [**Table 2**]

A total of 867 patients (417 in the TL group and 392 in the control group, one study did not report the number of patients per group) were followed up to observe the occurrence of adverse events. In the TL group, the most frequently reported adverse events were: paraesthesia (n=13, 3.1%), unpleasant taste (n=12, 2.9%), and

Table 1a Study characteristics

	First author year	Total N and population (in/out clinic)	CVC type	Study design	Patients (CVCs)		Age in yrs, mean or median* (SD or range)		Lock characteristics		
					TL group	Control group	TL group	Control group	TL group	Control group	Frequency and ml
HD	Winnicki 2017	106 Adult (in)	Tunneled	RCT Partially blind[a]	52 (52)	54 (54)	56 (15)	58 (15)	T1.35 C4 H500(2x)/ U25,000(1x)	C4	2.3ml 3x/wk
	Zwiech 2016	53 Adult (in)	(Non)-tunneled	RCT Open	24 (24)	29 (29)	56 (12)	57 (15)	T1.35 C4 H500	H5000	CVC volume +/-0.1ml after use
	Filiopoulos 2011	119 Adult (in)	Non-tunneled	RCT Open	59 (76)	60 (74)	75* (36-95)	72* (50-80)	T1.35 C4	G40 H5000	2.0ml after use
	Solomon 2010	107 Adult (in)	Tunneled	RCT Double blind	53 (56)	54 (56)	60 (15)	57 (17)	T1.35 C4	H5000	CVC volume after use
	Betjes 2004	58 Adult (in)	(Non)-tunneled	RCT Open	- (37)	- (39)	58 (16)	50 (20)	T1.35 C4	H5000	CVC volume + 0.1ml after use
Oncology	Gudiol 2020	141 Adult[b] (in)	Non-tunneled	RCT Double blind	72 (-)	69 (-)	56* (-)	57* (-)	T1.35 C4 H100	H1000	2.5ml 3x/wk
	Longo 2017	160 Adult (in/out)	VAP	RCT Open	84 (84)	76 (76)	62 (54-70)	61 (53-69)	T1.35 C4	S0.9	3.0ml after use
	Handrup 2013	112 Pediatric (in)	Tunneled , VAP	RCT Open	58 (64)	54 (65)	6* (0-19)	5* (0-16)	T1.35 C4 H100	H250	2.5ml after use
	Dumichen 2012	71 Pediatric (in)	Tunneled	RCT Open	35 (35)	36 (36)	9* (8)	8* (6)	T1.35 C4	H100	CVC volume after use

CVC; Central Venous Catheter, SD; Standard Deviation, RCT; Randomized Controlled Trial, RC; Retrospective Cohort Study, PC; Prospective Cohort Study, CO; Cross-over, -; Missing, NA; Not Applicable, TL; Taurolidine Lock, T; Taurolidine %, C; Citrate, H; Heparin IU/ml, G; Gentamicin mg/ml, U; Urokinase IU/ml, SL; Saline %, VAP; Vascular Access Port, HD; Haemodialysis, TPN; Total Parenteral Nutrition.

[a] Partially blinded: blinding of patients, laboratory staff, and assessors. Nurses and physicians were not blinded.

[b] Only patients in neutropenia.

Table 1b Study characteristics

	First author year	Total N and population (in/out clinic)	CVC type	Study design	Patients (CVCs)		Age in yrs, mean or median* (SD or range)		Lock characteristics		
					TL group	Control group	TL group	Control group	TL group	Control group	Frequency and ml
TPN	Wouters 2018	105 Adult (out)	(Non)-tunneled, VAP	RCT Double blind	53 (53)	52 (52)	59-47* (-)[a]	55-47* (-)[a]	T2	S0.9	5.0ml 2-7x/wk
	Tribler 2017	41 Adult (out)	Tunneled	RCT Double blind	20 (20)	21 (21)	56 (13)	58 (12)	T1.35 C4 H100	H100	2.0-4.0ml 2-7x/wk
	Klek 2015	30 Adult (out)	Tunneled	RCT Open	10 (10) and 10 (10)	10 (10)	44 (-) and 46 (-)	46 (-)	T2 and T1.35 C4	S0.9	-ml after use
	Bisseling 2010	30 Adult (out)	Tunneled, VAP	RCT Open	16 (16)	14 (14)	55 (13)	49 (16)	T2	H150	5.0ml -
Other	Lyszkowska 2019	86 Pediatrics <2yrs old undergoing surgery (in)	(Non)-tunneled	RCT Open	- (48)	- (49)	- (-)	- (-)	T- C-	-	2.0ml after use

CVC; Central Venous Catheter, SD; Standard Deviation, RCT; Randomized Controlled Trial, RC; Retrospective Cohort Study, PC; Prospective Cohort Study, CO; Cross-over, -; Missing, NA; Not Applicable, TL; Taurolidine Lock, T; Taurolidine %, C; Citrate, H; Heparin IU/ml, G; Gentamicin mg/ml, U; Urokinase IU/ml, SL; Saline %, VAP; Vascular Access Port, HD; Haemodialysis, TPN; Total Parenteral Nutrition.

[a] Patients were divided in a new CVC - pre-existing CVC group for the baseline characteristics.

Table 2a Study outcomes

	First author year	Study design (N)	Lock type		Infection events, total (GP/GN isolates[c])		CVC-days		CVC-related bloodstream infection IR per 1000 CVC-days		CVC-related bloodstream infection IRR per 1.000 CVC days (CI), p-value	CVC-related bloodstream infection definition
			TL	Control	TL	Control	TL	Control	TL	Control		
HD	Winnicki 2017	RCT Partially blind[a] (106)	TCHL/UL	CL	6 (4/4)	18 (5/19)	8982	6708	0.67	2.68	0.25 (0.09-0.63), <0.01	Symptoms, CVC BC+, no other source OR defervescence after removal
	Zwiech 2016	RCT Open (53)	TCHL	HL	0 (0/0)	26 (26/0)	-	7558[b]	0.00	3.44	NA	Routine BC+
	Filiopoulos 2011	RCT Open (119)	TCL	GHL	8 (8/0)	6 (3/3)	2180[b]	2190[b]	3.67	2.74	1.34[b] (0.47-3.86), 0.78[b]	Symptoms, CVC BC+, no other source
	Solomon 2010	RCT Double blind (107)	TCL	HL	11 (10/2)	23 (12/12)	8129	9642	1.35	2.39	0.57[b] (0.28-1.16), 0.16[b]	Symptoms, CVC BC+
	Betjes 2004	RCT Open (58)	TCL	HL	0 (0/0)	4 (4/0)	1519	1885	0.00	2.12	NA	Symptoms, CVC BC+, no other source

CVC; Central Venous Catheter, IR; Incidence Rate, IRR; Incidence Rate Ratio RCT; Randomized Controlled Trial, GP; Gram-positive, GN; Gram-negative, BC; Blood Culture, -; Missing, TCL; Taurolidine Citrate Lock; TCHL; Taurolidine Citrate Heparin Lock, HL; Heparin Lock, GHL; Gentamicin Heparin lock, SL; Saline lock, UL; Urokinase Lock, HD; Haemodialysis.

[a] Partially blinded: blinding of patients, laboratory staff, and assessors. Nurses and physicians were not blinded.

[b] Estimated by hand since no IRR and/or CVC-days were given in the article.

[c] The total number of GP/GN isolates can be less than the total number of infections since yeast and fungi infections are not reported here, and might also be higher since the isolates of combined GP and GN infection episodes were reported separately.

Table 2b Study outcomes

	First author year	Study design (N)	Lock type		Infection events, total (GP/GN isolates[c])		CVC-days		CVC-related bloodstream infection IR per 1000 CVC-days		CVC-related bloodstream infection IRR per 1.000 CVC days (CI), p-value	CVC-related bloodstream infection definition
			TL	Control	TL	Control	TL	Control	TL	Control		
Oncology	Gudiol 2020	RCT Double blind (141)	TCHL	HL	2 (2/0)	1 (1/0)	719[b]	690[b]	2.78	1.45	1.92 (0.18-20.66), 1.00[b]	Symptoms, peripheral BC+ (2xBC+ commensals), no other source.
	Longo 2017	RCT Open (160)	TCL	SL	1 (1/0)	4 (4/0)	10,000[b]	10,000[b]	0.1	0.4	0.23 (0.03-2.06), 0.21	Peripheral BC+ with same organism as exudate/CVC segment/BC with DTP of >2h.
	Handrup 2013	RCT Open (112)	TCHL	HL	7 (5/4)	26 (13/11)	17,500[b]	18,571[b]	0.4	1.4	0.26 (0.09-0.61), <0.01	CVC BC+ >2h before peripheral BC+. If no peripheral BC available: symptoms, BC+ (2xBC+ for commensals), no other source.
	Dümichen 2012	RCT Open (71)	TCL	HL	2 (-/-)	9 (-/-)	6576	7233	0.30	1.24[a]	0.24[b] (0.05-1.13), 0.09[b]	Symptoms, BC+ (2xBC+ for commensals), no other source.

CVC; Central Venous Catheter, IR; Incidence Rate, IRR; Incidence Rate Ratio, RCT; Randomized Controlled Trial, GP/GN; Gram-positive/negative, BC; Blood Culture, TCL; Taurolidine Citrate Lock; TCHL; Taurolidine Citrate Heparin Lock, HL; Heparin Lock, SL; Saline lock, DTP; Differential Time to Positivity.

[a] The authors describe a different incidence rate of 1.3 for the control group which we cannot trace back to the data described in the artic le.

[b] Estimated by hand since no IRR and/or CVC-days were given in the article.

[c] The total number of GP/GN isolates can be less than the total number of infections since yeast and fungi infections are not reported here, and might also be higher since the isolates of combined GP and GN infection episodes were reported separately.

Table 2c Study outcomes

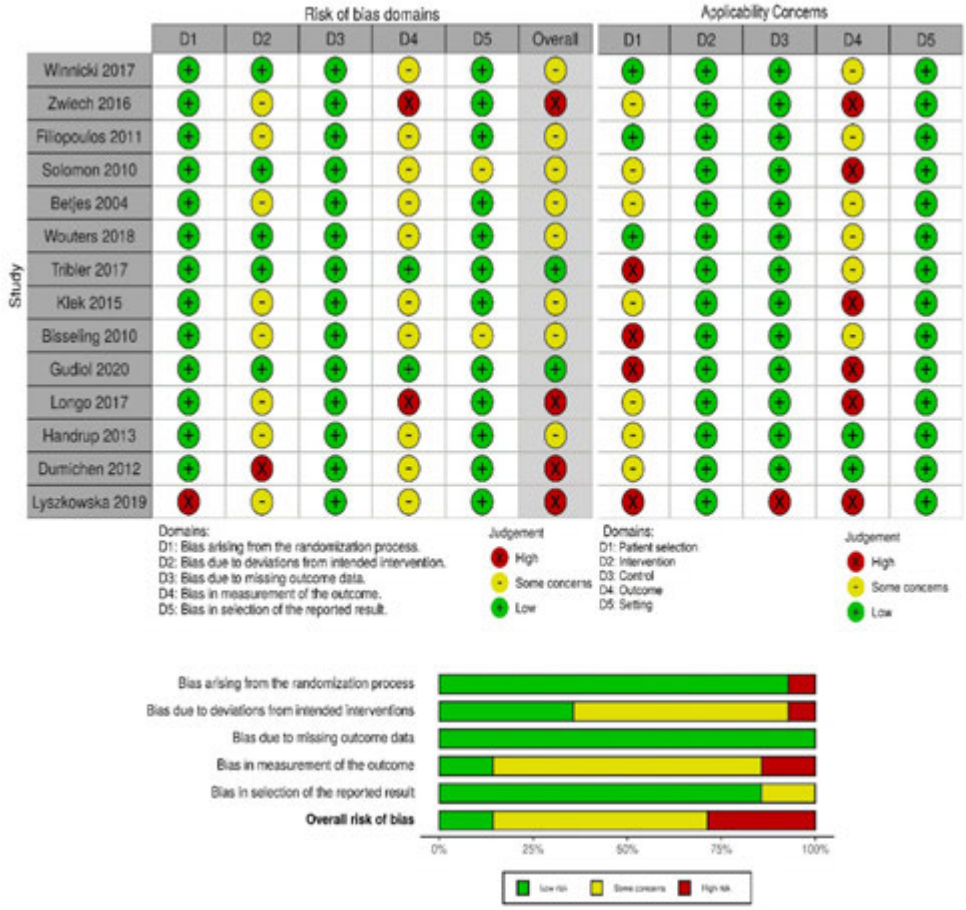
	First author year	Study design (N)	Lock type		Infection events, total (GP/GN isolates[b])		CVC-days		CVC-related bloodstream infection IR per 1000 CVC-days		CVC-related bloodstream infection IRR per 1.000 CVC days (CI), p-value	CVC-related bloodstream infection definition
			TL	Control	TL	Control	TL	Control	TL	Control		
TPN	Wouters 2018	RCT Double blind (105)	TL	SL	5 (4/1)	18 (7/10)	15,318	12,493	0.33	1.44	0.23 (0.07-0.63), <0.01	Symptoms, CVC BC+ (2xBC+ for commensals), no other source
	Tribler 2017	RCT Double blind (41)	TCHL	HL	0 (0/0)	7 (4/2)	9622	6956	0.00	1.01	NA	Symptoms, CVC BC+, no other source
	Klek 2015	RCT Open (30)	TL; TCL	SL	0 (0/0); 1 (0/1)	0 (0/0)	3658; 3650	3660	0.00; 0.27	0.00	NA	Symptoms, BC+
	Bisseling 2010	RCT Open (30)	TL	HL	1 (0/0)	10 (7/3)	5370	4939	0.19	2.02	0.09[a] (0.01-0.72), <0.01[a]	Symptoms, 2x BC+, no other source
Other	Lyszkowska 2019	RCT Open (86)	TCL	-	1 (1/0)	14 (12/2)	942	976	1.06	14.34	0.07[a] (0.01-0.56), <0.01[a]	Symptoms, BC+

CVC; Central Venous Catheter, IR; Incidence Rate, IRR; Incidence Rate Ratio RCT; Randomized Controlled Trial, GP/GN; Gram-positive/negative, BC; Blood Culture, -; Missing, TL; Taurolidine Lock, TCL; Taurolidine Citrate Lock; TCHL; Taurolidine Citrate Heparin Lock, HL; Heparin Lock, SL; Saline lock, TPN; Total Parenteral Nutrition.

[a] Estimated by hand since no IRR and/or CVC-days were given in the article.

[b] The total number of GP/GN isolates can be less than the total number of infections since yeast and fungi infections are not reported here, and might also be higher since the isolates of combined GP and GN infection episodes were reported separately.

Figure 2 Risk of bias (RoB 2.0) and applicability concerns of randomized controlled trials.



nausea/vomiting (n=5, 1.2%). In the control group, four patients reported adverse events. [**Table 3**]

A significant difference between the groups regarding the IRs of malfunctions and/or administration of thrombolysis was observed by two RCTs, one favouring the TL group (Winnicki 2017) and one favouring the control group (Solomon 2010). (83, 85) [see web-only **Supplementary Table S1**]

Results of syntheses

The pooled overall CVC-related bloodstream infection IRR including all patient groups together comparing TLs to non-antibiotic locks was 0.30 (0.19-0.46 95%CI), favoring the TL. Subgroup analyses showed IRRs of 0.63 (0.38-1.02 95%CI) for Gram-positive bloodstream infections (Gram-positive prophylaxis was reported by three studies), and 0.21 (0.11-0.40 95%CI) for Gram-negative bloodstream infections (Gram-negative prophylaxis use was not reported by these studies). Further subgroup analyses showed IRRs of 0.36 (0.18-0.71 95%CI) for studies with a HL as comparator, and 0.30 (0.15-0.59 95%CI) for studies including oncology patients only, all favoring the TL. Not enough RCTs were identified to perform analyses for haemodialysis and TPN patients, pediatric and adult patients per CVC indication, and other comparator lock solutions (i.e. saline and citrate). Sensitivity analyses showed no major differences in the pooled IRR compared to the primary analyses. [**Table 4** or see web-only **Supplementary Figure S1** and **S2**]

Reporting bias and quality of evidence assessment

The quality of evidence was reduced from "high" to "moderate" or "low" due to a high risk of bias and indirectness of evidence. After evaluation of the funnel plots, reporting bias was not suspected [see web-only **Supplementary Table S2** and **Figure S3**].

DISCUSSION

This comprehensive review and meta-analysis suggests that the use of TLs is promising and safe for the prevention of CVC-related bloodstream infections. Adverse events observed were all mild and scarce. The quality of evidence however, is not yet high due to a high risk of bias and indirectness of evidence observed, as described in more detail below. These results are in accordance with previously performed reviews and meta-analyses. (32-36, 88-92)

Table 3 Adverse events

	First author year	TL lock (total number of patients)	Control lock (total number of patients)	TL aspirated	TL group adverse events (number of patients)	Control lock aspirated	Control group adverse events (number of patients)
HD	Filiopoulos 2011	T1.35 C4 (59)	G40 H5000 (60)	Yes	0	Yes	0
	Betjes 2004	T1.35 C4 (X)	H5000 (X)	Yes	0	Yes	0
Oncology	Gudiol 2020	T1.35 C4 H100 (72)	H1000 (69)	Yes	0	Yes	0
	Longo 2017	T1.35 C4 (84)	S0.9 (76)	Yes	local paresthesia (9), body warm sensation (4), unpleasant taste (1), pain (1)	No	-
	Handrup 2013	T1.35 C4 H100 (58)	H250 (54)	-	unpleasant taste (-)	-	0
	Dumichen 2012	T1.35 C4 (35)	H100 (36)	Yes	discomfort chest/neck (1), perioral dysesthesia (1), unpleasant taste (2), nausea (2), vomiting (1)	Yes	0
TPN	Wouters 2018	T2 (53)	S0.9 (52)	-	unpleasant taste (1), dizziness (1), erhythema exit-site (1)	-	flushing (1)
	Tribler 2017	T1.35 C4 H100 (20)	H100 (21)	No	unpleasant taste (8), paresthesia (3), nausea/vomiting (2)	No	heartburn/acid reflux (1), paresthesia (1), dizziness (1)
	Klek 2015	T2 (10)	S0.9 (10)	No	0	No	0
		T1.35 C4 (10)	"	No	0	No	-
	Bisseling 2010	T2 (16)	H150 (14)	-	0	-	0

RCT; Randomized Controlled Trial, RC; Retrospective Cohort Study, PC; Prospective Cohort Study, CO; Cross-over study, -; Missing, TL; Taurolidine Lock, T; Taurolidine %, H; Heparin IU/ml, C; Citrate %, G; Gentamicin mg/ml, S; Saline %, TPN; Total Parenteral Nutrition, HD; Haemodialysis.

Table 4 Forest plot summary table

Population	Primary or sensitivity analyses	Studies	Studies/outcomes included in the analysis	IRR (95%CI)	I^2, p-value
All patients	Primary analyses	9	All RCTs	0.30 (0.19-0.46)	14%, <0.01
		7	Only Gram-positive CVC infections as outcome	0.63 (0.38-1.02)	0%, 0.06
		4	Only Gram-negative CVC infections as outcome	0.21 (0.11-0.40)	0%, <0.01
		5	All RCTs comparing TLs with a heparin-only lock solution	0.36 (0.18-0.71)	33%, <0.01
	Sensitivity analyses	6	Excluding RCTs with antibiotic prophylaxis	0.28 (0.16-0.49)	26%, <0.01
		8	Excluding RCTs with citrate locks as comparator	0.30 (0.18-0.50)	23%, <0.01
		6	Excluding RCTs with non-tunneled CVCs	0.33 (0.21-0.50)	0%, <0.01
		8	Excluding RCTs with only high risk patients	0.31 (0.20-0.48)	11%, <0.01
Oncology patients	Primary analyses	4	All RCTs	0.30 (0.15-0.59)	0%, <0.01
	Sensitivity analyses	3	Excluding RCTs with non-tunneled CVCs	0.25 (0.12-0.51)	0%, <0.01

IRR; Incidence Rate Ratio, RCT; Randomized Controlled Trial, CI; Confidence Interval, CVC; Central Venous Catheter, TL; Taurolidine containing Lock solution.

The outcomes of the subgroup analyses for Gram-positive and Gram-negative isolates suggests that TLs may be more effective against Gram-negative compared to Gram-positive bacteria, as also reported by previous authors. (34, 77, 83, 85) *In vitro* studies on the other hand, did not show this difference in effect. (15, 28) This finding, might be explained by the limitations of the CVC-related bloodstream infections definitions used, resulting in the registration of positive bloodcultures as a CVC-related bloodstream infection instead of colonization, contamination or a non-CVC-related bloodstream infection. (10, 93)

Strengths of this review and meta-analysis are that it provides an updated summary of the available evidence regarding the efficacy of TLs, that data on all possible confounders are collected, and that subgroup and sensitivity analyses are performed. In addition, it underlines the importance of further qualitative research in larger populations with the aim to significantly reduce the high IR of CVC-related bloodstream infections. We identified several aspects that are important for future research and the correct interpretation of the results from CVC lock studies, that were not always taken into account in the included studies.

Future RCTs should ideally be double-blind or at least assessor-masked. Only a small number of studies used a double-blinded design and two non-blinded studies used an assessor-masked design to avoid bias. (78, 79, 81, 83-86) Furthermore, the CVC-related bloodstream infection definition should be clear and at least include clinical symptoms and a positive blood culture, exclude other sources of infections, and ideally use the central line-associated bloodstream infection (CLABSI) or catheter-related bloodstream infection (CRBSI) definition. (10, 93) This was done by 10 (71.4%) of the included studies. (74-79, 81, 84-86) Additionally, confounding factors, such as diagnosis, CVC type, CVC insertion days, antibiotic prophylaxis and TPN administration, CVCs that were already in situ at the beginning of the study, previous

CVC-related infections, lock dwell time and lock frequency should be equally distributed between the intervention groups. (10, 27) Most of these factors were not taken into account in many of the included studies.

Indirectness of evidence was also suspected. First, due to the inclusion of studies including only high risk patients (i.e. patients with a history of CVC-related bloodstream infections), resulting in the use of TLs as secondary instead of primary prophylaxis. (75) Second, due to the use of inappropriate (i.e. not following the minimal requirements as described above) CVC-related bloodstream infection definitions. (80, 82, 83, 87)

We did not observe a high heterogeneity between the studies (i.e. I^2 values <50%). However, the minimal heterogeneity that was observed, could be explained by the differences between the study populations included, CVC types inserted, lock solutions and protocols used, and outcome measures observed. (10, 22) Gudiol 2020 reported an IRR of >1.00. This might be explained by the inclusion of only non-tunneled CVCs. The sensitivity analysis excluding RCTs with non-tunneled CVCs also showed a much lower I^2 value compared to the primary meta-analysis. Other additional and sensitivity meta-analyses performed, suggested no major differences in the effect of TLs against CVC-related bloodstream infections.(78)

Filiopoulos 2011 used a gentamicin lock instead of a non-antibiotic lock as a comparator and was therefore excluded from the meta-analysis. They reported an IRR of >1.00, p-value >0.05. This might suggest a similar or even superior efficacy of gentamicin locks compared to TLs. (77) Compared to TLs however, gentamicin and other antibiotic locks might increase the risk of microbial resistance and the use of these locks is therefore not preferred. Microbial resistance to taurolidine has not been observed. (27, 28)

Limitations of this review are that not all articles could be included in the meta-analysis since the IRRs along with their 95%CIs were not given or could not be estimated due to data not reported in the article or the presence of zero events. Additionally, not enough RCTs were identified to perform analyses for haemodialysis, TPN and paediatric patients separately. The efficacy of TL might differ between these populations due to the differences in the aetiology and primary risk of CVC-related bloodstream infections between these groups caused by the underlying disease, treatments received, and CVC protocols used (e.g. high risk chemotherapy, TPN, antibiotic prophylaxis, total CVC insertion days, CVC types and lock frequency). (10, 22)

Large scale RCTs for each patient population, including cost-effectiveness analyses, are required to draw more robust conclusions on the efficacy of TLs for the prevention of CVC-related bloodstream infections. Additionally, further research is required to provide information about the efficacy of TLs for the prevention of Gram-positive CVC-related bloodstream infections.

CONCLUSION

The results of this review and meta-analysis suggest that the use of TLs for the prevention of CVC-related bloodstream infections is promising. The quality of the evidence was limited due to a high risk of bias and indirectness of evidence, mainly due to the presence of non-blinded study designs, confounding factors and a wide heterogeneity in populations observed and outcome definitions used. In the future, large blinded RCTs, including cost-effectiveness analyses, should be performed investigating the efficacy of TLs for the primary prevention of CVC-related bloodstream infections in different patient groups and the efficacy of TLs against Gram-positive CVC-related bloodstream infections specifically.

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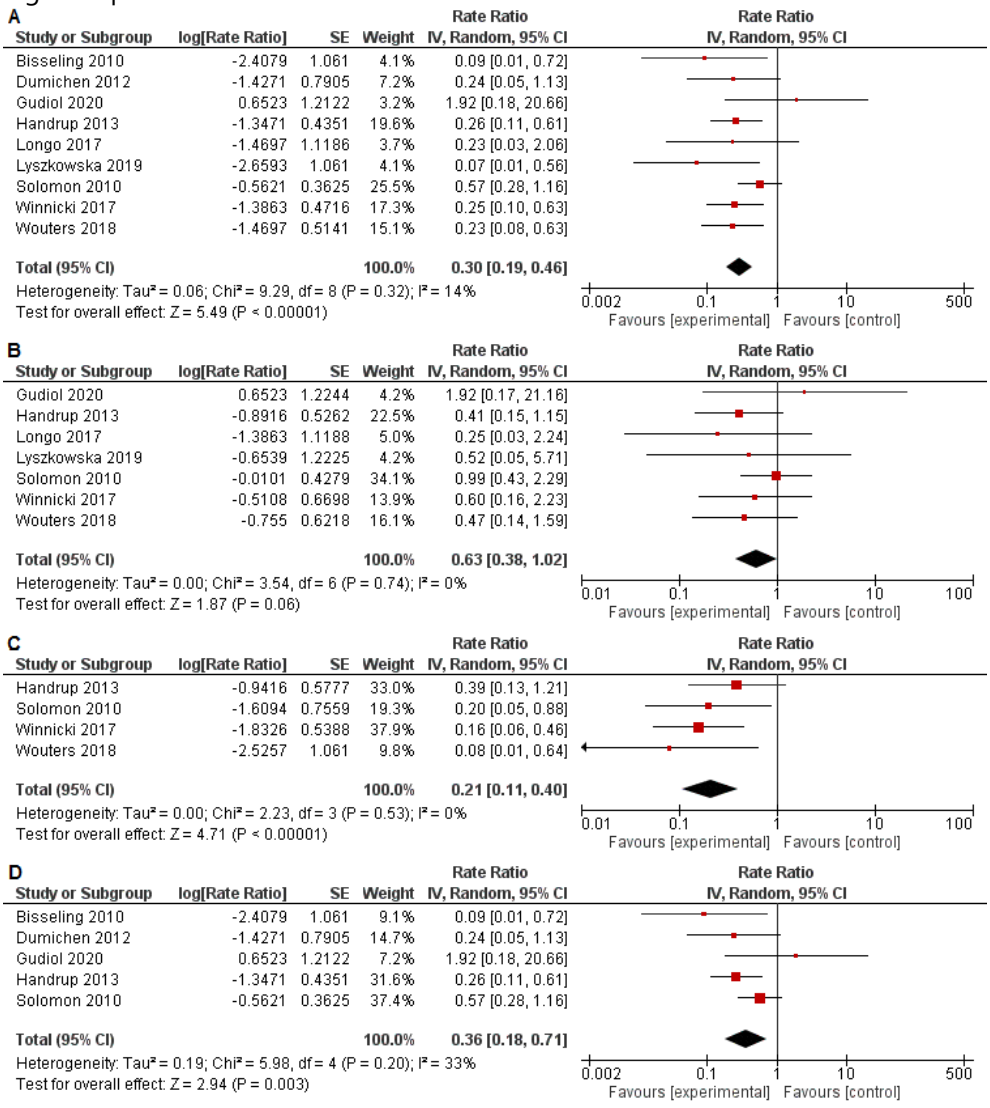
SUPPLEMENTARY FILES

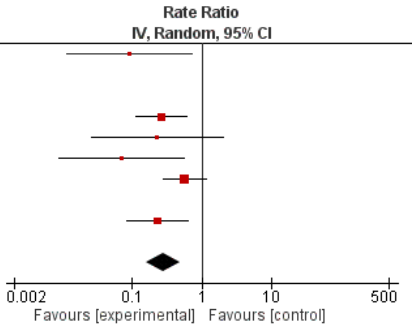
Supplementary Figure S1 Forest plots in all patient populations: (A) all RCTs together, (B) Gram-positive CVC-related bloodstream infections, (C) Gram-negative CVC-related bloodstream infection, (D) all RCTs with heparin-only lock as comparator, (E) sensitivity analysis excl. studies with antibiotic prophylaxis, (F) sensitivity analysis excl. studies with citrate as comparator, (G) sensitivity analysis excl. studies with non-tunneled CVCs, (H) sensitivity analysis excl. studies with only high risk patients.



E

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Bisseling 2010	-2.4079	1.061	6.7%	0.09 [0.01, 0.72]
Dumichen 2012	-1.4271	0.7905	0.0%	0.24 [0.05, 1.13]
Gudiol 2020	0.6523	1.2122	0.0%	1.92 [0.18, 20.66]
Handrup 2013	-1.3471	0.4351	26.6%	0.26 [0.11, 0.61]
Longo 2017	-1.4697	1.1186	6.0%	0.23 [0.03, 2.06]
Lyszkowska 2019	-2.6593	1.061	6.7%	0.07 [0.01, 0.56]
Solomon 2010	-0.5621	0.3625	32.6%	0.57 [0.28, 1.16]
Winnicki 2017	-1.3863	0.4716	0.0%	0.25 [0.10, 0.63]
Wouters 2018	-1.4697	0.5141	21.4%	0.23 [0.08, 0.63]
Total (95% CI)			**100.0%**	**0.28 [0.16, 0.49]**

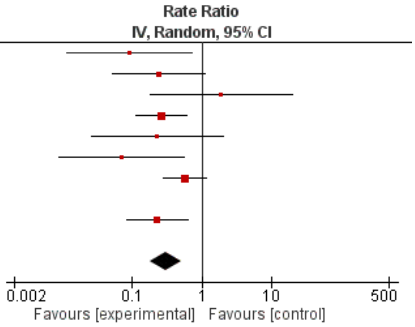
Heterogeneity: Tau² = 0.12; Chi² = 6.72, df = 5 (P = 0.24); I² = 26%
Test for overall effect: Z = 4.45 (P < 0.00001)



F

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Bisseling 2010	-2.4079	1.061	5.7%	0.09 [0.01, 0.72]
Dumichen 2012	-1.4271	0.7905	9.6%	0.24 [0.05, 1.13]
Gudiol 2020	0.6523	1.2122	4.5%	1.92 [0.18, 20.66]
Handrup 2013	-1.3471	0.4351	22.8%	0.26 [0.11, 0.61]
Longo 2017	-1.4697	1.1186	5.2%	0.23 [0.03, 2.06]
Lyszkowska 2019	-2.6593	1.061	5.7%	0.07 [0.01, 0.56]
Solomon 2010	-0.5621	0.3625	28.0%	0.57 [0.28, 1.16]
Winnicki 2017	-1.3863	0.4716	0.0%	0.25 [0.10, 0.63]
Wouters 2018	-1.4697	0.5141	18.4%	0.23 [0.08, 0.63]
Total (95% CI)			**100.0%**	**0.30 [0.18, 0.50]**

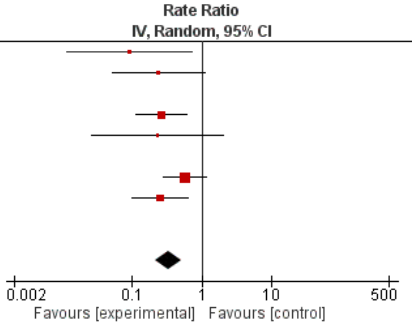
Heterogeneity: Tau² = 0.12; Chi² = 9.06, df = 7 (P = 0.25); I² = 23%
Test for overall effect: Z = 4.52 (P < 0.00001)



G

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Bisseling 2010	-2.4079	1.061	4.3%	0.09 [0.01, 0.72]
Dumichen 2012	-1.4271	0.7905	7.7%	0.24 [0.05, 1.13]
Gudiol 2020	0.6523	1.2122	0.0%	1.92 [0.18, 20.66]
Handrup 2013	-1.3471	0.4351	25.5%	0.26 [0.11, 0.61]
Longo 2017	-1.4697	1.1186	3.9%	0.23 [0.03, 2.06]
Lyszkowska 2019	-2.6593	1.061	0.0%	0.07 [0.01, 0.56]
Solomon 2010	-0.5621	0.3625	36.8%	0.57 [0.28, 1.16]
Winnicki 2017	-1.3863	0.4716	21.7%	0.25 [0.10, 0.63]
Wouters 2018	-1.4697	0.5141	0.0%	0.23 [0.08, 0.63]
Total (95% CI)			**100.0%**	**0.33 [0.21, 0.50]**

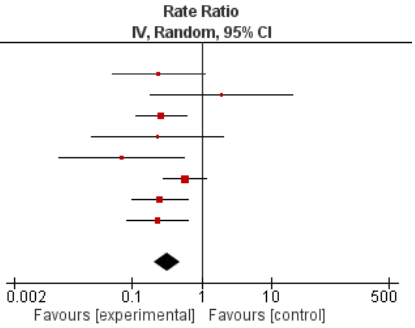
Heterogeneity: Tau² = 0.00; Chi² = 4.68, df = 5 (P = 0.46); I² = 0%
Test for overall effect: Z = 5.11 (P < 0.00001)



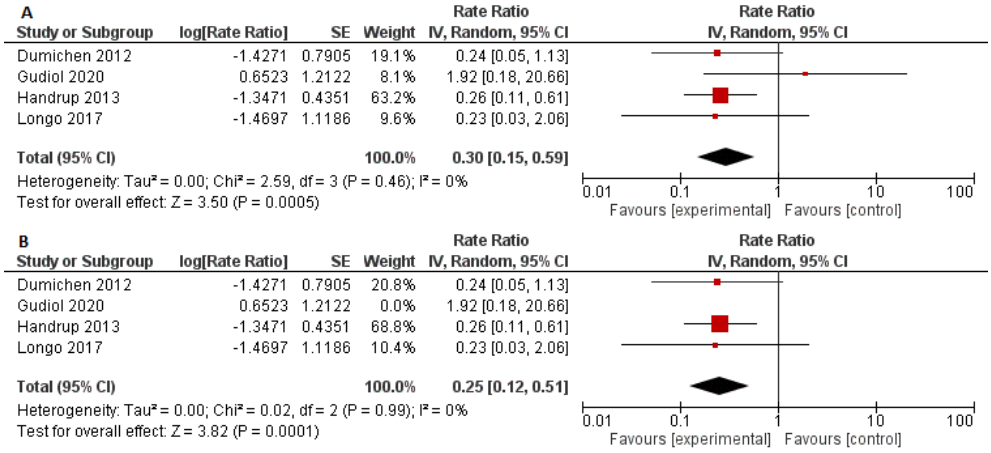
H

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Bisseling 2010	-2.4079	1.061	0.0%	0.09 [0.01, 0.72]
Dumichen 2012	-1.4271	0.7905	7.2%	0.24 [0.05, 1.13]
Gudiol 2020	0.6523	1.2122	3.2%	1.92 [0.18, 20.66]
Handrup 2013	-1.3471	0.4351	20.6%	0.26 [0.11, 0.61]
Longo 2017	-1.4697	1.1186	3.7%	0.23 [0.03, 2.06]
Lyszkowska 2019	-2.6593	1.061	4.1%	0.07 [0.01, 0.56]
Solomon 2010	-0.5621	0.3625	27.4%	0.57 [0.28, 1.16]
Winnicki 2017	-1.3863	0.4716	18.1%	0.25 [0.10, 0.63]
Wouters 2018	-1.4697	0.5141	15.6%	0.23 [0.08, 0.63]
Total (95% CI)			**100.0%**	**0.31 [0.20, 0.48]**

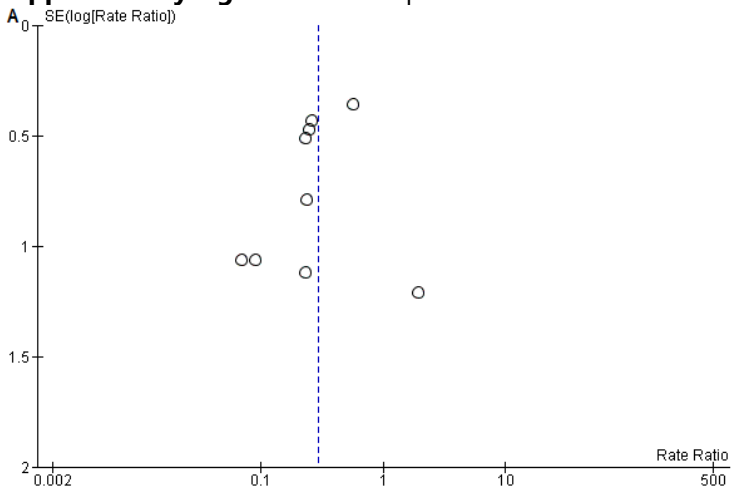
Heterogeneity: Tau² = 0.04; Chi² = 7.91, df = 7 (P = 0.34); I² = 11%
Test for overall effect: Z = 5.27 (P < 0.00001)



Supplementary Figure S2 Forest plots of RCTs in oncology patients: (A) all studies and (B) sensitivity analysis excl. studies with non-tunneled CVCs.



Supplementary Figure S3 Funnel plot



Supplementary Table S1 Incidence of malfunctions, thromboses and administration of thrombolysis

First author year	Lock type		Events thrombolysis (tl), thrombosis (tb) or malfunction (mal)		Incidence rate per 1000 CVC-days		IRR (CI 95%), p-value
	TL group	Control group	TL group	Control group	TL group	Control group	
Winnicki 2017	TL1.35 CL4 HL500(2x)/ UL25,000(1x)	CL4	34 (tl) 168 (mal)	66 (tl) 297 (mal)	3.79 (tl) 18.70 (mal)	9.84 (tl) 44.28 (mal)	0.38 (0.25-0.58), <0.01 0.42 (0.34-0.51), <0.01
Filiopoulos 2011	TL1.35 CL4	GL40 HL5000	9 (mal)	11 (mal)	4.13 *	5.02*	0.82* (0.34-1.98), 0.83*
Solomon 2010	TL1.35 CL4	HL5000	79 (tl)	38 (tl)	9.72*	3.94*	2.47* (1.68-3.63), <0.01*
Wouters 2018	TL2	SL0.9	2 (mal)	5 (mal)	0.13*	0.40*	0.33* (0.06-1.68), 0.30*
Tribler 2017	TL1.35 CL4 HL100	HL100	2 (mal)	1 (mal)	2.08*	1.44*	1.45* (0.13-15.94), 1.00*
Klek 2015	TL2	SL0.9	1 (mal)	0 (mal)	0.27*	0.00*	NA
Longo 2017	TL1.35 CL4	SL0.9	1 (tb)	0 (tb)	0.10*	0.00*	NA
Dumichen 2012	TL1.35 CL4	HL100	3 (tb)	2 (tb)	0.46*	0.28*	1.65* (0.28-9.87), 0.91*
Lyszkowska 2019	TLX CLX	X	1 (tb)	1 (tb)	1.06	1.02	1.04* (0.07-16.6), 1.00

CVC; Central Venous Catheter, RCT; Randomized Controlled Trial, PC; Prospective Cohort Study, CO; Cross-over study, X; Missing, TL; Taurolidine Lock %, CL; Citrate Lock %. HL; Heparin Lock IU/ml, SL; Saline lock %, UL; Urokinase Lock UI/ml, GL; Gentamicin Lock mg/ml, NA; Not Applicable, HD; Haemodialysis, TPN; Total Parenteral Nutrition.

*Calculated by hand since no IRR and/or CVC-days were given in the article.

Supplementary Table S2 GRADE Assessment

Certainty assessment							Summary of the results		Importance	Comments
Outcomes	**Studies (patients)**	**Factors that may decrease certainty of evidence**					**Pooled IRR (95% CI)**	**Certainty of evidence**		
		Risk of bias[a]	**Inconsistency[b]**	**Indirect evidence[c]**	**Imprecision[d]**	**Other factors[e]**				
Pooled IRR RCTs	9 (918)	Serious	Not serious	Serious	Not serious	Strong association	0.30 (0.19-0.46)	⊕⊕⊕◯ Moderate	Crucial (8)	No comments
RCTs GP	7 (817)	Serious	Not serious	Serious	Not serious	No other factors	0.63 (0.38-1.02)	⊕⊕◯◯ Low	Important (6)	No comments
RCTs GN	4 (430)	Serious	Not serious	Serious	Not serious	Strong association	0.21 (0.11-0.40)	⊕⊕⊕◯ Moderate	Important (6)	No comments
RCTs HL as comparator	5 (461)	Serious	Not serious	Serious	Not serious	Strong association	0.36 (0.18-0.71)	⊕⊕⊕◯ Moderate	Important (6)	No comments
Oncology patients	4 (484)	Serious	Not serious	Serious	Not serious	Strong association	0.30 (0.15-0.59)	⊕⊕⊕◯ Moderate	Crucial (8)	No comments
Adverse events	10 (867)	Serious	Not serious	Serious	Not serious	No other factors	See comments	⊕⊕◯◯ Low	Crucial (8)	Adverse events were more frequently reported in the TL groups, all were mild and scarce.
Malfunction events	9 (815)	Serious	Not serious	Serious	Not serious	No other factors	See comments	⊕⊕◯◯ Low	Important (6)	A difference in malfunction events was observed by two studies, one favoring the TLs and one favoring the non-antibiotic locks.

IRR; Incidence Rate Ratio, RCT; Randomized Controlled Trial, GP; Gram-positive, GN; Gram-negative, CI; Confidence Interval, HD; Hemodialysis, TL; Taurolidine containing Lock solution, HL; Heparin-only lock solution, TPN; Total Parenteral Nutrition, NA; Not Applicable.

[a] Risk of bias was scored "Very serious" if in the majority of the studies the risk of bias was scored "High/Critical", risk of bias was scored "Serious" if the risk of bias in the majority of the studies was scored "Moderate/Some concerns".

[b] Inconsistency was scored "Serious" if the I^2 was >50% and "Very serious" if the I^2 was >80%.

[c] Indirect evidence was scored "Very serious" if the majority of the studies included high risk patients, "Serious" was scored if the majority of the studies used central line infection criteria that were not ideal in the eyes of the authors based on the applicability concerns.

[d] Imprecision was scored "Not serious" for all outcomes since the confidence intervals were not wide.

[e] A "Strong association" was scored if the IRR was <0,50 and a "Very strong association" was scored if the IRR was <0,20. Additionally, publication bias was assessed using funnel plots.

CHAPTER 8

The effect of taurolidine on the time-to-positivity of blood cultures

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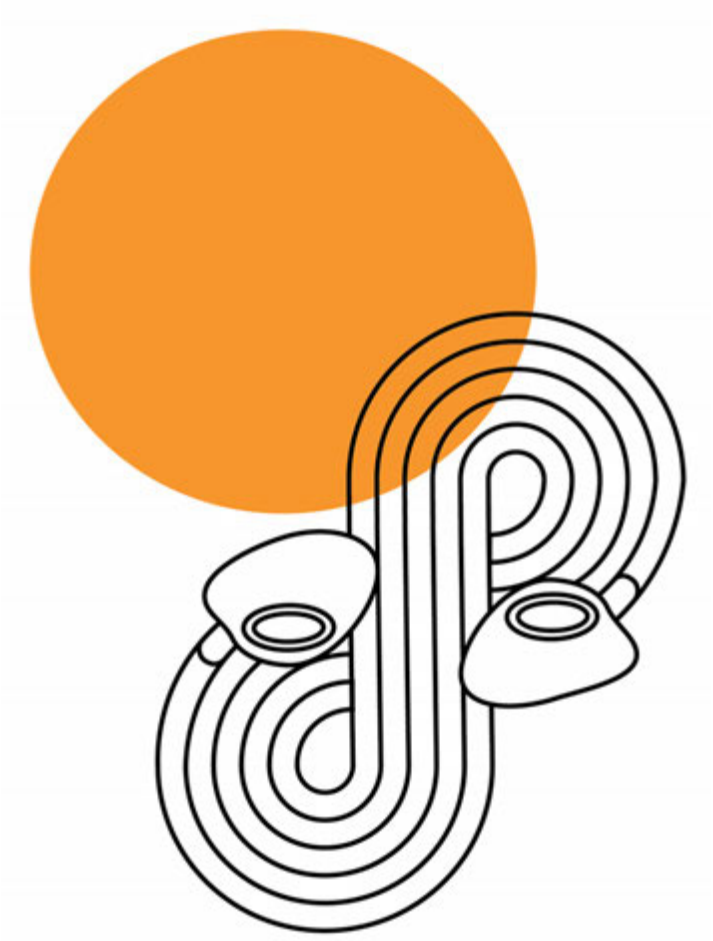

ABSTRACT

Background Taurolidine containing lock solutions (TL) are a promising method for the prevention of central line associated bloodstream infections. Per accident, the TL may not always be aspirated from the central venous catheter (CVC) before blood cultures are obtained. The TL could, unintentionally, end up in a blood culture vial, possibly altering the results. The aim of this study was to investigate the effect of the TLs on the detection of microbial growth in blood culture vials.

Methods Different lock solutions (taurolidine-citrate-heparin (TCHL), taurolidine, heparin, citrate or NaCl) were added to BD BACTEC™ blood culture vials (Plus Aerobic/F, Lytic/10 Anaerobic/F or Peds Plus/F) before spiking with Staphylococcus aureus (ATCC 29213 or a clinical strain) or Escherichia coli (ATCC 25922 or a clinical strain) in the presence and absence of blood. Subsequently, blood culture vials were incubated in the BD BACTEC FX instrument with Time-to-positivity (TTP) as primary outcome. In addition, the effect of the TCHL on a variety of other micro-organisms was tested.

Discussion In the presence of taurolidine, the TTP was considerably delayed or vials even remained negative as compared to vials containing heparin, citrate or NaCl. This effect was dose-dependent. The delayed TDD was much less pronounced in the presence of blood, but still notable.

Conclusion This study stresses the clinical importance of discarding TLs from the CVC before obtaining a blood culture.

BACKGROUND

Central venous catheters (CVCs) play an important role in the treatment of paediatric oncology patients. Central line associated bloodstream infections (CLABSIs) are common in this patient group, with reported incidence rates of 1.51-1.63 per 1000 catheter days (1, 2). CLABSIs have a large impact on the quality of life of patients due to hospital admissions, removal of the CVC, postponement of treatment, intensive care unit admissions and in some cases even death (1, 2). Research investigating preventative methods is therefore crucial.

In between treatments, the lumen of the CVC is filled with a lock solution. Currently, heparin or NaCl locks, are the standard of care (3). The use of antimicrobial locks (with or without the addition of an anticoagulant such as citrate and/or heparin) has been suggested as a promising method for the prevention of CLABSIs in paediatric oncology patients (4, 5). Taurolidine is one of the most promising antimicrobial lock solutions available since it is effective against Gram-positive bacteria, Gram-negative bacteria, and yeasts/fungi, microbial resistance has not been reported, it is available in combination with an anticoagulant, and side-effects are rare and mild (4, 6). Multiple in vitro studies investigated the susceptibility of various microbial strains to taurolidine. These studies found that most micro-organisms (Gram-negative bacteria and Gram-positive bacteria) were inhibited at a range of 250-2000 mg/L taurolidine, whereas *Candida albicans* was inhibited at a range of 2048-4096 mg/L (7-10). It is thought that the active components of taurolidine are derivatives that arise after it breaks down in aqueous solutions (7). Suggested explanations for the mechanism of action are the irreversible binding of its methyl groups to the microbial cell wall and a chemical interaction with endotoxins and exotoxins that are produced by the bacteria (7-10). These mechanisms could affect microbial adhesion to surfaces and inhibit microbial pathogenicity (7, 8). Clinical studies also show promising results in various patient groups, including paediatric oncology patients, with a pooled CVC-

related bloodstream infection incidence rate ratio of 0.30 (95%CI 0.19–0.46), in favour of taurolidine containing locks (TL) as compared to non-antimicrobial locks (6, 9).

The summary of product characteristics of TLs advice to aspirate and discard the TLs before a blood culture is obtained, since it might alter the blood culture results if it enters the blood culture vial. However, per accident, the TLs may not always be discarded first and could thereby unintentionally end up in the blood culture vial. The presence of 1.0-1.5 ml (the expected intraluminal volume of the CVC) of 1.35% taurolidine in a blood culture vial could reach concentrations up to 500 µg/ml, exceeding the minimal inhibitory concentration $(MIC)_{50}$ for many microorganisms (9, 10). Potentially, this might lead to a delay in the Time To Positivity (TTP) or even false-negative blood cultures. This could have serious clinical (i.e., delay of adequate treatment) and research (i.e., overestimation of the efficacy of the TLs) implications. However, as far as we know, no studies are available investigating this hypothesis and the extent of this possible effect. The aim of this study is therefore to investigate the effect of TLs on the detection of microbial growth in blood culture vials if not discarded.

METHODS

The experiments were performed at the Medical Microbiology Department of the University Medical Centre Utrecht (UMCU), the Netherlands, in collaboration with the Princess Máxima Centre for Paediatric Oncology, the Netherlands. Three experiments under various conditions (with/without blood, various microorganisms in amounts of 10 or 100 colony forming units (CFU), various blood culture vial types and with the addition of TCHL in various concentrations, heparin or NaCl) were performed, details described below. Due to resource restrictions regarding donor blood, the first two experiments (different conditions tested in monoplicate, using 30 and 60 blood culture vials in total) were performed without the presence of blood in the vials to

observe if the hypothesis that TLs have an effect on microbial growth in blood culture vials is true. Additionally, in the last experiment (48 vials), blood was added to mimic the clinical setting and investigate the size of the impact on the clinical setting.

Microbial strains and spiking

The microbial strains used for the experiments were chosen based on their potential pathogenicity and high prevalence in paediatric oncology patients (2). The following American Type Culture Collection (ATCC) strains and paediatric oncologic patient isolates were used: *Escherichia coli* (ATCC 25922 and a patient blood culture isolate), *Staphylococcus aureus* (ATCC 29213 and a patient blood culture isolate); *Staphylococcus epidermidis* (ATCC 49134), *Enterococcus faecalis* (ATCC 29212), and *Candida albicans* (ATCC 10231).

The microbial strains used were thawed, cultured for 24h, and their identity was confirmed with the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) Biotyper® sirius CA system (Bruker Daltonik GmbH, Bremen, Germany), before use. 0.5 McFarland suspensions were serially diluted with NaCl 0.9% and the blood culture vials were spiked with 1 ml suspension containing 10 or 100 CFU). This number of CFU per vial approximates the number of CFU per blood culture vial clinically, considering 3-8 ml of blood is drawn from paediatric patients during a bacteraemia episode (11). To check the actual number of CFU administered, microbial suspensions were plated on Mueller-Hinton agar (MHA) for bacteria and malt extract plates for yeast and CFUs were counted by visual inspection after overnight incubation at 37°C.

Lock solutions

The blood culture vials were filled with 1.5 ml (the approximate intraluminal volume of the CVC) of the taurolidine 1.35%, citrate 4.0% and heparin 100 IU/ml lock (TCHL)

(TauroLock-Hep100™, TauroPharm GmbH, Waldbüttelbrunn, Germany), 1.5 ml taurolidine 1.35% (obtained by dilution with NaCl 0.9% from NutriLock™, TauroPharm GmbH, Waldbüttelbrunn, Germany, which contains taurolidine 4%), citrate 4.0% (Citra-Lock™, Citra-Gen®, Oss, the Netherlands), heparin 100 IU/ml, or NaCl 0.9%. For some experiments, TCHL was diluted 3.16-fold and 10-fold with NaCl 0.9% before 1.5 ml was added to the blood culture vials.

Blood

Blood from healthy donors from the Mini Donor Service (University Medical Centre Utrecht, Utrecht, the Netherlands) was used for the experiments. The blood culture vials were filled with 2 ml (Peds Plus/F vial) or 8 ml (Plus Aerobic/F vial) blood.

BD BACTEC™ FX system

The blood culture vials used were the BD BACTEC™ Plus Aerobic/F, Lytic/10 Anaerobic/F, and PEDS Plus/F (Becton, Dickinson and Company, Franklin Lakes, New Jersey, United States of America). First, the blood (if applicable, depending on the experiment) and lock solutions were added to the blood culture vials. It should be noted that, for the experiments without blood, the vials contained a lower overall volume and thereby higher lock concentration (i.e., 30-40 mL media solution depending on the vial type, 1.0 mL spike solution and 1.5 mL lock solution), since the blood (2-8 mL depending on the vial type) was not added. Subsequently, microbial suspensions were added, immediately followed by placement of the vials in the BD BACTEC™ FX instrument for incubation at 35°C for a maximum of five days (bacteria) or seven days (yeasts). Vials detected as positive by the instrument were taken from the machine, the TTP was noted and the content was subcultured on agar to confirm that the blood culture became positive with the micro-organism used for spiking. Vials that remained negative after five or seven days were also subcultured for 48 hours. The vials were confirmed negative if there was no growth detected.

Outcome measurements

The primary outcome was the TTP of the spiked blood culture vials in the presence of the TCHL or taurolidine-only versus citrate-only, heparin-only or NaCl-only, with and without blood.

RESULTS

As shown in **Table 1**, Peds Plus/F and Plus Aerobic/F blood culture vials spiked with 100 CFU *S. aureus* (ATCC 29213) or *E. coli* (ATCC 25922) and containing taurolidine (TCHL or taurolidine-only), remained negative after 5 days of incubation. The TTP of the Lytic/10 Anaerobic vials was delayed for 37-42 hours (*S. aureus*) and 3-5 hours (*E. coli*) as compared to vials containing citrate, heparin or NaCl. The TTP between vials containing TCHL and taurolidine-only was comparable. Also, the TTP of vials containing citrate, heparin and NaCl appeared comparable. In the following experiments, we continued only with the TCHL, since TTP was comparable to taurolidine-only, and since this is the most researched lock solution in paediatric oncology patients. The TCHL was compared to heparin and NaCl locks since these are currently the standard of care in most hospitals (4-6).

The inhibitory effect of the TCHL could also be found when Plus Aerobic/F or Lytic/10 Anaerobic vials were spiked with 10 CFU or 100 CFU of other micro-organisms, **Table 2**. Plus Aerobic/F vials spiked with *S. epidermidis* (ATCC 49134), also remained negative in the presence of TCHL, similar to *S. aureus* ATCC (29213) and *E. coli* (ATCC 25922). TCHL prolonged the TTP in vials spiked with *E. faecalis* (ATCC 29212). On the other hand, TCHL had almost no effect on the TTP of *C. albicans* (ATCC 10231) in Plus

TABLE 1 Time to positivity of blood culture vials spiked with 100 CFU *Staphylococcus* aureus (ATCC 29213) and *Escherichia coli* (ATCC 25922) and with 1.5 ml TCHL, taurolidine 1.35%, citrate 4%, heparin 100 IU/ml, or NaCl 0.9%, without blood.

	***Staphylococcus aureus* (ATCC 29213)**			***Escherichia coli* (ATCC 25922)**		
	PB	AE	AN	PB	AE	AN
TCHL	Negative	Negative	2:02:44	Negative	Negative	0:14:56
Taurolidine	Negative	Negative	2:07:13	Negative	Negative	0:12:54
Citrate	0:15:39	0:20:39	0:13:08	0:09:55	0:10:25	0:09:34
Heparin	0:14:08	0:14:38	0:13:28	0:09:55	0:10:34	0:09:23
NaCl	0:13:08	0:14:38	0:13:07	0:10:06	0:10:15	0:09:24

CFU; Colony Forming Units, TTP; Time To Positivity (days:hours:minutes), AE; Plus Aerobic/F vials, AN; Lytic/10 Anaerobic vials, PB; Peds Plus/F vial, TCHL; Taurolidine-Citrate-Heparin Lock
The CFUs counted for the quantity check (target 100 CFU) were 124 and 121 for *Staphylococcus aureus* (ATCC 29213) and *Escherichia coli* (ATCC 25922), respectively.

Aerobic/F vials. Moreover, *C. albicans* did not grow at all in Lytic/10 Anaerobic/F vials under all study conditions tested.

Next, blood was added to the blood culture vials in order to represent blood cultures in a clinical setting more closely. In addition to the ATCC strains, two clinical strains were used for spiking (100 CFU/vial), i.e. *S. aureus* and *E. coli* blood culture isolates from paediatric oncology patients. Also, 3.16 fold and 10-fold dilutions of TCHL were tested (representing a TCHL volume of approximately 470 µl and 150 µl per vial, respectively). Without blood, the results with undiluted TCHL were essentially similar to the previous experiments, i.e., blood culture vials remaining negative or showing a marked delay in TTP in the presence of TCHL for both *S. aureus* and *E. coli* (**Table 3**). A 10-fold dilution of TCHL still affected the TTP in vials spiked with *S. aureus* with a delay ranging from around 4-19 hours. The TTP in vials spiked with *E. coli* was much less affected by a 10-fold dilution of TCHL, with a delay of <1 hour. A higher dose (3.16-fold dilution of TCHL) modestly affected the TTP of vials containing *E. coli* with a delay of around 1-2 hours. Notably, the effect of the TCHL on the TTP was mitigated, but still demonstrated, in the presence of blood, both in Plus Aerobic/F vials (containing 8 ml of blood) and Peds Plus vials (containing 2 ml of blood). Most vials eventually became positive, also in the presence of the highest dose of TCHL

TABLE 2 Time to positivity of blood culture vials spiked with 100 and 10 CFU of various micro-organisms and with 1.5 ml TCHL, heparin 100 IU/m or NaCl 0.9%, without blood.

***Staphylococcus epidermidis* (ATCC 49134)**					***Escherichia coli* (ATCC 25922)**			
	10 CFU		100 CFU		10 CFU		100 CFU	
	AE	AN	AE	AN	AE	AN	AE	AN
TCHL	Negative	1:17:55	Negative	1:19:23	Negative	0:14:32	Negative	0:13:50
Heparin	1:22:18	0:22:01	1:18:53	0:18:47	0:12:42	0:11:01	0:11:40	0:10:10
NaCl	1:18:44	0:22:10	1:18:23	0:19:07	0:12:41	0:12:11	0:11:40	0:11:20
***Enterococcus faecalis* (ATCC 29212)**					***Staphylococcus aureus* (ATCC 29213)**			
	10 CFU		100 CFU		10 CFU		100 CFU	
	AE	AN	AE	AN	AE	AN	AE	AN
TCHL	3:07:25	0:22:49	1:18:52	0:22:58	Negative	2:01:47	Negative	2:00:46
Heparin	0:12:16	0:11:46	0:10:33	0:10:22	0:13:39	0:16:09	0:14:28	0:11:58
NaCl	0:12:06	0:11:56	0:10:22	0:10:22	0:17:08	0:13:58	0:15:07	0:11:47
***Candida albicans* (ATCC 10231)**								
	10 CFU		100 CFU					
	AE	AN	AE	AN				
TCHL	1:04:11	Negative	1:01:13	Negative				
Heparin	1:03:10	Negative	1:00:12	Negative				
NaCl	1:03:10	Negative	1:00:11	Negative				

CFU; Colony Forming Units, TTP; Time To Positivity (days:hours:minutes), AE; Plus Aerobic/F vials, AN; Lytic/F Anaerobic vials, TCHL; Taurolidine-Citrate-Heparin Lock. The CFUs counted for the quantity check (target 100 CFU) were 51, 180, 36, 256 and 240 for *Staphylococcus epidermidis* (ATCC 49134), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC) 29213 and *Candida albicans* (ATCC 10231), respectively.

(i.e. 1.5 ml of undiluted TCHL), with the exception of the Plus Aerobic/F vial spiked with the *S. aureus* patient isolate that remained negative after five days of incubation. A dose-dependent delay in TTP was observed in all settings ranging from < 1 hour to several days [**Table 3**].

For all experiments, subcultures of positive vials only showed the spiked micro-organisms and subcultures of negative vials did not show growth. The conditions that were repeated across the three experiments for *Staphylococcus aureus* and *Escherichia coli* ATCC isolates, showed comparable results.

TABLE 3 Time to positivity of spiked blood cultures vials spiked with *Staphylococcus aureus* (ATCC 29213 and patient isolate) or *Escherichia coli* (ATCC 25922 and patient isolate) with and without blood and different concentrations of TCHL or NaCl.

***Staphylococcus aureus* (ATCC 29213)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	1:11:27	1:12:40	Negative	3:17:40
TCHL 3.16x	0:14:26	0:17:08	2:10:36	1:04:09
TCHL 10x	0:12:24	0:13:38	0:23:04	0:16:38
NaCl	0:11:56	0:12:49	0:14:06	0:12:07
***Staphylococcus aureus* (patient isolate)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	Negative	3:15:18	Negative	Negative
TCHL 3.16x	0:19:14	0:23:11	Negative	2:13:36
TCHL 10x	0:13:16	0:15:10	1:18:43	1:00:45
NaCl	0:12:58	0:12:37	0:23:05	0:15:09
***Escherichia coli* (ATCC 25922)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	0:17:03	0:17:05	Negative	Negative
TCHL 3.16x	0:11:04	0:11:23	0:12:35	0:11:15
TCHL 10x	0:10:26	0:10:46	0:10:56	0:10:26
NaCl	0:10:18	0:10:17	0:10:38	0:09:58
***Escherichia coli* (patient isolate)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	0:16:20	2:10:21	Negative	Negative
TCHL 3.16x	0:10:47	0:10:17	0:12:17	0:10:46
TCHL 10x	0:09:58	0:09:37	0:10:37	0:09:58
NaCl	0:10:09	0:09:48	0:10:18	0:09:29

PB; Peds Plus/F, CFU; Colony Forming Units, TTP; Time To Positivity (days:hours:minutes), AE; Plus Aerobic/F vials, TCHL; Taurolidine-Citrate-Heparin Lock

The CFUs counted for the quantity check (target 100 CFU) were 94, 312, 101, 76 and 75 for *Staphylococcus aureus* (ATCC 29213 AE), *Staphylococcus aureus* (ATCC 29213 PB), *Staphylococcus aureus* (patient isolate AE and PB), *Escherichia coli* (ATCC 25922 AE and PB), and *Escherichia coli* (patient isolate AE and PB), respectively.

DISCUSSION

The presence of taurolidine in blood culture vials seems to affect the growth of various microorganisms, with vials remaining negative or delaying the TTP. The higher the concentration of taurolidine in the blood culture, the larger the effect. Blood mitigates this inhibitory effect, but does not fully counteract it. Still delays of hours were observed in vials with blood in combination with a 3.16-fold TCHL dilution (approximately 470 µl TCHL per blood culture vial). In addition, delays of multiple days were observed if a complete (i.e. 1.5 ml) non-diluted taurolidine lock was added to the vial. Possible explanations for the mitigation by blood are that blood creates a better environment for microbial growth, that taurolidine binds to albumin or other components in blood or that the derivatives of taurolidine (e.g., formation of radicals) are neutralized by blood. Nonetheless, even a TTP delay of hours can have important clinical implications, since adequate antimicrobial therapy might be postponed in seriously ill patients. Moreover, not all laboratories are open 24/7 and a positive blood culture with a delayed TTP around closing hours could be noticed only the next day. All blood cultures containing blood eventually did became positive except for one. This suggests that the potential impact of taurolidine (accidentally present in blood culture vials when not discarded) on the results of research projects investigating taurolidine locks to prevent CLABSI may be less prominent.

All vials used in the experiments contain a non-ionic adsorbing resin and a cationic exchange resin, designed to bind antimicrobial agents. The cationic exchange resin binds positively charged antimicrobial agents, whereas the non-ionic adsorbing resin binds most antimicrobial agents through interaction with hydrophobic regions (12). It is unknown whether these resins bind and inactivate taurolidine, but our experiments show that taurolidine still inhibits microbial growth in the presence of the resins. Possible explanations might be that the resins do not bind taurolidine, do

not inactivate taurolidine, or that too much taurolidine is present for the resins to bind/inactivate all taurolidine completely. An alternative explanation of the observed inhibitory effect of taurolidine in this study could be that taurolidine interferes with the detection itself, i.e. CO_2 related fluorescence of the sensor in the vials. However, this seems unlikely because 1) the detection of *Candida albicans* was hardly affected by taurolidine and 2) subculture of the negative vials did not show any growth, suggesting inhibition of microbial growth, rather than interference with detection is the mechanism of action. Limitations of this study were that only five micro-organisms were investigated (of which only two in the presence of blood), that the taurolidine susceptibility was not tested for the different micro-organisms, blood came from healthy non-paediatric oncology patients, and only one blood culture system and its corresponding vials were tested.

This study underlines the importance of discarding taurolidine after aspiration from the CVC before blood cultures are obtained. In our opinion, clinical guidelines and method sections of trials focussing on the efficacy of TLs should specifically state this and may encourage to register that the TLs are discarded before a blood culture is taken. If this is not done correctly, it can have an important impact on the treatment of patients.

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CHAPTER 9

The applicability of the central line-associated bloodstream infection (CLABSI) criteria for the evaluation of bacteraemia episodes in paediatric oncology patients

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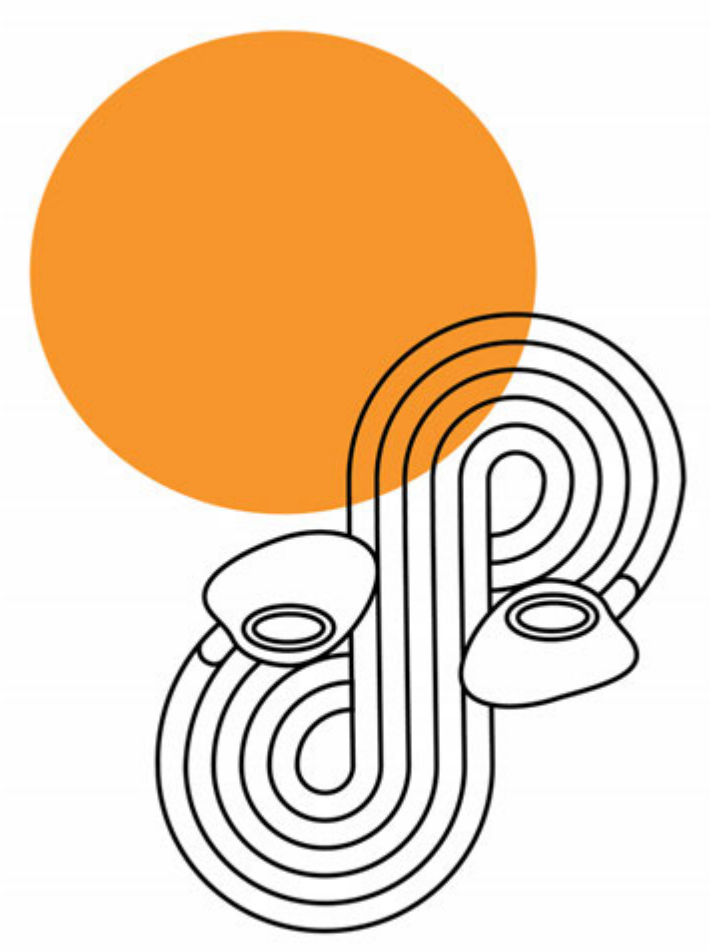


ABSTRACT

Background The aim of this study was to investigate the applicability of the central line-associated bloodstream infection (CLABSI) criteria of the Centers for Disease Control and Prevention in pediatric oncology patients.

Methods Bacteremia episodes from 2020-2022 from a prospective cohort of pediatric oncology patients with a central venous catheter were included. Episodes were classified by three medical experts following the CLABSI criteria as either a CLABSI or non-CLABSI (i.e. contamination, other infection source, or mucosal barrier injury-laboratory confirmed bloodstream infection (MBI-LCBI)). Subsequently**,** they were asked if and why they (dis)agreed with this diagnosis following the criteria. The primary outcome was the percentage of episodes where the experts clinically disagreed with the diagnosis given following the CLABSI criteria.

Results Overall, 84 bacteremia episodes in 71 patients were evaluated. Following the CLABSI criteria, 34 (40%) episodes were classified as CLABSIs and 50 (60%) as non-CLABSIs. In 11 (13%) cases the experts clinically disagreed with the diagnosis following the CLABSI criteria. The discrepancy between the CLABSI criteria and clinical diagnosis was significant; McNemar's test $p<0.01$. Disagreement by the experts with the CLABSI criteria mostly occurred when the experts found an MBI-LCBI a more plausible cause of the bacteremia than a CLABSI due to the presence of a gram negative bacteremia (*Pseudomonas aeruginosa* n=3) and/or mucositis.

Conclusions A discrepancy between the CLABSI criteria and the evaluation of the experts was observed. Adding *Pseudomonas aeruginosa* as an MBI pathogen and incorporating the presence of mucositis in the MBI-LCBI criteria, might increase the applicability.

Trial registration number NCT05740150.

INTRODUCTION

Central venous catheter (CVC)-related bloodstream infections are frequently observed in pediatric oncology patients. For clinical, research and surveillance purposes multiple definitions have been developed to classify a bacteremia as CVC-related. However, most definitions are based on studies including critically ill patients with temporary non-tunneled CVCs with a distinct underlying pathophysiology which influences their risk of a bacteremia. Due to the difference in pathophysiology, different preventative and treatment strategies are needed per patient group. In international pediatric oncology literature and for surveillance purposes, the central line-associated bloodstream infection (CLABSI) criteria of the Centers for Disease Control and Prevention (CDC) are used predominantly(1, 2). These criteria are preferred for this patient group since, in contrast to the catheter-related bloodstream infection (CRBSI) criteria of the Infectious Diseases Society of America (IDSA)(3), no peripheral blood cultures (i.e. extra skin punctures) are req uired to classify a bacteremia as CVC-related. Additionally, the CLABSI criteria take into account bacteremia caused by mucosal barrier injury-laboratory confirmed bloodstream infections (MBI-LCBI), which occur during periods of prolonged neutropenia in patients receiving chemotherapy. An MBI-LCBI is a frequent cause of bacteremia in children with cancer(1, 4). However, criteria always have their disadvantages which can cause a mismatch between the clinical diagnosis given by physicians and the developed criteria. For research and surveillance purposes it is important to be aware of these disadvantages that cause mismatches per patient group, so that they can be taken into account in the interpretation of results and the development of strategies. A better classification of events enhances attribution and thereby contributes to more effective preventative interventions to address underlying causes. Therefore, this study was performed to investigate how often and why a mismatch between the CLABSI criteria and the clinical diagnosis given by experts occurs.

METHODS

Study design and participants

For this study, the data of patients included in the CATERPILLAR-study (ClinicalTrials.gov NCT05740150) between October 2020 and November 2022 were partially used. Only patients in whom a bacteremia was reported during the follow-up period of the study were included. The CATERPILLAR-study is a randomized controlled study in pediatric oncology patients investigating the efficacy of a lock solution containing taurolidine, heparin and citrate (intervention) compared to heparin only (control group) for the prevention of CLABSIs. Details about the CATERPILLAR study design are described in the published trial protocol(5). Children younger than 19 years old receiving a CVC in the Princess Máxima Centre for Pediatric Oncology, Utrecht, the Netherlands, were included in this study. The Princess Máxima Centre for Pediatric Oncology is a specialized pediatric oncology and hematological stem cell transplantation hospital with an average bed occupancy in 2022 of 69(6). During the study period 1529 CVCs were inserted and remained in situ for a mean of 314 days and with an average CLABSI rate of 2.64 per 1,000 CVC-days(7). Due to the descriptive nature of this part of the study, no sample size calculation was performed. The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research registered under number 20/370 (https://www.metcutrecht.nl/). All patients gave their written informed consent. The "strengthening the reporting of observational studies in epidemiology" (STROBE) checklist was completely adhered to(8).

Outcomes

The primary study outcome was the percentage of episodes where the experts disagreed with the diagnosis given following the CLABSI criteria based on the clinical evaluation of the patient files. The secondary outcome was a description of the different reasons for these disagreements.

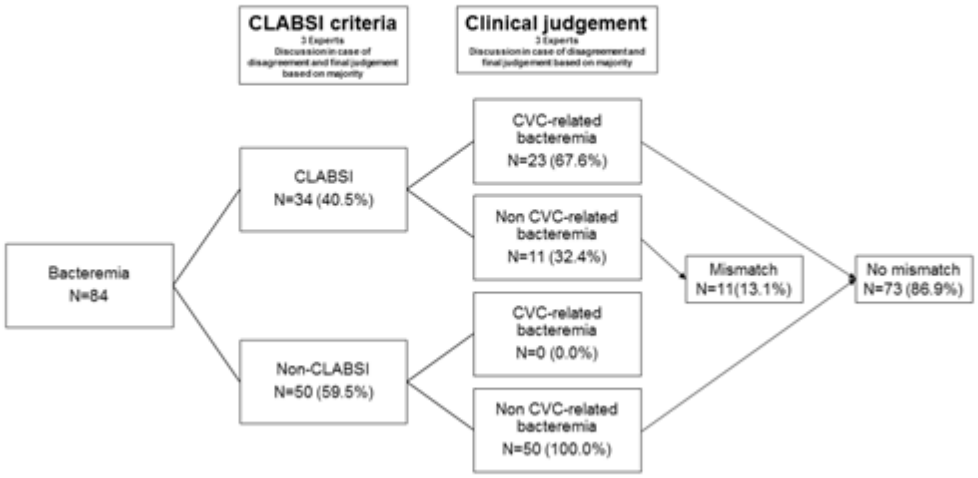
Study procedure and data-management

All bacteremia episodes that occurred during follow-up were independently evaluated by a pediatric infectiologist and two medical microbiologists. They classified all episodes following the CLABSI criteria as CLABSI or non-CLABSI (i.e., mucosal barrier injury-laboratory confirmed bloodstream infection (MBI-LCBI) or other non-CLABSI reasons such as CVC inserted for <48hours, contamination/colonization or another infection source)(1). If a non-CLABSI was caused by common commensals, the experts checked if at least >1 blood culture set was obtained, which is needed to be able to diagnose a common commensal CLABSI. Furthermore, the experts were asked if they agreed with the result they gave following the CLABSI criteria as compared to their clinical evaluation of the electronic patient files. If they disagreed with the result from the CLABSI criteria, they were subsequently asked to provide the reasons for their disagreement. All non-unanimous classifications were discussed between the experts. The CDC was contacted if the experts had questions concerning the CLABSI criteria. If the experts still disagreed after the discussion and contacting the CDC, final diagnosis was based on the presumed diagnosis given by the majority. (**Figure 1**) The physicians of the patients were contacted if information was missing. If data could not be retrieved from the patient files and physician, it was registered as missing.

Definitions

The CLABSI criteria are described by the CDC in detail(1). These criteria are designed for surveillance rather than clinical purposes. To summarize, a bacteremia was scored as a CLABSI if the patient met one of the following criteria: (1) a recognized pathogen was cultured from ≥one blood cultures, or (2) the same matching common commensal was cultured from ≥two blood cultures drawn on separate occasions, and at least one of the following signs was observed: fever, chills, or hypotension.

FIGURE 1 Flow-chart for the evaluation of bacteremia



CLABSI; Central Line Associated Bloodstream Infection, CVC; Central Venous Catheter.

Furthermore, a CLABSI could only be scored if the CVC was in place for more than 48 hours on the date of the event, if no CLABSI with the same microorganism was scored in the past two weeks, if the pathogen cultured was not related to an infection at another site, and if no MBI-LCBI could be scored. An MBI-LCBI was scored if (1) only recognized pathogens of intestinal origin were cultured or (2) only viridans streptococci were cultured, and if the patient was in neutropenia ($<500x10^6$/L on two separate occasions), was diagnosed with gastro-intestinal graft versus host disease grade III/IV or if the patient had >1L/24H diarrhea of any type during allogenic stem cell transplantation)(1, 9). (**Figure 2**)

Statistical analysis

For the baseline characteristics and outcomes, descriptive statistics were used, i.e. absolute counts and percentages. McNemar's test (with continuity correction) was used to test whether or not counts were consistent across experts opinion and the CLABSI criteria. For this test, the individual bacteremia episodes were considered as

unique events. IBM SPSS Statistics for Windows version 26.0 (United States of America) was used to perform all analyses.

RESULTS

In total, 71 patients with a median age of 5 years were included. Eighty-four bacteremia episodes were observed and evaluated. The majority of patients were diagnosed with a hemato-oncologic disease and received a totally implantable venous access port (TIVAP) as compared to a tunneled CVC. The majority of bacteremia episodes were caused by gram positive bacteria (73%); coagulase-negative staphylococci specifically (35%). (**Table 1**)

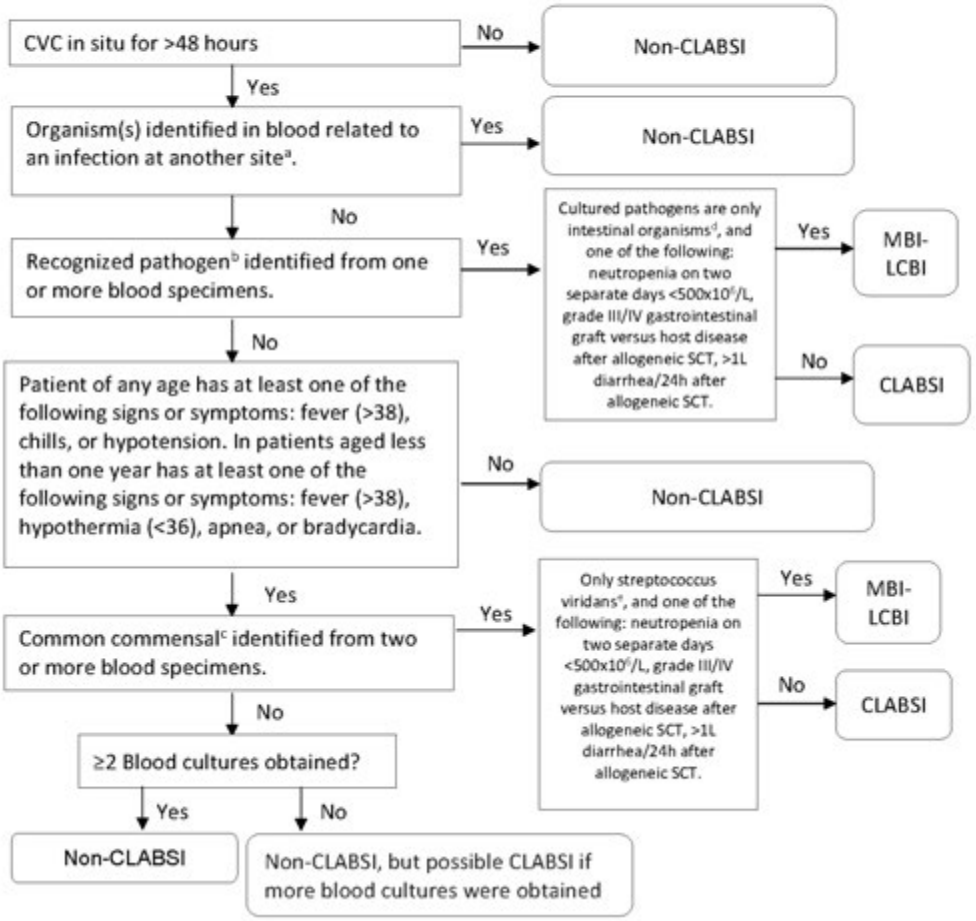
CLABSI criteria

In 17 out of 84 (20%) bacteremia episodes, the diagnosis given using the CLABSI criteria was not unanimous. After a discussion between the experts and/or consultation with the CDC, an unanimous decision was reached in all (100%) cases.
In total, 34 (40%) episodes were classified as a CLABSI and 50 (60%) as a non-CLABSI. (Fig. 1) Of the CLABSIs, 15 (44%) were caused by common commensals and 19 (56%) by recognized pathogens. Of the non-CLABISs, six (12%) were diagnosed as an MBI-LCBI. Of all 84 episodes, 10 (12%) non-CLABSIs were caused by a common commensal while only one blood culture was obtained, and therefore a CLABSI might have been scored if multiple blood cultures were obtained.

Clinical judgement

For all episodes, the experts evaluated and discussed if they (dis)agreed with the diagnosis given by the CDC criteria; in five (6%) cases the experts could not come to an unanimous decision if they agreed or disagreed with the CLABSI criteria and the final judgement was therefore made based on the majority. Following the clinical

FIGURE 2 Flow-chart summarizing the CLABSI criteria (1)



CLABSI; Central Line Associated Bloodstream Infection, CVC; Central Venous Catheter, MBI-LCBI; Mucosal Barrier Injury – Laboratory Confirmed Bloodstream Infection, SCT; Stem Cell Transplantation.

[a] Use the secondary bloodstream infection guide provided by the Centers for Disease Control and Prevention (CDC) (1).

[b] Recognized pathogens are pathogens that are not included on the CDC common commensal list (e.g. *S. Aureus*) (1). The following micro-organisms are not included in the common commensal list but are not recognized pathogens: *Campylobacter, C. difficile, Enterpopathogenic E. coli, Listeria spp., Salmonella spp.,* and *Yersinia spp*.

[c] Common commensals are micro-organisms that are included on the NHSN common commensal list (e.g. *Coagulase-negative staphylococci, Viridians group streptococci, Bacillus spp., Diphtheroids, Aerococcus spp.,* and *Micrococcus spp.)* (1).

[d] Micro-organisms registered as MBI Organisms on the NHSN common commensal list (e.g. *Escherichia coli, Enterobacteriaceae,* and *Enterococci)* (1).

[e] Viridans streptococci: e.g. *S. mitis, S. oralis, S. salivarius, S. thermophilus, S. vestibularis, S. anginosus, S. sanguinis, S. parasanguinis, S. gordonii, S. mutans,* and *S. sobrinus.*

TABLE 1 Baseline characteristics

		Total patients N=71, (median range or N %)			
Age at inclusion in years		5 (0-17)			
Gender	Male	43 (60.6%)			
	Female	28 (39.4%)			
Diagnosis	Hemato-oncology/lymphoma	60 (84.5%)			
	Neuro-oncology	1 (1.4%)			
	Solid tumor	10 (14.1%)			
CVC type	Tunneled external CVC	28 (39.4%)			
	TIVAP	43 (60.6%)			
		Total episodes N=84, (N %)	**CLABSIs N=34, (N %)**	**Non-CLABSIs N=50, (N %)**	
				MBI-LCBI N=7	**Other non-CLABSIs N=43**
Micro-organisms	Only GP bacteria	61 (72.6)	20 (58.8)	2 (28.6)	39 (90.7)
	CoNS[a]	29 (34.5)	9 (26.5)	0 (0.0)	20 (46.5)
	S. aureus	3 (3.6)	3 (8.8)	0 (0.0)	0 (0.0)
	Enterococci[b]	1 (1.2)	0 (0.0)	1 (14.3)	0 (0.0)
	Other GP[c]	13 (15.4)	4 (11.8)	0 (0.0)	9 (20.9)
	Polymicrobial GP[d]	15 (17.9)	4 (11.8)	1 (14.3)	10 (23.3)
	Only GN bacteria	10 (11.9)	3 (8.8)	4 (57.1)	3 (7.0)
	Enterobacterales[e]	5 (6.0)	0 (0.0)	3 (42.9)	2 (4.7)
	Nonfermenting GN[f]	2 (2.4)	1 (2.9)	0 (0.0)	1 (2.3)
	Other GN[g]	2 (2.4)	1 (2.9)	1 (14.3)	0 (0.0)
	Polymicrobial GN[h]	1 (1.2)	1 (2.9)	0 (0.0)	0 (0.0)
	Candida spp.[i]	1 (1.2)	1 (2.9)	0 (0.0)	0 (0.0)
	Polymicrobial mixed[j]	12 (14.3)	10 (29.4)	1 (14.3)	1 (2.3)

TIVAP; Totally Implantable Venous Access Port, CVC; Central Venous Catheter, GP; gram positive, GN; gram negative, CoNS; Coagulase-negative staphylococci, CLABSI; Central Line Associated Bloodstream Infection, MBI-LCBI; Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection. The table describes 71 patients with 84 bacteremia episodes. Micro-organisms cultured (N of episodes): [a]*S. capitis* (1) *S. epidermidis* (19) *S. haemolyticus* (3) *S. hominis* (5), *S. pasteuri* (1). [b]*Enterococcus faecium* (1). [c]*Actinomyces odontolyticus* (1) *Bacillus circulans* (1) *Brevibacterium casei* (1*) Micrococcus* spp. (5) *Pediococcus pentasaceus* (1) *Peptoniphilus* spp. (1), *Rothia mucilaginosa* (2), *Kocuria rhizophila* (1). [d]*S. hominis* and *S. condimenti* (1), *S. hominis, S. epidermidis, Aerococcus viridans,* and *Bacillus cereus* (1), *S. mitis* and *S. hominis* (1), *S. mitis* and *S. oralis* (1), *Micrococcus luteus* and *Kocuria rhizophila* (1), *S. hominis* and *Micrococcus luteus* (2), *S. mitis* and *S. epidermidis* (1), *S. haemolyticus* and *S. salivarius* (1), *S. hominis, S. epidermidis,* and *Micrococcus luteus* (1), *S. epidermidis* and *S. salivarius* (1), *S. epidermidis* and *Micrococcus luteus* (1), *S. epidermidis, S. haemolyticus,* and *Granulicatella adiacens* (1), *S. mitis*, *S. epidermidis,* and *S. hominis* (1), *S. haemolyticus* and *S. hominis* (1). [e]*Enterobacter cloacae* complex spp. (1) *Escherichia coli* (2), *Klebsiella* spp. (2). [f]*Pseudomonas* spp. (2). [g]*Fusobacterium* spp. (1), *Paracoccus yeei* (1). [h]*Citrobacter freundii, Klebsiella pneumoniae,* and *Enterobacter cloacae* complex (1). [i]*Candida parapsilosis* (1). [j]*Moraxella osloensis, Granulicatella adiacens,* and *S. mitis* (1), *Granulicatella adiacens, S. epidermidis,* and *E. coli* (1), *S. hominis,* and *Delftia acidovorans* (1), *Moraxella osloensis, S. hominis,* and *S. epidermidis* (1), *Candida kefyr*, and *S. epidermidis* (1), *Acinetobacter baumanii,* and *S. epidermidis* (1), *Paracoccus yeei, Micrococcus* spp., and *S. oralis* (1), *S. mitis,* and *Pseudomonas aeruginosa* (1), *Actinomyces odontolyticus, S. epidermidis,* and *Capnocytophaga sputigena* (1), *Bacillus cereus, E. coli,* and *S. sciuri* (1), *Moraxella osloensis,* and *Micrococcus luteus* (1), *S. epidermidis,* and *E. coli* (1)

judgment of the experts, in 73 (87%) cases the experts agreed with the CLABSI criteria and in 11 (13%) the experts disagreed with the CLABSI criteria. (**Figure 1**)

Mismatches between CLABSI criteria and clinical judgement

The McNemar's test showed that there is a significant discrepancy between the CLABSI criteria and the clinical diagnosis given by experts (p=0.00257). In all mismatch cases, a CLABSI was diagnosed following the CLABSI criteria, but the experts found a non CVC-related cause more probable. Contamination or colonization was more probable following the experts than a CLABSI in six cases and an MBI-LCBI was more probable than a CLABSI in five cases. More specifically, *Pseudomonas aeruginosa* (n=3) is registered as a non-MBI related recognized pathogen, but could also be related to an MBI-related bloodstream infection in the eyes of the experts. In two cases where *Pseudomonas aeruginosa* was found in the blood culture, it was also found in the rectal swab obtained for active surveillance testing during the presence of mucositis and severe neutropenia, which made an MBI-related bloodstream infection a more probable cause in the eyes of the experts. In two cases, an MBI micro-organism was cultured, mucositis was suspected or present (i.e. peri-anal ulcerations and rectal blood loss), but there was no presence of neutropenia or stem cell transplant history. Therefore, a CLABSI was scored, but an MBI-LCBI was a more probable cause as judged by the experts. Furthermore, the experts disagreed with the classification of micro-organisms as a recognized pathogen in three of the mismatch cases. In the eyes of the experts *Moraxella osloensis* (n=2) is a commensal with low virulence and *Paracoccus yeei* (n=2) is an environmental low virulent micro-organism rather than a recognized pathogen. Making contamination or colonization of the CVC a more probable cause. In one case, the micro-organism was cultured from two instead of all three CVC lumina, which the experts found more suggestive for colonization or contamination than a CVC-related bloodstream infection. Finally, in one case, many different micro-

organisms (including two similar common commensals) were cultured which the experts found more suggestive for colonization or contamination instead of a CVC-related bloodstream infection. [**Table 2**]

TABLE 2 Summary of reasons for mismatch

CLABSI criteria	Clinical diagnosis	Mismatch reason	(N %)
CLABSI	Contamination or colonization	Disagreement with registration of *Moraxella osloensis* N=2 and *Paracoccus yeei* N=2 as recognized pathogen instead of common commensal.	4 (36.4)
		Various common commensals cultured.	1 (9.1)
		Common commensals cultured from 2/3 CVC lumina.	1 (9.1)
	MBI related bloodstream infection	Disagreement with registration of *Pseudomonas aeruginosa* as non MBI instead of MBI pathogen.	1 (9.1)
		Disagreement with registration of *Pseudomonas aeruginosa* as non MBI instead of MBI pathogen AND mucositis, neutropenia and *Pseudomonas aeruginosa* cultured from the blood matched the pathogen cultured from a rectal swab for active surveillance testing.	2 (18.2)
		MBI micro-organism cultured and (suspicion of) mucositis, but no neutropenia and no stem cell recipient.	2 (18.2)

MBI; Mucosal Barrier Injury, CVC; Central Venous Catheter, CLABSI; Central Line Associated Bloodstream Infection, MBI-LCBI; Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection

DISCUSSION

Overall, a significant discrepancy between the diagnosis following the CLABSI criteria and the clinical diagnosis given by experts was observed. The experts disagreed with the result from the CLABSI criteria in almost one-third of the cases and only if a CLABSI was diagnosed following the criteria. On the other hand, the diagnosis following the CLABSI criteria and clinical diagnosis aligned in all cases when a CLABSI was ruled out following the criteria. To summarize, the use of the CLABSI criteria of the CDC may lead to an overestimation of the number of bacteremia episodes caused by the CVC in pediatric oncology patients.

In the majority of cases, the experts disagreed with the CLABSI criteria when there was a presence or suspicion of mucositis (not an element scored in the definition of an MBI-LCBI), making mucosal barrier injury (MBI) a more plausible cause of the bacteremia episode than a CLABSI. In the eyes of the experts conducting this study, the presence of mucositis is more suggestive for an MBI related bloodstream infection than severe neutropenia, as also reported by Herbers et al. (2014)(10). Especially, if the micro-organism cultured from the blood, exactly matches the micro-organism from a rectal swab obtained for active surveillance testing (specifically not taken into account following the CDC criteria) (1). Therefore, integrating the presence of mucositis into the MBI-LCBI criteria might improve the applicability of the CLABSI criteria in (pediatric) oncology patients during chemotherapy.

The classification of *Pseudomonas aeruginosa* as a non-MBI pathogen by the CDC was questioned by the experts for this patient group. Especially in hospitalized cancer patients, intestinal carriage of *Pseudomonas aeruginosa* is prominent(11). Furthermore, the experts disagreed with the classification of *Moraxella osloensis* and *Paracoccus yeei* as recognized pathogens following the CDC criteria for this patient group. Importantly, both microorganisms are occasionally observed in pediatric oncology patients; i.e. 4% and 2% of all bacteremia episodes during this study, respectively.

Also, when various common commensals are cultured, the experts agreed that identification of two similar common commensals is rather a coincidence, indicating contamination instead of a CLABSI. The experts also stated that a CVC-related bloodstream infection is mostly suspected if the common commensal is cultured from all CVC lumen. However, in case of a triple lumen CVC, where positive cultures are found in two of the three lumen, this will result in the classification of the episode as a CLABSI following the CDC criteria, whereas two out of three of the experts find

contamination or CVC colonization a more probable cause for the bacteremia. Triple lumen CVCs however, are much less common than single or double lumen CVCs. Therefore, the influence on the accuracy of the CLABSI criteria should be minimal.

Furthermore, the experts had some additional comments not specifically related to any of the cases described above. The MBI micro-organisms list, is in their eyes, more focused on lower rather than upper gastro-intestinal tract bacteria. However, MBI occurs in the whole gastro-intestinal trajectory, especially in pediatric oncology patients(12), and therefore also micro-organisms related to upper gastro-intestinal MBI, e.g. *Actinomyces* spp., should be called MBI-related micro-organisms in their opinion. Also, in some cases, only one blood culture before the start of antibiotic treatment is obtained (especially in patients with a single lumen CVC). This automatically excludes the presence of a common commensal CLABSI and hypothetically results in an underestimation of true CVC-related bloodstream infections since the diagnosis of a common commensal CLABSI requires two positive blood cultures. For neonates, which were not included in this study, the same problem has been observed. Heijting et al. (2021) proposed neonatal CLABSI criteria for this; if only one common commensal is identified by a blood culture, and the C-reactive protein level is above 10mg/L within 36 hours following blood culture collection, a CLABSI can be scored(13).

Strengths of this study are that, to our knowledge, the applicability of the CLABSI criteria for pediatric oncology patients has not been investigated previously. This is of importance since previous studies were mostly performed in critically ill patients with non-tunneled CVCs. As a result, the criteria are mainly based on patients with a distinct pathophysiology which requires different preventative strategies. Another strength is that three experts were independently involved in each episode evaluation (with consultation of the CDC when needed to further clarify specific parts

of the criteria), which is important since inaccurate use of the criteria is a known problem(14-19). Limitations are that important data might have been missing in the patient files during evaluation. Also, It remains difficult to diagnose a CVC related bloodstream infection with certainty in pediatric patients as compared to adults since no peripheral blood cultures (which can be used to calculate a differential time to positivity) are obtained and the catheter tip is mostly not cultured due to the limited diagnostic and therapeutic value (i.e. CVC mostly removed under antibiotic therapy)(4, 20). Furthermore, only bacteremia in the first 90 days after CVC insertion were included(5). Therefore, it is possible that these results cannot be extrapolated to bacteremia episodes after 90 days, since these might have occurred under different circumstances (e.g. consolidation instead of induction chemotherapy). Finally, we would be interested in similar data from other hospitals using the CLABSI-criteria, but did not identify studies during our literature review investigating this subject.

In conclusion, this study shows that the CLABSI criteria may lead to an overestimation of the number of bacteremia episodes caused by the CVC in pediatric oncology patients. On the other hand, for surveillance purposes, the current CDC criteria are very practical, the possible overestimation is less important if it remains constant over time, and the criteria are useful to compare results between different centers. Future research and surveillance projects focusing on the monitoring and decrease of CLABSIs, should take into account the reasons causing mismatches since bacteremia episodes that have been falsely diagnosed as a CLABSI may require different prevention and treatment methods, and including them in a research or surveillance project may lead to bias(21). Furthermore, adding *Pseudomonas* aeruginosa as an MBI pathogen and involving the presence of mucositis in the MBI-LCBI criteria, might increase the applicability of the CLABSI criteria for pediatric oncology patients.

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CHAPTER 10

CATERPILLAR-study protocol: an assessor-blinded randomised controlled trial comparing taurolidine-citrate-heparin to heparin-only lock solutions for the prevention of central line-associated bloodstream infections in paediatric oncology patients

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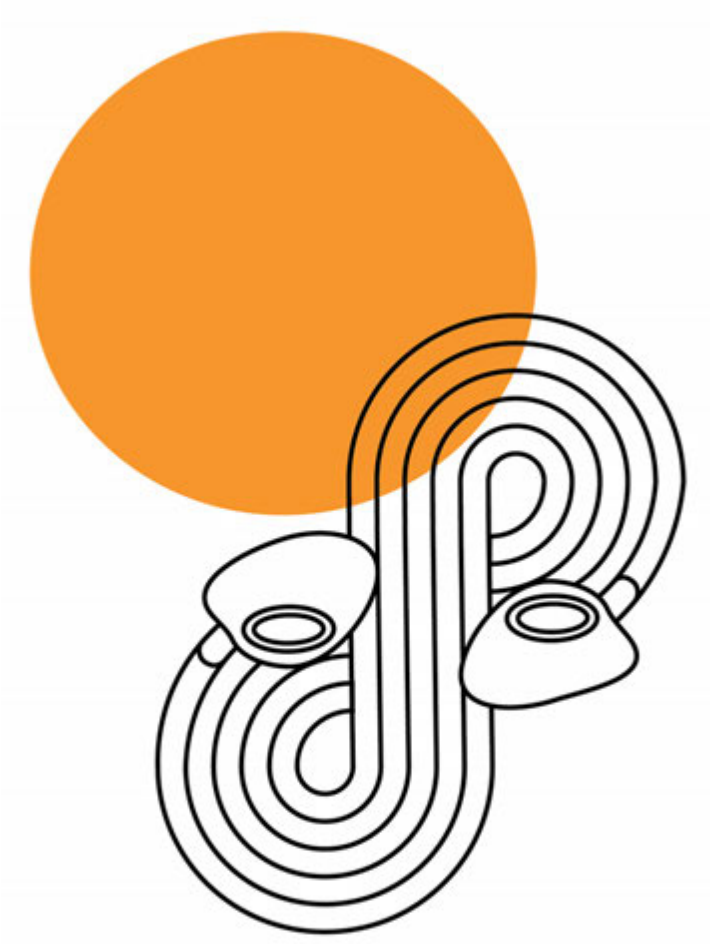

ABSTRACT

Introduction The efficacy of taurolidine containing lock solutions for the prevention of central line associated bloodstream infections (CLABSI) in paediatric oncology patients is still unknown. If the taurolidine-citrate-heparin lock appears to decrease the incidence of CLABSIs, we hope to increase the quality of life of children with cancer by subsequently reducing the central venous access device (CVAD)-removal rates, dispense of antibiotics, hospital admissions and incidence of severe sepsis resulting in intensive care unit admission.

Methods and analysis This assessor blinded randomized controlled trial including 462 patients was designed to compare the taurolidine-citrate-heparin lock to the heparin-only lock for the prevention of CLABSIs in paediatric oncology patients. Patients receiving their first CVAD at the Princess Máxima Centre for Paediatric Oncology, Utrecht, the Netherlands, were eligible for inclusion. The primary outcome of this study is the incidence of first CLABSIs from CVAD insertion until the end of the study, maximum follow-up of 90 days. An intention-to-treat and per-protocol analysis will be performed. An interim analysis will be performed after the inclusion of 50% of the patients. The results of the interim analysis and overall conduct of the trial will be discussed by a data safety monitoring board (DSMB). Inclusion of the study began on the 27th of October 2020. We expect that the planned number of patients will be recruited in 29 months from the defined source population.

Ethics and dissemination The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research registered under number 20/370. Written informed consent for participation in this trial and publication of the trial data is obtained from all patients and/or their parents/guardians. The results of this trial will be published in a peer-reviewed journal and subsequently the data will be made available after publication of the main results manuscript upon reasonable requests.

Trial registration number ClinicalTrials.gov NCT05740150

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Designed as an assessor blinded randomized controlled trial
- Stratification for central venous access device type and diagnosis will be performed
- Large paediatric oncology patient cohort (N=462)
- Inclusion and randomization should take place as soon as possible after insertion of the central venous access device, which is not always possible due to clinical and psychological circumstances.
- Locks are instilled once a week during the study since the maximum number of taurolidine-citrate-heparin locks that can be given during a certain time period is currently unknown, more frequent instillations of the lock might result in a higher efficacy.

INTRODUCTION

Central venous access devices (CVAD) are fundamental in paediatric oncology since they provide long-term venous access. The most commonly used CVADs in paediatric oncology patients are the totally implantable venous access ports (TIVAP) and external tunnelled CVADs. In this patient group, the incidence of central line-associated bloodstream infections (CLABSI) is high. (1) CLABSI incidence rates of 0.1-2.3 per 1,000 CVAD-days have previously been reported, mostly depending on the patient population, CVAD-type and infection definitions used. (2) In our hospital, the Princess Máxima Centre for paediatric oncology, a CLABSI incidence rate of 1.51 per 1,000 CVAD-days has been reported; at least one CLABSI was observed in 30% of the children receiving a CVAD. (3) CLABSI episodes often result in hospital admission, postponement of anticancer treatment, early CVAD removal (15% of all CVADs inserted) and can lead to severe sepsis requiring intensive care unit admission (5% of all patients receiving a CVAD). (3) CLABSIs therefore have a great impact on the quality of life of children diagnosed with cancer and result in high healthcare costs. (1, 4)

Taurolidine-citrate(-heparin) lock solutions (TCHL) are suggested as a promising and safe method for the prevention of CLABSIs. (5, 6) Taurolidine and citrate have anticoagulant, antimicrobial and anti-biofilm properties. No antimicrobial resistance to taurolidine has been reported, which makes taurolidine a more attractable option compared to other antimicrobial lock solutions. (7) Taurolidine causes a chemical reaction with the bacterial cell wall, endotoxins and exotoxins, resulting in irreversible damage to the bacteria, inhibition of bacterial pathogenicity and inhibition of surface adhesion of bacteria. (5, 7-11) The current standard of care in the Netherlands for paediatric oncology patients, is to lock CVADs with a heparin-only lock (HL) solution for the prevention of malfunctions. The HL however, does not have antimicrobial activity and its use is barely supported by literature. (5) Our meta-analysis including

all randomized controlled trials comparing the efficacy of taurolidine containing lock solutions to heparin-, saline- and citrate-only locks in haemodialysis, total parenteral nutrition, and oncology patients showed a pooled incidence rate ratio (IRR) of 0.30 (CI95% 0.19-0.46) in favour of the taurolidine containing lock solutions. Adverse events were all rare and mild. (6) However, these studies were associated with a serious risk of bias and indirectness of evidence. (6) More specifically, in paediatric oncology patients, only two open-labelled randomized controlled trials (N≤112) and four non-randomized controlled trials, have been performed. (12-17) To summarize, these studies did show promising results of the TCHL, but this was not enough evidence to implement the TCHL in paediatric oncology patients. (12-17)

Therefore, this assessor blinded randomized controlled trial including a large patient cohort was designed to compare the TCHL to the HL for the prevention of CLABSIs in paediatric oncology patients. If the TCHL appears to be safe and decreases the incidence of CLABSI, we hope to increase the quality of life for children with cancer by subsequently reducing the CVAD-removal rate, dispense of antibiotics, days of hospital and incidence of severe sepsis resulting in intensive care unit admission.

METHODS AND ANALYSIS

Design and setting

The CATERPILLAR-study is an investigator-initiated, assessor blinded, randomized controlled superiority parallel trial comparing the incidence of CLABSI between the TCHL to the HL in paediatric oncology patients with a CVAD (i.e. TIVAP and external tunnelled CVAD). The information in this manuscript aligns with the latest protocol, version number 4.0, 19-07-2022. In total 462 patients with a CVAD are expected to be recruited from the Princess Máxima Centre for paediatric oncology, Utrecht, the Netherlands over 29 months. The Princess Máxima Centre is the centralized hospital for paediatric oncology in the Netherlands (i.e. all patients diagnosed with a paediatric oncologic disease are treated here). Patients will be randomized (1:1) into

the HL or TCHL study arm. Patients will be followed up from CVAD insertion until the first CLABSI episode (primary outcome), CVAD-removal, second CVAD insertion or death with a maximum study period of 90 days, whichever comes first. The maximum study period of 90 days was chosen since a great deal of the CLABSI episodes occurs within the first 90 days after insertion (median of 60 days after insertion). (1-3)

In the first months after diagnosis, patients will receive their oncologic treatment at the Princess Máxima Centre. After one-two months, a minority of the patients will also be treated in one of the 15 shared care hospitals (**see supplementary file 1**) close to their homes. These patients will return at least every three weeks to the Princess Máxima Centre. The randomized locks (HL or TCHL) will be given when the patient visits the Princess Máxima Centre. The locks are instilled after each treatment cycle, with a maximum of once weekly. When the CVAD is used in between these moments (i.e. more frequent than once a week, in the home care setting, or at one of the shared care hospitals), for both groups, the CVAD will be temporarily locked with a non-study related HL. This was done since the maximum lock frequency for this patient group is unknown and the administration of study locks in all shared care hospitals and the home care setting would logistically be to difficult and the costs would be to high. The effect of this method is deemed minimal since the vast majority of patients visits the Princess Máxima Centre once a week and will then receive their randomized lock as soon as possible. The total number of lock days per patient will be taken into account/corrected for during the analyses as described below. Shared care data of the included patients will be shared with the Princess Máxima Centre.

Subjects can leave the study at any time if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons, if the patient is admitted in a hospital outside the Netherlands or non-participating shared care centre for more than three weeks, or if

the patient experienced a hypersensitivity reaction after instillation of the TCHL solution.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule for enrolment, interventions and assessments is described in **Figure 1**, the SPIRIT checklist was completed (see **supplementary file 2**). This trial is registered at ClinicalTrials.gov (NCT05740150). The items from the World Health Organization Trial Registration Data Set can be found in **Table 1**. All research staff working on this study is BROK®-certified (https://nfu-ebrok.nl/), (see **supplementary file 3** for the roles and responsibilities of the study team).

Patient and public involvement

The patient association Vereniging Kinderkanker Nederland (VKN; https://www.kinderkankernederland.nl/) was involved in the design of this study. The VKN reviewed the protocol and patient information forms, and they assessed the burden for patients to participate in the research. Currently yearly meetings are held between the researcher and VKN to discuss the progress of the trial. The advice given by the VKN is strongly taken into account by the researchers. Furthermore, the VKN will be involved in the plan for the dissemination of the trial results after completion of the trial.

Participants

All consecutive paediatric oncology patients (hematologic, solid and neurologic malignancies), treated at the Princess Máxima Centre for Paediatric Oncology, ranging from 0-19 years old, receiving a CVAD (tunnelled external CVAD or totally implantable venous access port (TIVAP)) for the first time or if their previous CVAD has been removed >12 months ago, will be asked to participate in this study by a research physician or nurse. Further inclusion criteria are: a radiological, cytological

Figure 1 The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule

	STUDY PERIOD				
	Enrollment	Allocation	Post-allocation		Close-out
TIMEPOINTS	Day 0-28 after CVAD surgery (preferably within 1 week)	Day 0-28 after CVAD surgery	Day 0-90 after CVAD surgery Visit 1-13*	Day 0-90 after CVAD surgery Daily patient file screening	Day 90 after CVAD insertion, CLABSI, CVAD removal, second CVAD insertion or death of patient, whichever comes first.
ENROLLMENT					
Eligibility screen	X				
Informed consent	X				
Review inclusion/ exclusion criteria	X				
Allocation		X			
INTERVENTIONS					
HL			X		
TCHL			X		
ASSESSMENTS					
Patient/CVAD characteristics	X	X			X
Lock characteristics			X		
Suspicion of CLABSI characteristics				X	X
Suspicion of local infection characteristics				X	X
Suspicion of CVT characteristics				X	X
(Serious) adverse event monitoring			X	X	X

Table 1a Items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05740150
Date of registration in primary registry	07-09-2017
Secondary identifying numbers	NTR6688 Nederlands Trial Register 12617 Dutch Cancer Society
Source(s) of monetary or material support	Monetary: Dutch Cancer Society (KWF) Material: Cablon Medical and TauroPharm
Primary sponsor	Princess Máxima Centre for Paediatric Oncology
Secondary sponsor(s)	Not applicable
Contact for public and scientific queries	Ceder Hildegard van den Bosch C.H.vandenBosch-4@prinsesmaximacentrum.nl +31625395632
Public title	Central line-associated bloodstream infection prevention using TauroLock-Hep100 in paediatric oncology patients.
Scientific title	The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunnelled central line-associated bloodstream infections in paediatric oncology patients, a randomized controlled, mono-centre trial.
Countries of recruitment	The Netherlands
Health condition(s) or problem(s) studied	Central line associated bloodstream infections
Intervention(s)	Experimental: TauroLock-Hep100 (taurolidine 1.35%, citrate 4%, heparin 100 IU/mL) Active Comparator: Heparin lock (heparin 100 IU/mL)

Table 1b Items from the World Health Organization Trial Registration Data Set

Data category	Information
Key inclusion and exclusion criteria	Inclusion criteria: • Age between 0 - <19 years • Radiological, cytological or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies) • Tunnelled external central venous access device or totally implantable venous access port to be inserted at the Princess Máxima Centre for Paediatric Oncology • Planned central venous access device insertion of >90 days • Written consent signed according to local law and regulations • Parents/guardians or patient are willing and able to comply with the trial procedure Exclusion criteria: • A previous central venous access device removed < 12 months ago. • Expected treatment for a majority of the follow-up time in a different hospital than the Princess Maxima Centre for paediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Centre at least once every 3 weeks. • Primary immunological disorder • Contra indications: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia. • Documented bacteraemia in the period from 24h before catheter insertion until inclusion • Insertion of the central venous access device at the same site as a previously confirmed central venous thrombosis • Pregnant, not willing to use adequate contraceptives, or breast-feeding
Study type	Interventional Allocation: Randomized in 2 arms 1:1 Masking: Assessor blinded Primary purpose: Prevention
Date of first enrolment	27-10-2020
Target sample size	462

Table 1c Items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary outcome(s)	Incidence of central line associated bloodstream infections
Key secondary outcomes	Time to first central line associated bloodstream infection Central line associated bloodstream infection incidence per 1,000 central venous access device-days Incidence of symptomatic central venous thrombosis Incidence of bacteraemia Incidence of local infections Dispense of thrombolysis/systemic antibiotic treatment due to central line associated bloodstream infections/ central venous thrombosis Incidence of and reasons for central venous access device-removal Cultured microorganisms causing central line associated bloodstream infections Days of hospital admission due to central line associated bloodstream infections/ central venous thrombosis Safety in terms of known side effects, severe adverse events, intensive care unit admission, and mortality rate due to central line associated bloodstream infections/central venous thrombosis

or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies), planned need for central vascular access of >90 days, written consent signed according to local law and regulations, parents/guardians or patient are willing and able to comply with the trial procedure. Exclusion criteria are: a previous CVAD removed < 12 months ago, expected treatment for a majority of the follow-up time in a different hospital than the Princess Maxima Centre for paediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Centre at least once every 3 weeks, primary immunological disorder, contra indications such as: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia, documented bacteraemia in the period from 24h before catheter insertion until inclusion, insertion of the CVAD at the same site as a previously confirmed central venous thrombosis (CVT), pregnant, not willing to use adequate contraceptives, or breast-feeding patients.

Informed consent procedure

Informed consent is obtained within one week after CVAD insertion, however, if this is not possible due to clinical circumstances, patients may be included within four weeks after CVAD insertion. Patients, parents and/or legal guardian are given verbal information and information in writing by the research physician or nurse. A dated and signed informed consent form will be obtained from each patient, parent and/or legal guardian depending on the age of the patients (see **Supplementary file 4**). The research physician or nurse will then also sign the consent form. A copy will be given to the patient and/or parents. The inclusion and exclusion criteria are thereafter checked by the researcher.

Randomization and blinding

Patients will be randomized by the research physician or nurse with a method of minimization into the HL or TCHL study arm (1:1) with the use of an online randomization service by internet called ALEA® (https://www.aleaclinical.eu/). Stratification will be done according to two factors: CVAD type (TIVAP or external tunnelled CVAD) and diagnosis (hematologic or solid, lymphoma, and neurologic malignancies). The expert panel, evaluating all possible CLABSI episodes, will be blinded for the allocated treatment. The allocated treatment will not be revealed to the expert panel or described in the parts of the electronic patient files which the expert panel will use to evaluate the possible CLABSI episodes. The patients, parents and/or legal guardians, and the rest of the research and clinical teams, will not be blinded. Complete blinding was logistically too difficult to execute and much more expensive since the design of the HL and TCHL ampoules is not similar.

Intervention

Patients will receive a lock solution of 0.8-1.5mL, depending on the CVAD-type as described in **Table 2**, containing taurolidine 1.35%, citrate 4.0%, and heparin 100

IU/mL (TauroLock-Hep100™, Cablon Medical, Leusden, the Netherlands and TauroPharm GmbH, Waldbüttelbrunn, Germany) or heparin 100 IU/mL at the Princess Máxima Centre after each treatment cycle with a maximum of once a week. The locks will remain in situ until the CVAD is used again. Before the CVAD is used again, the previously instilled study locks (TCHL and HL) will be removed from all lumina. If a blood culture is obtained while the lock is still in situ, at least 2mL of blood is aspirated and discarded for the prevention of false negative blood culture results. A dedicated research nurse will train the hospital staff, patients and parents/guardians and will monitoring adherence to the intervention study protocol as described above. All co interventions that are needed during the trial can be used as in usual clinical practice.

Table 2 Lock volumina

CVAD	Type	Diameter (Fr)	Maximal catheter volume (ml)	Lock volume (ml)
TIVAP	Babyport®	4.5	0.80	1.0
	Low-profile®	6.5	1.04	1.5
	Standard®	6.5	1.28	1.5
External tunnelled CVAD	Single lumen	6.6	0.74	1.0
	Double lumen	6.0 or 7.0	0.70/0.70 or 0.90/0.80	1.0/1.0
	Triple lumen	6.0	0.75/0.62/0.62	1.0/0.8/0.8

CVAD; Central Venous Access Device, TIVAP; Totally Implantable Venous Access Port.

Outcomes

The primary outcome of this study is the incidence of first CLABSIs from CVAD insertion until the end of follow-up. A blinded expert panel of one paediatric infectiologist and two medical microbiologists will judge each positive blood culture episode during the study period as a CLABSI or non-CLABSI bacteraemia following the Centres for Disease Control and Prevention CLABSI criteria. The CLABSI criteria were chosen since they are the most applicable criteria for paediatric oncology patients, since no peripheral blood cultures are obtained in this patient group, which are needed for other existing diagnostic criteria. (18) Judgement of the episodes will

be performed based on the patient files and by contacting the treating physician if necessary, the randomization group will not be described in the parts of the patient files that the experts will access for their assessment. All non-unanimous judgements will be discussed between the experts until they all agree. If the experts still disagree, the final judgement is based on the judgement of the majority. Additionally, all experts will be asked to answer if their result following the CLABSI criteria aligns with their clinical judgement.

The secondary outcomes of this study are (measured from CVAD insertion until the end of follow-up): the time to first CLABSI, CLABSI incidence per 1,000 CVAD days, the incidence of symptomatic central venous thromboses (CVT) (i.e. if the patient has (1) peripheral veins that have a non-compressible segment, or (2) there is an echogenic intra-luminal thrombus or an absence of flow in the central venous system (76)), bacteraemia episodes (i.e. every non-CLABSI related positive blood culture), local infections (i.e. positive exit-site culture, erythema, purulent drainage or tenderness within 2 cm of the CVAD track and exit-site), CVAD-removal (incl. reasons why CVAD was removed), cultured micro-organisms causing CLABSI, days of hospital admission due to CLABSIs/CVTs, the dispense of thrombolysis and systemic antibiotic treatment due to CLABSIs/CVTs, and safety of the locks in terms of (serious) adverse events, and intensive care unit admission or mortality due to CLABSIs/CVTs.

Data collection and management

Data is entered pseudonymized from paper case report forms and electronic patient files in Castor EDC (Castor EDC v2021.1, CATERPILLAR-study v.6.21, password-protected access) by trained local data managers in the Princess Máxima Centre. In Castor EDC range checks for data values are incorporated. All study information will be stored in locked cabinets in areas with limited access. Records with personal identifiers, will be stored separately from records identified by a code number. Study

information of the patients will not be released outside of the study without written permission of the patients. All data (incl. shared care hospital data) should be entered within 90 days after the end of study date of each patient. Regular quality checks are performed by a central data manager and independent monitor three times a year. The database will be locked after all data has been cleaned and all necessary changes have been made. The principal investigator and research physician will have access to the final trial dataset after completion of the trial. The data will be stored for at least 15 years. After the main results manuscript is published, the data will become available upon reasonable requests.

The following data will be collected: patient characteristics (age, gender, diagnosis, treatment protocol, administration of prophylactic systemic antibiotics (i.e. trimethoprim/sulfamethoxazole, ciprofloxacin, or anti-mycotics)), CVAD characteristics (surgery date, type, introduction method, lumen amount/diameter, access vein and side, complications during procedure, removal date and reason), lock characteristics (date instillation and removal, type, method of removal, (serious) adverse events during lock instillation and removal (following common terminology criteria for adverse events (CTCAE) version 5.0, November 27, 2017)), treatment for possible malfunction (i.e. impossibility to aspirate or flush the CVAD)), suspicion of CLABSI characteristics (start date episode, symptoms, neutropenia (incl. duration and lowest neutrophil count during episode: very severe <100, severe 500-1,000, moderate 500-1,000, mild 1,000-1,500x10^6/L)), blood culture results, treatment method of CLABSI, hospital/intensive care unit admission days, death, judgement of episode by expert panel (i.e. CLABSI, mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI), or bacteraemia due to other reasons), reasons for non-CLABSI related bacteraemia (i.e. not enough blood cultures obtained, contamination/colonization, CVAD in situ for <48 hours, infection at a different site)), suspicion of local infection characteristics (start date episode, symptoms, culture

results, treatment, hospital/intensive care unit admission days, death), suspicion of a CVT characteristics (start date episode, symptoms, radiological imaging, location, treatment, hospital/intensive care unit admission days, death) and end of the study reasons. Data of patients that prematurely drop-out of the study, will be collected until the day they dropped out.

Safety considerations

(Serious) adverse events with a possible or definite relationship to the locks are registered during the study (CTCAE version 5.0, November 27, 2017). Registration of all (serious) adverse events would lead to the registration of too many adverse events in these oncologic patient groups. Adverse events of special interest, due to their known relationship to the HL or TCHL are: oral dysesthesias, neck/chest wall pain, dysgeusia, nausea, vomiting, allergic reactions, and heparin induced thrombocytopenia. Patients will be followed-up for the occurrence of (serious) adverse events until 30 days after the last study lock was given. The Princess Máxima Centre will report serious adverse events within the appropriate time-frame (i.e. within 7 days of first knowledge in case of life threatening situations or death, and within 15 days in all other cases) to the accredited ethics committee that approved the protocol. The sponsor has a liability and subject insurance.

Data safety monitoring board (DSMB)

A DSMB is established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. Three DSMB meetings will be held: one start of the study session, a second closed session after the inclusion of 50% of the patients where the interim analysis will be presented, and a third session at the end of the study. The results of the interim analysis will only be presented to the principal and coordinating investigators, trial statistician, and DSMB members. The DSMB will not be blinded

and consists of a paediatric surgeon, infectious disease specialist and medical statistician. All three members are independent from the sponsor and have no competing interests. The DSMB will give an advice to the principal investigator, who will make the final decision to terminate or continue the trial (see supplementary file 5 for the DSMB charter).

Statistical methods

Sample size calculation

Assuming a CLABSI rate of 12.8%, an estimated total number of 412 patients is needed to detect a difference between group proportion of 7.8%, with a two-sided α of 0.05 and power of 80% (two-sided Z-Test with unpooled variance). (19-24) The CLABSI rate of 12.8% was based on the data from the CVAD complication database of the Princess Máxima Centre, partially published by van den Bosch et al. 2019, using the same inclusion and exclusion criteria and follow-up period as described for this study. (3) The estimated reduction of 12.8% to 5.0% was based on previously performed randomized controlled trials (RCT), of which the vast majority showed a reduction of at least more than 60%; IRR of 0.30 (CI95%0.19-0.46). For paediatric oncology specifically, two RCTs have been performed which showed reductions of 74% and 77%. (6) For each patient that prematurely drops-out of the study an extra patient will be included, we estimated that an extra 50 patients would be needed to account for potential drop-outs. The drop-out inflated total sample size is therefore calculated as 462 patients, 231 per group.

Interim analysis

An interim analysis will be performed after the inclusion of 231 patients. A stopping rule was defined for a one sided test at an α level of 0.025 for the null hypothesis: experimental incidence ≥ control incidence. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the

experimental. The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on α- and β-spending functions. As α-spending function we have chosen the Jennison and Turnbull power family function with ρ = 2.35 and as β-spending function we have chosen the Jennison and Turnbull power family function with ρ = 3.2.

Statistical analysis

The primary data analyses will be performed with the intention-to-treat (ITT) principle (i.e. inclusion of all patients that were randomized). Additionally, a per-protocol (PP) analysis will be performed excluding patients who were not included within one week after CVAD insertion, patients who never received the intervention and patients who missed three or more of the minimal amount (once every three weeks) of locks during the follow-up period. Categorical data will be presented as contingency tables (frequencies and percentages). All patients will be analysed in the intervention group they were initially randomized in. For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. Differences between treatment groups with respect to baseline characteristics will be analysed by using a Chi-square (or Fisher Exact in the presence of small numbers), and two-tailed t-test for categorical or continuous variables respectively. In case of violation of the normality assumption a non-parametric test such as the Wilcoxon rank test will be applied.

For the primary outcome, the percentages and incidence rates (IR) of first CLABSIs per 1,000 CVAD-days will be reported for both study groups and compared by computing an IRR. The exact confidence limits for the IRRs will be based on the polynomial algorithm for person time data (25, 26). The nominal alpha level for the

primary outcome in the final analysis will be equal to 0.045 due to the interim analysis (19-24).

The cumulative incidence of CLABSI from CVAD insertion will be estimated by using a competing risk model (27) with CVAD removal due to non-CLABSI related reasons or death as competing events. To assess the difference between the cumulative incidence for the intervention (TCHL) and control (HL) group, the Gray's test will be used. (28)

To estimate the effect of risk factors on the occurrence of CLABSI, a Cox specific proportional hazard regression model from CVAD insertion will be estimated. Well known time fixed risk factors for a CLABSI to be incorporated into the model are diagnosis (haematological disease versus other diagnoses), CVAD type (TIVAP versus tunnelled external CVADs). Furthermore, total parenteral nutrition (TPN) administration will be used in the model as time-dependent covariate). (27)
A landmark analysis at 28 days after CVAD insertion will be performed. The same risk factors as discussed above will be incorporated in the Cox specific hazard regression model with additional covariate number of lock days. The landmark point of 28 days was chosen based on clinical reasons, the first lock should have been given within the first four weeks after CVAD insertion. (29)

For the secondary outcomes, the percentages and IRs per 1,000 CVAD-days will be reported and compared by computing IRRs. Furthermore, the above described analyses will be repeated for subgroups based on diagnosis and CVAD type.
All analyses concerning the competing risk model will be performed in RStudio version 1.3.1093 (United States of America) environment by using the cmprisk library. IBM SPSS Statistics for Windows version 26.0 (United States of America) will be used to perform all other statistical analyses.

Study timeline

Inclusion of the study began on the 27th of October 2020. We expect that the planned number of patients can be recruited in 29 months from the defined source population. The planned study timeline is described in **Table 3**.

Table 3 Planned study schedule

Months after start inclusion	What?	Description
0	Start inclusion	Planned start of the study
14.5	Interim database lock and interim analysis	After the inclusion of 50% of the patients
29	Stop inclusion	After the inclusion of 462 patients
32	Stop follow-up	After a period of 3 months after the inclusion of the last patient
32 - 36	Database lock, statistical analysis, writing the clinical study reports, and drafting of the manuscript based on the clinical study reports.	From the stop of follow-up until manuscript submission.
36	Manuscript submission	Four months after the study has stopped.

ETHICS AND DISSEMINATION

The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research registered under number 20/370, a copy of the trial protocol submitted to the ethics committee can be in the supplementary files (see supplementary file 6). Modifications to the protocol that impact the conduct of the study will require a formal amendment which will be agreed upon by the medical ethics committee. Written informed consent is obtained from al patients and/or their parents/guardians for participation in the trial and for the publication of their data. The results of this trial will be published in an open access peer-reviewed journal, presented at international congresses and subsequently the data (stored for at least 15 years) will be made available after publication of the main results manuscript upon reasonable requests. The VKN will be involved in the plan for the dissemination of the trial results to the participants and public after completion of the trial. All

eventually listed authors of the publication of the main results manuscript will have made a substantial, direct, intellectual contribution to the work.

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SUPPLEMENTARY FILES NOT INCLUDED IN THIS THESIS

Supplementary File 1 List of shared care centers where data will be collected

Supplementary File 2 SPIRIT Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT Outcomes 2022 items)

Supplementary File 3 Organizational structure and responsibilities

Supplementary File 4 Patient Information Letter and Informed Consent Form

Supplementary File 5 Data Safety Monitoring Board Charter

Supplementary File 6 Research protocol CATERPILLAR-study

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CHAPTER 11

The CATERPILLAR-study: An assessor blinded randomized controlled trial comparing a taurolidine-citrate-heparin lock solution to a heparin-only lock solution for the prevention of central-line associated bloodstream infections in paediatric oncology patients.

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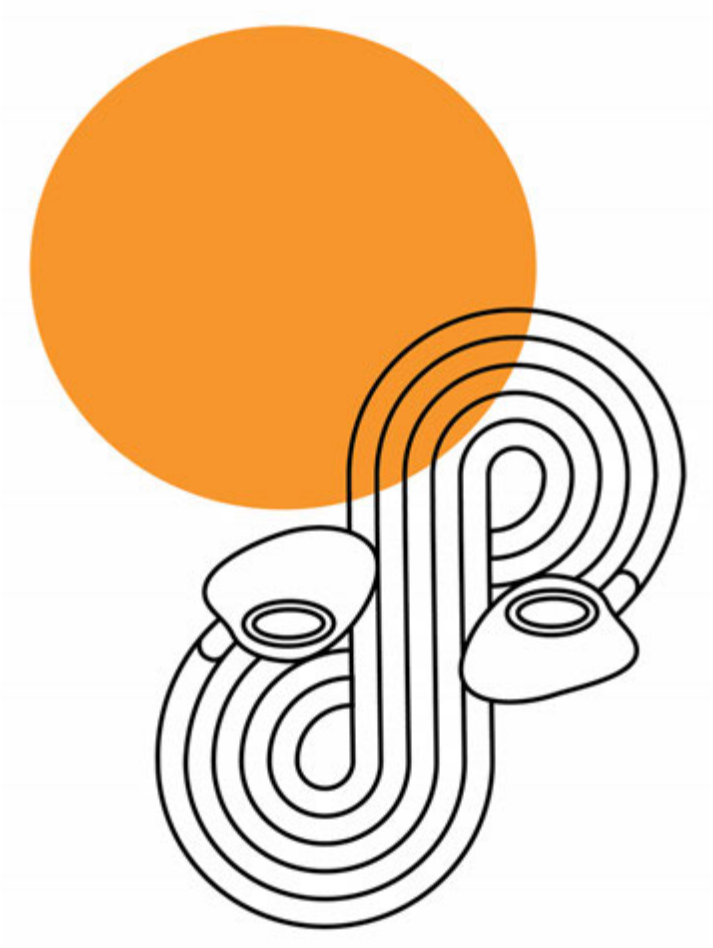


ABSTRACT

Background Taurolidine-citrate(-heparin) lock solutions (TCHL) are suggested as a promising and safe method for the prevention of central line-associated bloodstream infections (CLABSI).

Methods An assessor blinded randomized controlled trial at the Princess Máxima Centre for paediatric oncology, Utrecht, the Netherlands, was performed from 2020-2023. Paediatric oncology patients receiving a tunnelled central venous access device (CVAD) were eligible for inclusion. A total of 462 patients was required to compare the TCHL to the heparin-only lock (HL) for the prevention of CLABSI. Patients were followed-up for the first 90 days after CVAD insertion. The lock solution was given in between treatments with a maximum of 1x/wk. The primary outcome was the incidence of the first CLABSI from CVAD insertion until the end of follow-up. Intention-to-treat and per-protocol analyses were performed.

Results In total, 463 patients were included; 232 were randomized in the HL and 231 in the TCHL-group. A total of 47 CLABSIs were observed. The intention-to-treat analysis showed that a CLABSI was observed in 26 (11.2%) of the HL-group patients versus 21 (9.1%) of the TCHL-group patients; incidence rate ratio (IRR) of 0.81 (CI95%0.46-1.45), in favour of the TCHL-group. The per-protocol analysis showed that a CLABSI was observed in 10 (7.9%) of the HL-group patients versus 6 (4.8%) of the TCHL-group patients; IRR of 0.59 (CI95%0.21-1.62) in favour of the TCHL-group. Adverse events were more common in the TCHL-group but rarely reported.

Conclusion No difference was detected between the TCHL and HL in the incidence of CLABSI in paediatric oncology patients.

Trial registration number: ClinicalTrials.gov NCT05740150

INTRODUCTION

Tunnelled central venous access devices (CVAD) are a fundamental part in the treatment of paediatric oncology patients since they provide long-term venous access. The incidence of central line-associated bloodstream infections (CLABSI) in this patient group is high. (1) CLABSI incidence rates of 0.1-2.3 per 1,000 CVAD-days have previously been reported, mostly depending on the patient population, CVAD-type and infection definitions used. (2) In our hospital, the Princess Máxima Centre for paediatric oncology, a CLABSI incidence rate of 1.51 per 1,000 CVAD-days has been reported; at least one CLABSI was observed in 30% of the children receiving a CVAD. (3) CLABSI episodes often result in hospital admission, postponement of anticancer treatment, early CVAD removal (15% of all CVADs inserted) and can lead to severe sepsis requiring intensive care unit admission (5% of all patients receiving a CVAD). (3) The quality of life of children with cancer is therefore highly impacted by these CLABSIs. Furthermore, these CLABSIs result in high health care costs. (1, 4)

Taurolidine-citrate(-heparin) lock solutions (TCHL) have been suggested as a safe and promising method to prevent CLABSIs due to its anticoagulant, antimicrobial, and anti-biofilm properties. (5, 6) Taurolidine is a more attractive choice as compared to other antimicrobials since no antimicrobial resistance has been reported. (7) Taurolidine damages the cell wall of bacteria, inhibits bacterial pathogenicity, and constrains bacterial surface adhesion. (5, 7-11) The heparin-only lock (HL) is currently the standard of care lock solution for the prevention of malfunctions in the Netherlands for paediatric oncology patients, but the HL has no antimicrobial activity, and its use is barely supported by literature. (5) We performed a meta-analysis including all randomized controlled trials (RCT) comparing the efficacy of taurolidine containing lock solutions to heparin-, saline- and citrate-only locks in haemodialysis, total parenteral nutrition, and oncology patients. According to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations)

approach, a serious risk of bias and indirectness of evidence was present in these studies. (12) However, they did show a pooled incidence rate ratio of 0.30 (CI95% 0.19-0.46) in favour of the taurolidine containing lock solutions. (6) Regarding paediatric oncology patients, only two open labelled RCTs (N≤112) and four non-RCTs, have been performed investigating taurolidine containing lock solutions with/without heparin and/or citrate. (13-18) These studies did not provide enough evidence for the direct implementation of TCHLs in paediatric oncology patients due to a high risk of bias and indirectness of evidence. (13-18)

Therefore, this assessor blinded RCT was designed. If the TCHL appears to be safe and effective for the prevention of CLABSI, the primary goal is to decrease the number of CLABSIs and thereby increase the quality of life for children with cancer by reducing the CVAD-removal rate, dispense of antibiotics, days of hospital admission and incidence of severe sepsis resulting in intensive care unit admission.

METHODS

The CATERPILLAR-study protocol has been published by *BMJ Open* in 2023 and can be found in **Chapter 10** of this thesis. (19) Patients were randomized (1:1) in either the HL or TCHL group and followed up for a maximum study period of 90 days. The locks were given at the Princess Máxima Centre for paediatric oncology after each treatment cycle, with a maximum of once weekly. The lock solution of 0.8-1.5mL per lumen depended on the CVAD type. The locks remained in situ until the CVAD was used again, lock duration thereby varied per patient and was registered during the study period. No amendments were made to the protocol since this publication. One extra patient was included since his/her informed consent came in after the pre-planned 462 patients were already included. The primary analyses were performed with the intention-to-treat (ITT) principle. Additionally, a per-protocol (PP) analysis was performed excluding patients who were not included within one week after CVAD insertion, patients who never received the intervention and patients that missed three or more of the minimal amount (once every three weeks) of locks during the follow-up period. The CONSORT 2010 checklist was completed and can be found as Supplementary File 1. [**Supplementary File 1**]

RESULTS

Between October 2020 and August 2023 (34 months of inclusion), 1034 patients were screened for eligibility. In total, 571 (55%) patients did not meet the inclusion/exclusion criteria, declined to participate, or were not included for other reasons such as advice of the oncologist to not approach certain families due to clinical or psychological circumstances. The remaining 463 (45%) patients were included after which the recruitment was stopped since the pre-determined sample size (N=462) was reached. In total, 232 patients were randomized in the HL-group and 231 in the TCHL-group. [**Figure 1**] No significant difference in baseline characteristics was observed between both groups. [**Table 1**] Patients were followed-

up for a total number of 36.957 CVAD-days during which they received a total number of 2.544 locks (68.8 locks per 1.000 CVAD-days). Of all included patients, 12 (2.6%) prematurely discontinued the intervention and 451 (97.4%) patients reached an endpoint as defined by the study protocol, i.e. 90 days of follow-up (n=368, 79.5%), CLABSI occurrence (n=47, 10.2%), CVAD-removal due to non-CLABSI related reasons (n=25, 5.4%), and a second CVAD insertion (n=10, 2.2%). One patient passed away (n=1, 0.2%). In total 463 patients were included in the intention-to-treat analysis and 252 patients in the per-protocol analysis.

Supplementary File 1 CONSORT 2010 Checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

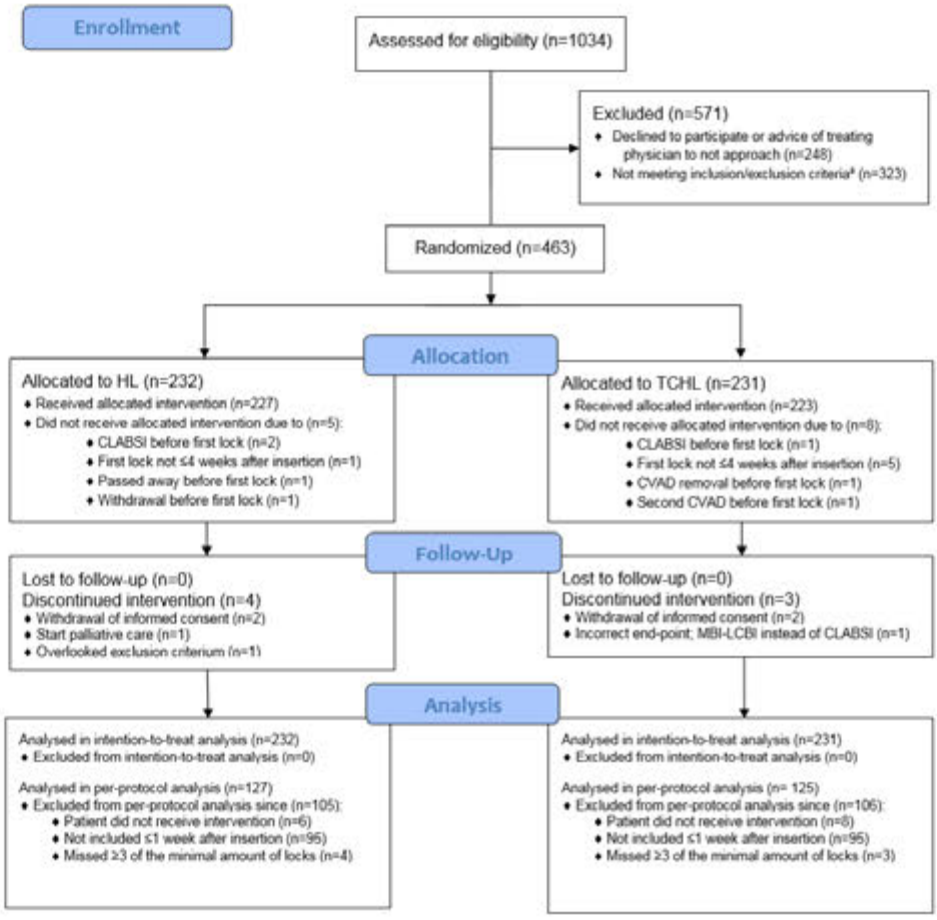
Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Protocol publication
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	Protocol publication
	4b	Settings and locations where the data were collected	Protocol publication
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Protocol publication
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Protocol publication

	6b	Any changes to trial outcomes after the trial commenced, with reasons	Protocol publication
Sample size	7a	How sample size was determined	Protocol publication
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Protocol publication
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol publication
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol publication
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol publication
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol publication
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Protocol publication
	11b	If relevant, description of the similarity of interventions	Protocol publication
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Protocol publication
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Protocol publication
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5 | Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	5 | Figure 1

Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5-7 | Tables & Figures
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5-7 | Tables & Figures
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	5-7 | Tables & Figures
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	5-7 | Table 2-3 & Figure 2
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	5-7 | Table 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7-9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	7-9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7-9
Other information			
Registration	23	Registration number and name of trial registry	2

Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

Figure 1 CONSORT 2010 Flow-chart



[a] Written informed consent was an inclusion criterion, these however, are counted under "declined to participate".

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CLABSI; Central Line Associated Bloodstream Infection.

Table 1a Baseline characteristics

		HL group (N=232)		TCHL group (N=231)		Total (N=463)		p-value[a]
Sex, N (%)	Male	134	57.8%	133	57.6%	267	57.7%	0.97
	Female	98	42.2%	98	42.4%	196	42.3%	
Age in years at inclusion, median (range)		8 (0-18)		8 (0-18)		8 (0-18)		0.94
Diagnosis, N (%)	Haemato-oncology	92	39.7%	94	40.7%	186	40.2%	0.34
	Lymphoma	45	19.4%	34	14.7%	79	17.1%	
	Neuro-oncology	23	9.9%	33	14.3%	56	12.1%	
	Solid tumour	72	31.0%	70	30.3%	142	30.7%	
CVAD type, N (%)	Tunnelled external	36	15.5%	36	15.6%	72	15.6%	1.00
	TIVAP	196	84.5%	195	84.4%	391	84.4%	
	Small	8	4.1%	7	3.6%	15	3.8%	0.97
	Medium	155	79.1%	155	79.5%	310	79.3%	
	Large	33	16.8%	33	16.9%	66	16.9%	
CVAD-days, sum, median (range)		18559, 90 (11-90)		18398, 90 (3-90)		36957, 90 (3-90)		0.94
Insertion method, N (%)	Ultrasound-guided	224	96.6%	225	97.4%	449	97.0%	0.26
	Landmark based	4	1.7%	2	0.9%	6	1.3%	
	Open	0	0.0%	2	0.9%	2	0.4%	
	Missing	4	1.7%	2	0.9%	6	1.3%	
Lumen number, N (%)	Single	200	86.2%	196	84.8%	396	85.5%	0.09
	Double	28	12.1%	35	15.2%	63	13.6%	
	Triple	4	1.7%	0	0.0%	4	0.9%	
Insertion vein, N (%)	Right subclavian	3	1.3%	5	2.2%	8	1.7%	0.73
	Left subclavian	10	4.3%	14	6.1%	24	5.2%	
	Right jugular	213	91.8%	203	87.9%	416	89.8%	
	Left jugular	3	1.3%	5	2.2%	8	1.7%	
	Right brachiocephalic	1	0.4%	0	0.0%	1	0.2%	
	Left brachiocephalic	2	0.9%	3	1.3%	5	1.1%	
	Missing	0	0.0%	1	0.4%	1	0.2%	
Complicated insertion, N (%)	No	222	95.7%	222	96.1%	444	95.9%	0.60
	Yes	8	3.4%	6	2.6%	14	3.0%	
	Missing	2	0.8%	3	1.3%	5	1.1%	

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CVAD; Central Venous Access Device, TIVAP; Totally Implantable Venous Access Port, Fr; French, CI; Confidence Interval.

[a] P-value calculated with a Chi-square test or Mann-Whitney U test, depending on the variable.

Table 1b Baseline characteristics

		HL group (N=232)		TCHL group (N=231)		Total (N=463)	
SAP[a] during study, N (%)	No	78	33.6%	88	38.1%	166	35.9%
	Yes	154	66.4%	143	61.9%	297	64.1%
IVIG during study, N (%)	No	229	98.7%	229	99.1%	458	98.9%
	Yes	3	1.3%	2	0.9%	5	1.1%
TPN during study, N (%)	No	216	93.1%	217	93.9%	433	93.5%
	Yes	16	6.9%	14	6.1%	30	6.5%
Locks given[c], sum, median (range)		1264, 6 (0-12)		1280, 6 (0-11)		2544, 6 (0-12)	
Lock days[d], sum, median (range)		6742, 29 (0-110)		7035, 30 (0-94)		13777, 29 (0-110)	
Endpoint, N (%)	CLABSI	26	11.2%	21	9.1%	47	10.2%
	90 Days follow-up	186	80.2%	182	78.8%	368	79.5%
	CVAD removal (non-CLABSI related)	11	4.7%	14	6.1%	25	5.4%
	Second CVAD or artery line	4	1.7%	6	2.6%	10	2.2%
	Withdrawal[d]	1	0.4%	2	0.9%	3	0.6%
	Passed away	1	0.4%	0	0.0%	1	0.2%
	Other[e]	3	1.3%	6	2.6%	9	1.9%

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CVAD; Central Venous Access Device, SAP; Systemic Antibiotic/Antifungal Prophylaxis, IVIG; Intravenous Immunoglobulin, TPN; Total Parenteral Nutrition, CI; Confidence Interval.

[a] SAP such as ciprofloxacin, trimethoprim/sulfamethoxazole, itraconazole, and micafungin.

[b] P-value calculated with a Chi-square test or Mann-Whitney U test, depending on the variable.

[c] A total of 14 (3.0%) patients never received a lock, six (42.9%) in the HL group and eight (57.1%) in the TCHL group, p=0.58. For a total of 21 (4.5%) patients the total number of lock days was missing since the removal date of one or more locks was missing, nine (42.9%) in the HL group and 12 (57.1%) in the TCHL group, p=0.50.

[d] Withdrawal occurred in two cases due to adverse effects (TCHL-group) and in one case due to unrest of the parents (HL-group).

[e] Other reasons were: first lock instillation not possible within four weeks after CVAD insertion (n=6), start palliative treatment (n=1), screen failure (n=1), incorrect diagnosis of CLABSI by the expert panel which incorrectly ended the follow-up (n=1).

CLABSI-related outcomes

In total, 123 episodes of bacteraemia in 105 patients were assessed by a blinded expert panel; 47 (38.2%) CLABSIs and 76 (61.8%) non-CLABSIs were scored. Reasons why a non-CLABSI instead of a CLABSI episode was scored: mucosal-barrier injury laboratory confirmed bloodstream infection (n=11, 8.9%), <2 blood cultures obtained (n=14, 11.4%), contamination (n=44, 35.8%), no symptoms (n=3, 2.4%), and presence of another infection source (n=4, 3.3%). The intention-to-treat analysis showed that a CLABSI was observed in 26 (11.2%) of the HL-group patients versus 21 (9.1%) of the TCHL-group patients; IRR of 0.81 (CI95%0.46-1.45), in favour of the TCHL-group. The per-protocol analysis showed that a CLABSI was observed in 10 (7.9%) of the HL-group patients versus 6 (4.8%) of the TCHL-group patients; IRR of 0.59 (CI95%0.21-1.62) in favour of the TCHL-group. All other secondary outcomes did not statistically differ between the HL and TCHL-group, as described in Table 2. [**Table 2**]

There was no statistically significant difference in the cumulative incidence of CLABSI between the HL and TCHL-group in both the ITT and PP analysis (p=0.65 and p=0.13, respectively). [**Figure 2**] Cause specific hazard ratio (HR_{CS}) for CLABSI are equal to 0.82 (CI95%0.46-1.46) and 0.80 (CI95%0.32-2.02), for the ITT and PP analysis respectively. Furthermore, the insertion of a totally implantable venous access port (TIVAP) compared to a tunnelled external CVAD appeared to be a protective factor for the development of a CLABSI in the ITT analysis and ITT landmark analysis at 28 days after CVAD insertion; HR_{CS} equal to 0.26 (CI95% 0.13-0.49) and 0.30 (CI95%0.13-0.69), respectively. TPN was a significant risk factor in both the ITT and PP analysis respectively; 2.84 (CI95%1.17-6.92) and 4.47 (CI95%1.21-18.98). The total number of lock days in the first 28 days after insertion did not appear to be a significant risk factor in both the ITT and PP landmark analyses. [**Table 3**] Subgroup analyses did not show a significant effect of the TCHL for certain groups based on diagnosis,

CVAD type, and TPN administration. [**Supplementary Table 1**] The subgroup analyses where a clinical CVAD-related infection instead of a CLABSI, as reported by the three experts, was taken as an outcome, no significant effect of the TCHL was observed. [**Supplementary Table 2**]

Among all CLABSI episodes, 19 (40.4%) were polymicrobial, 21 (44.7%) were caused by gram-positive bacteria only, 6 (12.8%) by gram-negative bacteria only and one (2.1%) by a *Candida* spp. There was no evidence of a difference between the HL and TCHL-group in micro-organisms cultured as described in Table 4. [**Table 4**]

Furthermore, the days from CVAD insertion until CLABSI, the occurrence and severity of neutropenia during CLABSI, and CLABSI-related hospital and PICU admission days, did not significantly differ between the HL and TCHL-group. [**Supplementary Table 3**]

Table 2 CLABSI-related outcomes for intention-to-treat (N=463) and per-protocol analysis (N=252).

		HL-group (N=232, 18.559 CVAD-days)			TCHL-group (N=231, 18.398 CVAD-days)			
		N of patients	**% of patients**	**IR per 1.000 CVAD-days**	**N of patients**	**% of patients**	**IR per 1.000 CVAD-days**	**IRR (CI95%)**
ITT analysis	**CLABSI**	26	11.2%	1.40	21	9.1%	1.14	0.81 (0.46-1.45)
	Common commensal CLABSI[a]	11	4.7%	0.59	8	3.5%	0.43	0.73 (0.30-1.82)
	Recognized pathogen CLABSI[a]	15	6.5%	0.81	13	5.6%	0.71	0.87 (0.42-1.84)
	CLABSI-related hospital admission	25	10.8%	1.35	18	7.8%	0.98	0.73 (0.40-1.33)
	CLABSI-related removal	8	3.4%	0.43	8	3.5%	0.43	1.01 (0.38-2.69)
	CLABSI-related PICU admission	3	1.3%	0.16	1	0.4%	0.05	0.34 (0.03-3.23)
	CLABSI-related death	0	0.0%	0.00	0	0.0%	0.00	Not applicable
		HL-group (N=127, 10.279 CVAD-days)			**TCHL-group (N=125, 10.502 CVAD-days)**			
		N of patients	**% of patients**	**IR per 1.000 CVAD-days**	**N of patients**	**% of patients**	**IR per 1.000 CVAD-days**	**IRR (CI95%)**
PP analysis	**CLABSI**	10	7.9%	0.97	6	4.8%	0.57	0.59 (0.21-1.62)
	Common commensal CLABSI[a]	4	3.1%	0.39	4	3.2%	0.38	0.98 (0.24-3.91)
	Recognized pathogen CLABSI[a]	6	4.7%	0.58	2	1.6%	0.19	0.33 (0.07-1.62)
	CLABSI-related hospital admission	9	7.1%	0.88	5	4.0%	0.48	0.54 (0.18-1.62)
	CLABSI-related removal	2	1.6%	0.19	3	2.4%	0.29	1.47 (0.25-8.79)
	CLABSI-related PICU admission	0	0.0%	0.00	0	0.0%	0.00	Not applicable
	CLABSI-related death	0	0.0%	0.00	0	0.0%	0.00	Not applicable

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CLABSI; Central Line Associated Bloodstream Infection, CVAD; Central Venous Access Device, IR; Incidence Rate, IRR; Incidence Rate Ratio, AE; Adverse event, SADE; Serious Adverse Device Event, CTCAE; Common Terminology Criteria for Adverse Events, ITT; Intention-To-Treat, PP; Per-Protocol.

[a] Common commensals are micro-organisms included in the National Healthcare Safety Network (NHSN) common commensal list (https://www.cdc.gov/nhsn/pdfs/validation/2019/2019-NHSN-Organisms-List-Validation.xlsx), recognized pathogens are micro-organisms not included in this list. If a common commensal and recognized pathogen are cultured, the CLABSI is scored as a recognized pathogen CLABSI.

Figure 2 (A) Competing risk intention-to-treat analysis (p-value = 0.65), (B) Competing risk per-protocol analysis (p-value =0.13).

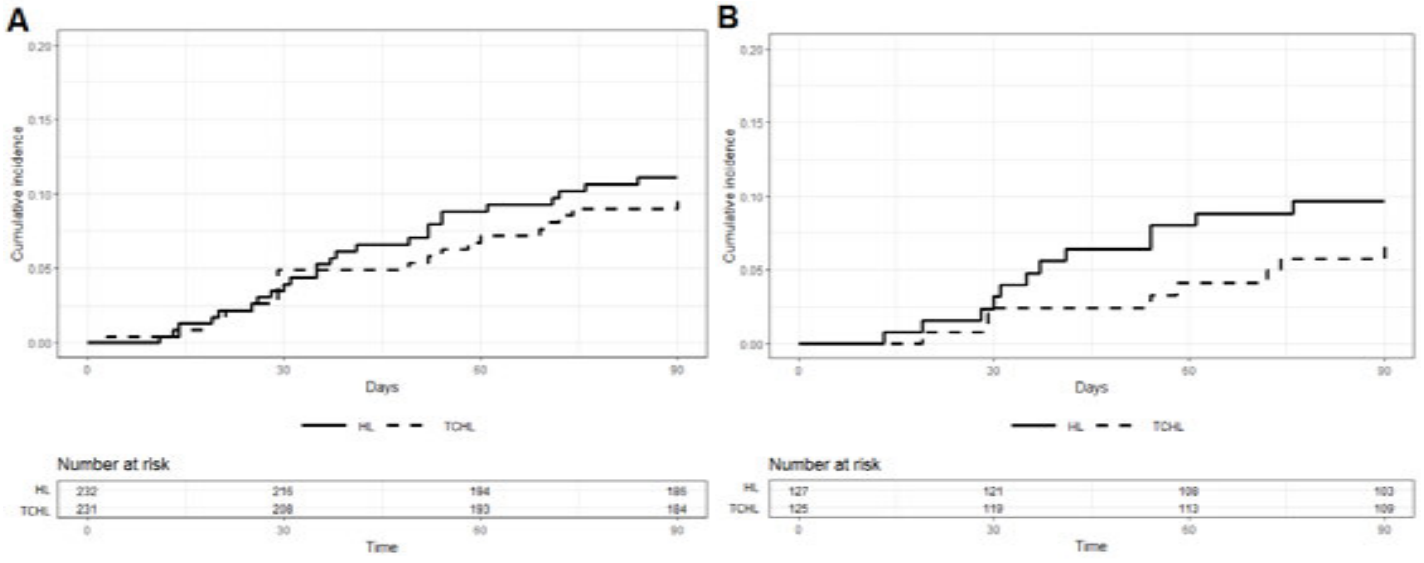


Table 3 Multivariable Cox-regression analysis

Risk factor		**Intention-to-treat analysis (N=463)**	**Intention-to-treat landmark (28 days) analysis (N=435)**	**Per-protocol analysis (N=252)**	**Per-protocol landmark (28 days) analysis (N=243)**
		Cox specific HR CLABSI (CI95%)	**Cox specific HR CLABSI (CI95%)**	**Cox specific HR CLABSI (CI95%)**	**Cox specific HR CLABSI (CI95%)**
Randomization group	HL	1	1	1	1
	TCHL	0.82 (0.46-1.46)	0.95 (0.46-1.95)	0.80 (0.32-2.02)	1.21 (0.41-3.37)
Diagnosis	Haemato-oncology	1	1	1	1
	Other	0.59 (0.33-1.06)	0.71 (0.34-1.50)	0.63 (0.25-1.61)	0.82 (0.26-2.62)
CVAD type	Tunnelled external	1	1	1	1
	TIVAP	0.26 (0.13-0.49)*	0.30 (0.13-0.69)*	0.40 (0.14-1.14)	0.32 (0.09-1.13)
TPN	No	1	1	1	1
	Yes	2.84 (1.17-6.92)*	2.43 (0.83-7.11)	4.47 (1.21-18.98)*	4.38 (0.98-19.24)
Lock days in first 28 days after insertion		NA	0.95 (0.88-1.02)	NA	0.95 (0.86-1.05)

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CLABSI; Central Line Associated Bloodstream Infection, CVAD; Central Venous Access Port, TIVAP; Totally Implantable Venous Access Port, TPN; Total Parenteral Nutrition, CI; Confidence Interval.

*Significant values

TPN is used in the model as a time-dependent covariate.

infection instead of a CLABSI, as reported by the three experts, was taken as an outcome, no significant effect of the TCHL was observed. [**Supplementary Table 2**]

Among all CLABSI episodes, 19 (40.4%) were polymicrobial, 21 (44.7%) were caused by gram-positive bacteria only, 6 (12.8%) by gram-negative bacteria only and one (2.1%) by a *Candida* spp. There was no evidence of a difference between the HL and TCHL-group in micro-organisms cultured as described in Table 4. [**Table 4**]

Furthermore, the days from CVAD insertion until CLABSI, the occurrence and severity of neutropenia during CLABSI, non-CLABSI related reasons, and CLABSI-related hospital and PICU admission days, did not significantly differ between the HL and TCHL-group. [**Supplementary Table 3**]

Local infections and thrombosis

In total, 63 local CVAD infection episodes with (N=17) or without (N=46) a positive exit-site culture were observed in 54 (11.7%) patients, 33 episodes in the HL-group and 30 in the TCHL-group (IRR 0.92, CI95%0.56-1.50). Six local infection episodes with a positive exit-site culture were observed in 6 (1.3%) patients, four episodes in the HL-group and two episodes in the TCHL-group (IRR 0.50, CI95%0.09-2.75). CVAD removal due to a local infection episode was necessary after eight (12.7%) of the 63 episodes, two episodes in the HL-group and six in the TCHL-group (IRR 3.03, CI95%0.61-15.00). In addition, during follow-up eight (1.7%) patients developed a CVAD-related central venous thrombosis (CVT), five (2.2%) patients in the HL-group and three (1.3%) patients in the TCHL-group (IRR 0.61, CI95%0.14-2.53). No CVADs were removed due to these CVT episodes.

Table 4 Micro-organisms cultured during CLABSI

	HL group (CLABSIs=26, 18559 CVAD-days)		TCHL group (CLABSI=21, 18398 CVAD-days)		Total (CLABSI=47)		IRR (CI95%)
Gram-positive, N (%)	13	50.0%	8	38.1%	21	44.7%	0.62 (0.26-1.50)
Coagulase-negative staphylococci[a]	7	26.9%	5	23.8%	12	25.5%	0.72 (0.23-2.27)
Staphylococcus aureus	3	11.5%	2	9.5%	5	10.6%	0.67 (0.11-4.02)
Viridans streptococci	0	0.0%	0	0.0%	0	0.0%	Undefined
Streptococcus pneumoniae	0	0.0%	0	0.0%	0	0.0%	Undefined
Enterococci	0	0.0%	0	0.0%	0	0.0%	Undefined
Other Gram-positive[b]	3	11.5%	1	4.8%	4	8.5%	0.34 (0.03-3.23)
Gram-negative, N (%)	3	11.5%	3	14.3%	6	12.8%	1.01 (0.20-5.00)
Enterobacterales[c]	1	3.8%	0	0.0%	1	2.1%	Undefined
Other Gram-negative[d]	2	7.7%	3	14.3%	5	10.6%	1.51 (0.25-9.06)
Fungi, N (%)	1	3.8%	0	0.0%	1	2.1%	Undefined
Candida spp.[e]	1	3.8%	0	0.0%	1	2.1%	Undefined
Polymicrobial[f], N (%)	9	34.6%	10	47.6%	19	40.4%	1.12 (0.46-2.76)
Gram-positive polymicrobial	3	11.5%	1	4.8%	4	8.5%	0.34 (0.03-3.23)
Gram-negative polymicrobial	1	3.8%	0	0.0%	1	2.1%	Undefined
Mixed polymicrobial	5	19.2%	9	42.9%	11	23.4%	1.82 (0.61-5.42)

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock.

[a] *S. epidermidis* (9), *S. haemolyticus* (1), *S. hominis* (1), *S. condimenti* and *S. hominis* (1).

[b] *Micrococcus luteus* (2), *Pediococcus pentasaceus* (1), *Peptoniphilus* spp. (1).

[c] *E. coli* (1)

[d] *Paracoccus yeei* (2), *Pseudomonas aeruginosa* (1), *Acinetobacter ursingii* (1), *Stenotrophomonas maltophilia* (1).

[e] *Candida parapsilosis* (1).

[f] *S. epidermidis*, *Moraxella osloensis*, and *S. hominis* (2), *S. oralis, Paracoccus yeei* and *Micrococcus spp.* (1), *Micrococcus luteus*, *S. hominis*, and *S. epidermidis* (1), *E. coli* and *S. epidermidis* (2), *E. coli*, *Granulicatella adiacens* and *S. epidermidis* (1), *Enterobacter cloacae*, *C. freundii*, *Klebsiella pneumoniae* (1), *Delftia acidovorans* and *S. hominis* (1), *Pseudomonas aeruginosa* and *S. mitis* (1), *Micrococcus luteus* and *S. hominis* (1), *S. epidermidis* and *Acinetobacter baumannii* (1), *S. salivarius* and *S. epidermidis* (1), *Micrococcus luteus* and *Moraxella osloensis* (1), *S. mitis, Granulicatella adiacens, Moraxella osloensis* (1), *S. hominis* and *Micrococcus luteus* (1), *Rothia mucilaginosa, S. hominis, Paracoccus yeei* (1), *S. capitis* en *Moraxella osloensis* (1), *Pseudomonas luteola* and *S. epidermidis* (1).

Supplementary table 1 Subgroup analyses

			HL-group		TCHL-group		
			CLABSIs	**CVAD-days**	**CLABSIs**	**CVAD-days**	**IRR (95%CI)**
Intention-to-treat analysis	**Diagnosis**	Hemato-oncology	11	7231	11	7096	1.02 (0.44-2.35)
		Lymphoma	8	3390	5	2502	0.85 (0.28-2.59)
		Neuro-oncology	0	2069	1	2876	Undefined
		Solid tumour	7	5869	4	5924	0.57 (0.17-1.93)
	CVAD type	Tunnelled external	11	2363	8	2621	0.66 (0.26-1.63)
		TIVAP	15	16196	13	15777	0.89 (0.42-1.87)
	TPN	No	21	17461	17	17340	0.82 (0.43-1.55)
		Yes	5	1098	4	1058	0.83 (0.22-3.09)
Per-protocol analysis	**Diagnosis**	Hemato-oncology	6	3711	2	3515	0.35 (0.07-1.74)
		Lymphoma	3	2299	2	1729	0.89 (0.15-5.30)
		Neuro-oncology	0	1439	1	1768	Undefined
		Solid tumour	3	2830	3	3490	0.81 (0.16-4.02)
	CVAD type	Tunnelled external	5	1387	1	1195	0.23 (0.03-1.99)
		TIVAP	7	8892	7	9307	0.96 (0.34-2.72)
	TPN	No	10	9644	7	10153	0.66 (0.25-1.75)
		Yes	2	635	1	349	0.91 (0.08-10.03)

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CLABSI; Central Line Associated Bloodstream Infection, CVAD; Central Venous Access Device, TIVAP; Totally Implantable Venous Access Port, TPN; Total Parenteral Nutrition, IRR; Incidence Rate Ratio, CI; Confidence Interval.

Supplementary table 2 Analysis with clinical CVAD-related infection instead of CLABSI

	HL-group		TCHL-group		
	Clinical CVAD-related infection	**CVAD-days**	**Clinical CVAD-related infection**	**CVAD-days**	**IRR (95%CI)**
ITT	21	18.559	15	18.398	0.72 (0.37-1.40)
PP	8	10.279	5	10.502	0.61 (0.20-1.87)

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CLABSI; Central Line Associated Bloodstream Infection, CVAD; Central Venous Access Device, IRR; Incidence Rate Ratio,

Supplementary table 3 Secondary outcomes

		CLABSIs in HL group (N=26)		CLABSIs in TCHL group (N=21)		p-value[a]
Days until CLABSI, median (range)		36 (11-84)		29 (3-74)		0.90
Non-CLABSI related reasons	MBI-LCBI	6	9.2%	7	11.7%	0.31
	<2 Blood cultures obtained	5	7.7%	9	15.0%	0.20
	Contamination	23	35.4%	21	35.0%	0.96
	No symptoms	2	3.1%	1	1.7%	0.61
	Another infection source	3	4.6%	1	1.7%	0.35
	CVAD in situ for <48 hours	0	0.0%	0	0.0%	n.a.
Neutropenia during CLABSI	No	7	31.8%	5	26.3%	0.70
	Yes	15	68.2%	14	73.7%	
	Very severe (<0.10x10^9/L)	8	57.1%	8	57.1%	0.48
	Severe (0.10-0.50 x10^9/L)	5	35.7%	3	21.4%	
	Moderate (0.50-1.00 x10^9/L)	1	7.1%	1	7.1%	
	Mild (1.00-1.50 x10^9/L)	0	0.0%	2	14.3%	
	Missing	1	9.0%	0	0.0%	
Neutropenia days during CLABSI, median (range)		15 (3-47)		18 (1-81)		0.82
CLABSI-related hospital admission days, median (range)		8 (1-38)		6 (2-19)		0.56
CLABSI-related PICU admission days, median (range)		6 (1-10)		0 (0-0)		Undefined

HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock, CVAD; Central Venous Access Device, CLABSI; Central Line Associated Bloodstream Infection, MBI-LCBI; Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection, PICU; Paediatric Intensive Care Unit, n.a.; not applicable.

[a] Calculated with a Chi-square or Mann-Whitney U test, depending on the variable.

Adverse events

In total, 2.544 locks were instilled (1.264 in the HL-group and 1.280 in the TCHL-group). A malfunction, i.e. the inability to flush and/or aspirate the lock, during removal was observed in 54 (4.3%) and 50 (3.9%) of the HL and TCHL instillations (p=0.61), respectively. In total, one (0.1%) adverse event was reported in the HL-group, graded as common terminology criteria for adverse events (CTCAE) grade I. In the TCHL-group 17 (1.3%) adverse events were reported during instillation, which was significantly more compared to the HL-group (p<0.01), and one (0.1%) adverse event was reported during lock removal. The adverse events in the TCHL-group were graded following the CTCAE as grade I (n=15), grade II (n=2) and grade III (n=1). All adverse events were observed in different patients and all of them were known side

effects. Two SAEs, one in the HL- and one in the TCHL-group, were reported with both a possible but unlikely relationship to the lock instillation, i.e. a lung embolism. [**Table 5**]

TABLE 5 Malfunctions and adverse events

	HL-group (locks=1264, patients=232)				TL-group (locks=1280, patients=231)				p-value[d]
	N of events	**% of locks**	**N of pts**	**% of pts**	**N of events**	**% of locks**	**N of pts**	**% of pts**	
Malfunction during lock removal[a]	54	4.3%	42	18.1%	50	3.9%	36	15.6%	0.61
AE[b]									
Lock instillation	1	0.1%	1	0.4%	17	1.3%	17	7.4%	<0.01*
Lock removal	0	0.0%	0	0.0%	1	0.1%	1	0.4%	0.33
SAE[c]	1	0.1%	1	0.4%	1	0.1%	1	0.4%	1.00

AE; Adverse Events, SAE; Serious Adverse Events, HL; Heparin Lock, TCHL; Taurolidine-Citrate-Heparin Lock.

*Significant values

[a] The inability to flush and/or aspirate the lock during study lock removal.

[b] AEs reported: oral dysgeusia (n=2), oral dysesthesia (n=2), allergic reaction (n=1), swelling of the eyelids (n=1), redness (n=1), chest pain (n=1), rash under TIVAP (n=1), pain (n=2), burning sensation (n=1), vasovagal reaction (n=1), tingling sensation on the skin (n=1) agitation/restless (n=1), nausea (n=2) and vomiting (n=2). CTCAE Grade I (n=16), grade II (n=2), grade III (n=1).

[c] SAE reported with a possible relationship to the lock instillation: lung emboli (n=2).

[d] P-value calculated with a Chi-square test.

DISCUSSION

No difference was detected between the TCHL and HL for all primary and secondary outcomes in our paediatric oncology population. Adverse events were reported more frequently in the TCHL group but were rare and mostly graded as mild. During this study, we did not identify subgroups based on diagnosis, CVAD type and TPN administration that would benefit significantly from the TCHL. The TCHL however, might still appear to be beneficial if administered more frequently, for specific patient groups (e.g., for patients with a history of multiple CLABSIs or patients receiving TPN), or for CVAD salvage during a CLABSI in larger randomized controlled trials.

Strengths and limitations

Strengths of the study are the large sample size (N=463) as compared to the previously published literature in haemodialysis, total parenteral nutrition and oncology populations (14 RCTs, N per RCT ≤164), the inclusion of a homogenous group (i.e., only children with a tunnelled CVAD), the assessor-blinded design using three experts, the strict use of the CLABSI criteria of the Centres for Disease Control and Prevention (CDC) and that stratification was performed based on CVAD-type and diagnosis. (20, 21)

Limitations of the study are the frequency in which locks were given as compared to other studies and/or the delay in the timing of the first lock instillation. A higher lock frequency and earlier first lock instillation might have resulted in a larger effect size. The causes for these limitations were (1) partially paediatric oncology specific, i.e., frequent and long hospital admissions as compared to other patient groups due to which less locks could be given and due to which, in some cases, the first lock was given 1-3 weeks after CVAD insertion, but are (2) presumably also caused by study design related factors, i.e., maximum lock frequency of once a week, lock instillation not in shared care centres, and signed informed consent required causing a delay in the timing of the first lock instillation. The per-protocol analysis, partially tackling these causes, did show a larger effect size, but the effect size was still not significant and the number of patients included was much smaller (N=252) than initially hypothesized. Also, in the per-protocol analysis, many high-risk patients (i.e. the patients receiving less locks due to frequent and long hospital admissions due to their severe immunocompromised state) were excluded, resulting in a lower CLABSI incidence rate in the control group than initially hypothesized. The multivariate analysis did not show a significant association between the number of lock days and the risk of a CLABSI, suggesting that increasing the number of lock days would

probably not drastically improve the effect size to such an extent that the TCHL would reach an acceptable number needed to treat and/or be cost-effective.

Potential sources of bias

Some concerns about the risk of bias due to deviations from the intended intervention might arise since patients, caregivers, and healthcare professionals were not blinded; e.g., withdrawal of informed consent due to TCHL-related adverse events. Furthermore, some concerns might arise about a risk of bias due to measurement of the outcome since the patients, caregivers and healthcare professionals treating the patients were not blinded, which could have influenced the outcomes; e.g. clinical interpretation of symptoms, barrier for blood culture testing, or reporting of side effects.

Imprecision

Compared to the previously performed RCTs, this study provided more accurate results due to the largest number of patients. (20) The effect size observed is smaller than the one used for computing the sample-size; i.e., CLABSI reduction of 11.2% to 9.1% instead of the initially expected reduction from 12.8% to 5.0%. As described above, this might have been caused by the lock frequency and/or the timing of the first lock instillation. The observed reduction requires a sample size of 3246 patients with 80% power, which is very challenging and time consuming in the paediatric oncology population.

Generalisability

In our opinion, the results of this study are generalizable for paediatric oncology institutes with comparable CLABSI incidence rates. However, it is possible that a benefit of the TCHL might be observed in institutes and subgroups with a higher risk of CLABSI. Within the paediatric oncology population, we did not identify subgroups

that would benefit from the TCHL specifically (e.g., patients at a higher risk of CLABSI such as patients diagnosed with a haemato-oncologic disease, with a tunnelled external CVAD, or receiving TPN). Furthermore, we do not know if the results of this study are generalizable to other patient populations with CVADs such as adult oncology patients, and patients receiving haemodialysis or total parenteral nutrition. These populations differ in terms of the CLABSI incidence (i.e., different risk factors such as: CVAD type, neutropenia, home treatment), CLABSI contamination routes, and lock frequency (i.e., the CVAD of paediatric oncology patients is generally locked less frequently). (20) Additionally, other taurolidine lock solutions with various compositions exist (with/without citrate and/or heparin). The results might therefore not be generalisable for other taurolidine lock solutions. The standard of care lock in the Netherlands is the heparin lock, therefore, during this study, a taurolidine lock solution containing heparin was chosen as the investigation lock.

Other relevant evidence

Handrup 2013 (N=112) and Dümichen 2012 (N=71) both performed comparable RCTs in the paediatric oncology population and described IRRs of 0.26 (CI95%0.09-0.61) and 0.24 (CI95%0.05-1.13) in favour of the taurolidine containing locks, respectively. (13, 14) These authors included much smaller samples of patients and designed the trials as open labelled introducing bias. The high heterogeneity between the studies might be explained by the high number of haematology patients and patients with an external tunnelled CVAD, other definitions used to diagnose a bloodstream infection as CVAD-related, and frequency of lock instillations in the previously performed studies.

Future perspectives

The TCHL might still appear to be beneficial if administered more frequently in the paediatric oncology population, for specific patient groups (e.g., for patients with a

history of multiple CLABSIs or patients receiving TPN), or for CVAD salvage during a CLABSI in larger randomized controlled trials. Future research should be performed to evaluate this.

CONCLUSION

No difference was detected between the TCHL and HL for all primary and secondary outcomes in paediatric oncology patients. Adverse events were reported more frequently in the TCHL group but were rare and mostly graded as mild. This quality of evidence provided by this study is high due to the assessor-blinded randomized design, stratification for two important risk factors during randomization, large patient cohort, strict use of the CLABSI criteria, and inclusion of a relatively homogenous patient group. The TCHL might still appear to be beneficial if administered more frequently in the paediatric oncology population, for specific patient groups (e.g., for patients with a history of multiple CLABSIs or patients receiving TPN), or for CVAD salvage during a CLABSI in larger randomized controlled trials. Future research should be performed to evaluate this.

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PART III

CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING TREATMENT

CHAPTER 12

Central venous catheter-related bloodstream infections caused by *Enterobacterales* in paediatric oncology patients; catheter salvage or removal

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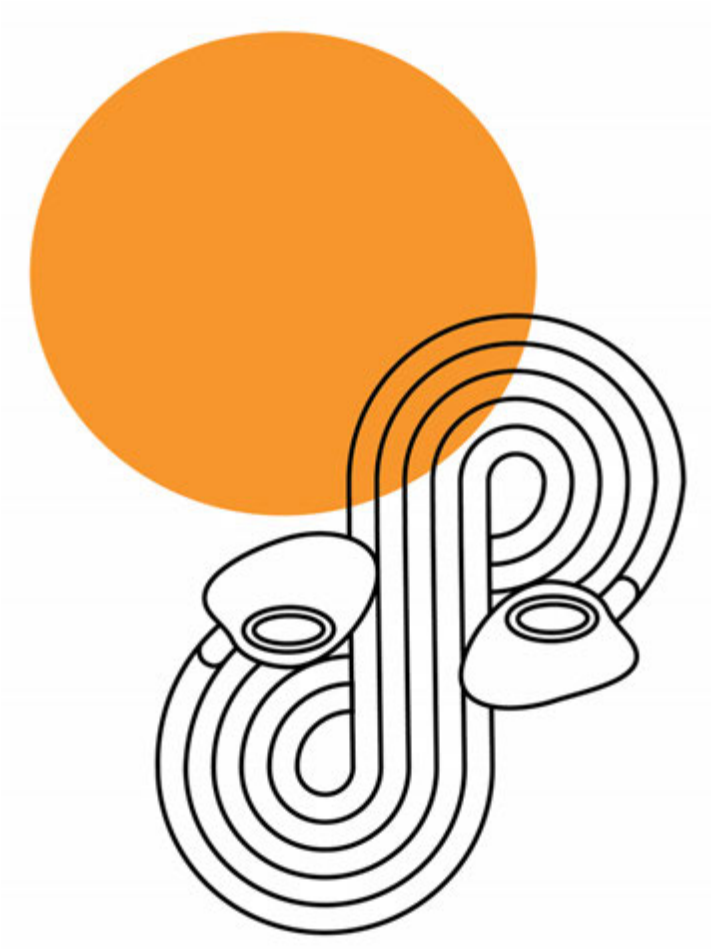


ABSTRACT

Background The aim was to determine whether salvage treatment with systemic antibiotics is a safe and effective strategy for Enterobacterales bloodstream infections (BSI) in pediatric oncology patients with a central venous catheter (CVC).

Methods A retrospective study was performed on oncology and stem cell recipient patients with a CVC and blood culture with Enterobacterales , at the Princess Máxima Centre for Pediatric Oncology, Utrecht, the Netherlands. Analyses were performed for all BSI and for episodes meeting central line-associated bloodstream infection (CLABSI) criteria. The cumulative incidence of an event (ie, removal, intensive care admission or death) was estimated after blood culture collection for episodes primarily treated with antibiotics. The effect of prognostic factors on the hazard of the event of interest was assessed by estimating a Cox proportional hazard regression model.

Results In total, 95 CVC-related Enterobacterales BSIs in 82 patients were included; 12 (13%) BSIs required immediate CVC removal and for 83 (87%) BSIs CVC salvage was attempted. The cumulative incidence of events at 60 days was 53.0% [95% confidence interval (CI): 41.7-63.1] for BSIs (n = 83), and 64.4% (95% CI: 48.3-76.7) for CLABSIs (n = 45). The events occurred after a median of 6 (Q1-Q3: 2-15) and 6 (Q1-Q3: 2-20) days for BSIs and CLABSIs, respectively. Intensive care admission after salvage treatment was required in 16% of the BSIs and CLABSIs, resulting in death in 5% and 2% of cases, respectively. No significant association between risk factors and events was found.

Conclusions The cumulative incidence of an event at 60 days after salvage treatment for Enterobacterales CLABSIs and BSIs in pediatric oncology patients is high. Immediate CVC removal appears recommendable for this patient group.

INTRODUCTION

Central venous catheters (CVCs) play a key role during the treatment of pediatric oncology patients.(1) One of the most common and severe CVC-related complications observed are bloodstream infections; 30% of pediatric oncology patient that receive a CVC develop one or multiple central line-associated bloodstream infections (CLABSI), incidence rate (IR) of 1.51 per 1,000 CVC-days.(2-4) CLABSIs not only necessitate antibiotic treatment but often lead to CVC removal, postponement of cancer treatment, prolonged hospital stays, and in some cases intensive care unit admissions or even death.(4, 5) Pediatric oncology patients are at particular risk of CLABSIs due to their immunocompromised and often neutropenic state.(6, 7)

In our hospital, *Enterobacterales* spp. were cultured during 12% of the reported CLABSIs.(4) The Infectious Diseases Society of America (IDSA) guidelines from 2009 recommend to remove a long-term CVC in patients with a Gram-negative CLABSI (excl. *Pseudomonas aeruginosa* where immediate removal is indicated), such as *Enterobacterales,* in case of persistent bacteremia or severe sepsis despite antibiotic (systemic and lock) therapy. They classify the strength of their recommendation as "poor". They additionally state that for pediatric patients, the benefits of removal should carefully be weighed against the difficulty of inserting a new CVC.(8) Evidence for the use of antibiotic lock therapy (ALT) for salvage in pediatric oncology patients is still scarce.(9, 10) Salvage treatment with systemic antibiotic treatment (SAT) over the CVC is therefore, in the majority of cases, the first treatment method of choice for *Enterobacterales* CLABSIs. Unsuccessful salvage treatment however, can potentially lead to uncontrolled infection, discontinuation of the oncological treatment, deterioration of the clinical status of the patient, intensive care unit admissions, and sometimes even death due to sepsis.(11)

Successful salvage rates for multiple micro-organisms have previously been investigated in a variety of patient populations.(12-21) However, no studies were identified investigating the outcome of salvage treatment with SAT only for CLABSIs caused by *Enterobacterales* in pediatric oncology patients. The aim of this study was therefore to determine whether salvage treatment with SAT can be safely and effectively achieved after the diagnosis of a CLABSI caused by *Enterobacterales* in pediatric oncology patients.

MATERIALS AND METHODS

Study design and participants

This retrospective study included all consecutive oncology and stem cell recipient patients with an *Enterobacterales* positive blood culture, cultured in the Princess Máxima Centre for pediatric oncology, Utrecht, the Netherlands, between April 2015 and July 2022. Since 2018, all pediatric oncology care in the Netherlands has been centralized at this hospital.

Eligible patients were identified from *Enterobacterales* positive blood culture lists of the microbiological laboratory system (CliniSys GLIMS, Gent, Belgium) of our hospital. Patients were screened for eligibility if they and/or their parents/legal guardians gave their written informed consent for the use of their data for research purposes. Inclusion criteria were: oncologic diagnosis or stem cell recipient treated in our hospital, and a CVC in situ during the *Enterobacterales* positive blood culture collection. Exclusion criteria were: multiple CVCs in situ at the onset of the positive blood culture episode, an *Enterobacterales* positive blood culture episode already included in the study in the last 60 days, and essential data (i.e., date or reason for CVC removal) missing for analysis. All patients were followed-up from date of blood culture collection until a maximum of 60 days or until CVC removal, whichever came first. A waiver for informed consent was obtained from the Medical Ethics Committee

NedMec, Utrecht, the Netherlands (file number 22-036). Adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies was maintained throughout this study.(22)

Outcomes and data-collection

The primary outcome of this study was the cumulative incidence of an event at 60 days after *Enterobacterales* blood culture collection for patients where salvage treatment was attempted for an *Enterobacterales* CLABSI (definition described below). Events were defined as CVC removal, intensive care unit (ICU) admission or death related to the primary episode.

Secondary outcomes were the incidence of immediate CVC removal, relapse, reinfection, intensive care unit admission, and death related to the primary CLABSI episode in the 60 days after *Enterobacterales* blood culture collection. Furthermore, the time to events since blood culture collection were recorded.

All outcomes were also described for all *Enterobacterales* bloodstream infection (BSI) episodes (i.e. positive blood culture with an *Enterobacterales*; CLABSI and non-CLABSI episodes).

Furthermore, the patient files were retrospectively assessed for patient characteristics (age, gender and underlying diagnosis), CVC characteristics (insertion and removal date, catheter type, lumen size/number, access vein, reason for removal) as well as risk factors for the occurrence of events (stem cell transplantation (SCT) 30 days prior to BSI onset, SCT >30 days prior to BSI onset and gastro-intestinal graft versus host-disease (GvHD) during episode, neutropenia at BSI onset, and adequate empirical antibiotic treatment). If data was not explicitly reported in the patient files, this was reported as missing data.

Definitions

Salvage treatment was defined as antibiotic treatment started upon *Enterobacterales* blood culture determination in patients where immediate CVC removal was determined as avoidable at the discretion of the treating physician. Immediate removal was defined as CVC removal within 48 hours after *Enterobacterales* blood culture determination where salvage treatment was not attempted at the discretion of the treating physician.

Central line-associated bloodstream infections (CLABSI) were defined following the CLABSI criteria of the Centers for Disease Control and Prevention (CDC), which are the preferred criteria for pediatric oncology patients since peripheral blood cultures, which are required for diagnosis by other known criteria, are rarely obtained in this patient group.(23) A CLABSI was scored if the patient met one of the following criteria: (1) the patient had a recognized pathogen cultured from ≥ 1 blood cultures, or (2) the patient had at least one of the following signs: fever (> 38°C), chills or hypotension, and the same matching potential contaminant micro-organism had to be cultured from ≥ 2 blood cultures drawn on separate occasions. A CLABSI could only be scored if the CVC was in place for >48h on the date of the event, if no CLABSI with the same micro-organism was scored in the past two weeks (infection relapse time frame), if the presence of a mucosal-barrier injury related laboratory confirmed bloodstream infection (MBI-LCBI) was excluded, and if the pathogen cultured was not related to an infection at another site. An MBI-LCBI was scored if only intestinal organisms from the MBI organism list were cultured and the patient met one of the following criteria: (1) allogeneic stem cell transplant recipient within the past year with documented grade III/IV gastro-intestinal graft versus host disease or diarrhea of ≥1L or more in 24 hours during the same hospitalization period as the positive blood culture, or (2) neutropenic on two separate days with an absolute neutrophil

count of <500 cells/mm^3 within three days before and after the positive blood culture.(4, 23)

CVC removal, pediatric intensive care unit (PICU) admission and/or death were scored as related to the primary episode if the *Enterobacterales* BSI was noted as the reason for the event, or was a contributing factor as determined by an infectious disease specialist (T.W.) based on the electronic patient files.

A relapse was defined as the isolation of the same micro-organism (i.e. the same species and resistance pattern) after finishing appropriate antibiotic treatment (i.e. antibiotics for which the micro-organism is sensitive) for the primary episode without a negative blood culture control being obtained in between. A reinfection was defined as the isolation of the same micro-organism after finishing appropriate antibiotic treatment for the primary episode and where a negative blood culture control was obtained in between.

The presence of neutropenia was defined as a neutrophil granulocyte count of less than $0.5x10^9$/L on at least two separate days, collected within a 7-day time period. Local infection and/or irritation was defined as redness, pain, purulent drainage and hematoma on the skin surrounding CVC exit site detected by visual inspection or through positive exit-site culture. Thrombosis of the CVC was diagnosed by radiological imaging.

Infection guidelines of the Princess Máxima Centre for pediatric oncology

In patients with fever in neutropenia, empirical SAT over the CVC lumen was started; i.e., ceftazidime (with vancomycin in case of severe mucositis, high-dose cytarabine treatment, hemodynamic instability, exit-site redness or fever after flushing the CVC), or another antibiotic such as meropenem in case of colonization with ceftazidime-

resistant Gram-negative bacteria. In patients with fever without neutropenia, the treating physicians carefully consider if SAT is necessary. If SAT is deemed necessary and no clear focus is present, a combination of amoxicillin/clavulanic acid and gentamicin, or ceftriaxone is given. When indicated, antibiotic treatment was tailored after identification and susceptibility testing results of the pathogen were obtained. The choice between immediate CVC removal or salvage treatment was made based on the discretion of the infectiologist, oncologist, and surgeon, taking into account the IDSA guidelines.(8) Immediate removal (i.e., within 48 hours after blood culture determination after which salvage with SAT was not attempted) was deemed necessary if a *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi, mycobacteria, *Acinetobacter baumannii* or *Stenotrophomonas maltophilia* next to the *Enterobacterales* was cultured, or in case of severe sepsis. After salvage treatment was started, removal was deemed necessary in case of severe sepsis, when blood cultures remained positive, or when the symptoms persisted after 72 hours of appropriate antibiotic therapy.(8) Antibiotic treatment was switched to oral antibiotics whenever deemed possible and safe. ALT is not used in our hospital due to the scarcity of evidence and recommendations for pediatric oncology patients. (9, 10)

Statistical analysis

Categorical data were presented as contingency tables; i.e. frequencies and percentages. For continuous data summary statistics of the median, mean, minimum-maximum, first quartile-third quartile, standard deviation, were presented. Different episodes within one patient were seen as independent. The cumulative incidence of an event (i.e., removal, ICU admission or death) from *Enterobacterales* blood culture collection was estimated by using a competing risk model, with CVC removal or death due to non-(CLA)BSI related reasons as competing events. (24, 25) To study the association between risk factors and the hazard of an event, a cause-specific Cox

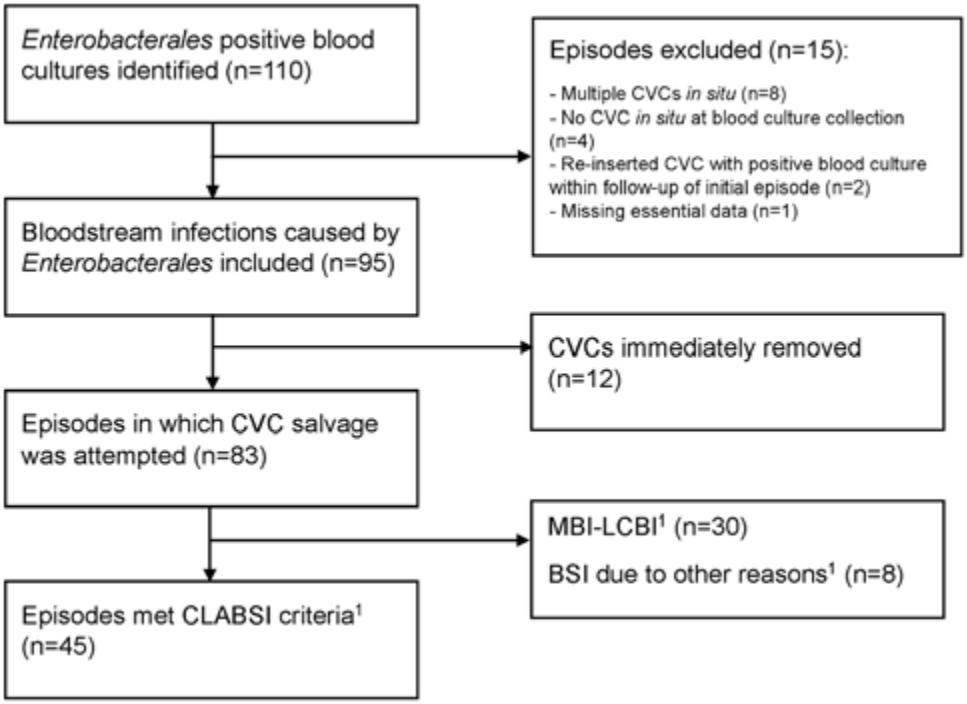
proportional hazard regression model was estimated. Prognostic factors incorporated in the model were based on known risk factors(4-6, 26-29): diagnosis (hematological malignancies/lymphomas versus solid tumors and benign stem cell recipients), CVC type (tunneled external CVC versus TIVAP and non-tunneled CVC), neutropenia at BSI onset (no versus yes), and adequate empirical antibiotics (yes versus no). Data was analyzed using IBM SPSS statistics (version 26.0.0.1) and R software environment (version 1.3.1093) by using the cmprisk library.(30, 31)

RESULTS

In total 110 *Enterobacterales* positive blood culture episodes were identified of which 15 (14%) were excluded based on the in- and exclusion criteria, see inclusion flow diagram in **Figure 1**. This resulted in the inclusion of 95 (86%) episodes which were observed in 82 patients. Immediate removal was deemed necessary in 12 (13%) of these episodes and salvage treatment was attempted in 83 (87%). Of these 83 episodes where salvage was attempted with systemic antibiotics, 45 (54%) episodes met the CLABSI criteria, 30 (36%) met the MBI-LCBI criteria and 8 (10%) were classified as a BSI due to other reasons.

The baseline characteristics of the patients and CVCs included in this study are described in **Table 1**. The majority of patients receiving salvage treatment were diagnosed with a solid tumor (42%), received a tunneled external CVC (51%) or totally implantable venous access device (TIVAD) (42%), and their CVCs were in situ for a median length of 113 days. During the 83 salvage treatment episodes, systemic antibiotic salvage treatment was given for a median of 10 (IQR: 4) days for the primary episode.

Figure 1 Flow diagram of all study participants.



CVC, central venous catheter; BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection; MBI-LCBI, mucosal barrier injury laboratory confirmed bloodstream infection.

[1] Centers of for Disease Control and Prevention.

Table 1a Baseline characteristics

		Salvage treatment (n=83)				Immediate removal (n=12)	
		Total (n=83)		CLABSI (n=45)			
Age at blood culture collection*, median (min-max)		4 (0-19)		3 (0-19)		4 (0-6)	
Gender*, n (%)	Female	35	42.2%	17	37.8%	4	33.3%
	Male	48	57.8%	28	62.2%	8	66.7%
Diagnosis*, n (%)	Solid tumor	38	45.8%	26	57.8%	9	75.0%
	Hemato-oncology and lymphomas	40	48.2%	15	33.3%	2	16.7%
	Benign stem cell recipient	5	6.0%	4	8.9%	1	8.3%
CVC days, median (min-max)		113 (2-1.276)		100 (2-647)		95 (4-384)	
CVC type, n (%)	Tunneled external CVC	42	50.6%	28	62.2%	8	66.7%
	TIVAD	35	42.2%	12	26.7%	2	16.7%
	Non-tunneled CVC	2	2.4%	2	4.4%	2	16.7%
	PICC-line	4	4.8%	3	6.7%	0	0.0%
Lumen number, n (%)	Single	38	45.8%	15	33.3%	4	33.3%
	Double	39	47.0%	29	64.4%	6	50.0%
	Triple	6	7.2%	1	2.2%	2	16.7%
Vein, n (%)	Jugular	62	74.7%	30	66.7%	9	81.8%
	Subclavian	11	13.3%	6	13.3%	2	18.2%
	Femoral	1	1.2%	1	2.2%	0	0.0%
	Brachial	3	3.6%	2	4.4%	0	0.0%
	Basilic	2	2.4%	2	4.4%	0	0.0%
	Missing	4	4.8%	4	8.9%	0	0.0%
Side, n (%)	Left	17	20.5%	9	20.0%	5	41.7%
	Right	62	74.7%	32	71.1%	7	58.3%
	Missing	4	4.8%	4	8.9%	0	0.0%
Stem cell recipient, n (%)	<30 days before BSI	6	7.2%	2	4.4%	0	0.0%
	>30 days before BSI and gastro-intestinal GvHD during episode	5	6.0%	3	6.7%	0	0.0%
	None of the above	71	85.5%	39	86.7%	12	100.0%
	Missing	1	1.2%	1	2.2%	0	0.0%

CLABSI; central line-associated bloodstream infection, CVC; central venous catheter, TIVAD; totally implantable venous access device, PICC; peripherally inserted central catheter, BSI; bloodstream infection, GvHD; graft versus host disease, NA; not applicable.

*Data described per episode, in total 95 episodes in 82 patients were included.

Table 1b Baseline characteristics

		Salvage treatment (n=83)				Immediate removal (n=12)	
		Total (n=83)		CLABSI (n=45)			
Neutropenia <0.5x10^9/L at BSI onset, n (%)	No	47	56.6%	38	84.4%	10	83.3%
	Yes	36	43.4%	7	15.6%	1	8.3%
	Missing	0	0.0%	0	0.0%	1	8.3%
Signs of local infection, n (%)	No	62	74.7%	32	71.1%	7	58.3%
	Yes	20[a]	24.1%	13	28.9%	5	41.7%
	Missing	1	1.2%	0	0.0%	0	0.0%
Signs of thrombosis, n (%)	No	10	12.0%	5	11.1%	1	8.3%
	Yes	4	4.8%	3	6.7%	0	0.0%
	No radiological imaging	69	83.1%	37	82.2%	11	91.7%
Empirical antibiotics adequate[b], n (%)	Yes	72	86.7%	38	84.4%	NA	NA
	No, adjustment required after antibiogram was available	11	13.3%	7	15.6%	NA	NA
Days of salvage antibiotic treatment, median (IQR)		10 (4)		10 (2)		NA	

CLABSI; central line-associated bloodstream infection, CVC; central venous catheter, TIVAD; totally implantable venous access device, PICC; peripherally inserted central catheter, BSI; bloodstream infection, GvHD; graft versus host disease, NA; not applicable.

*Data described per episode, in total 95 episodes in 82 patients were included.

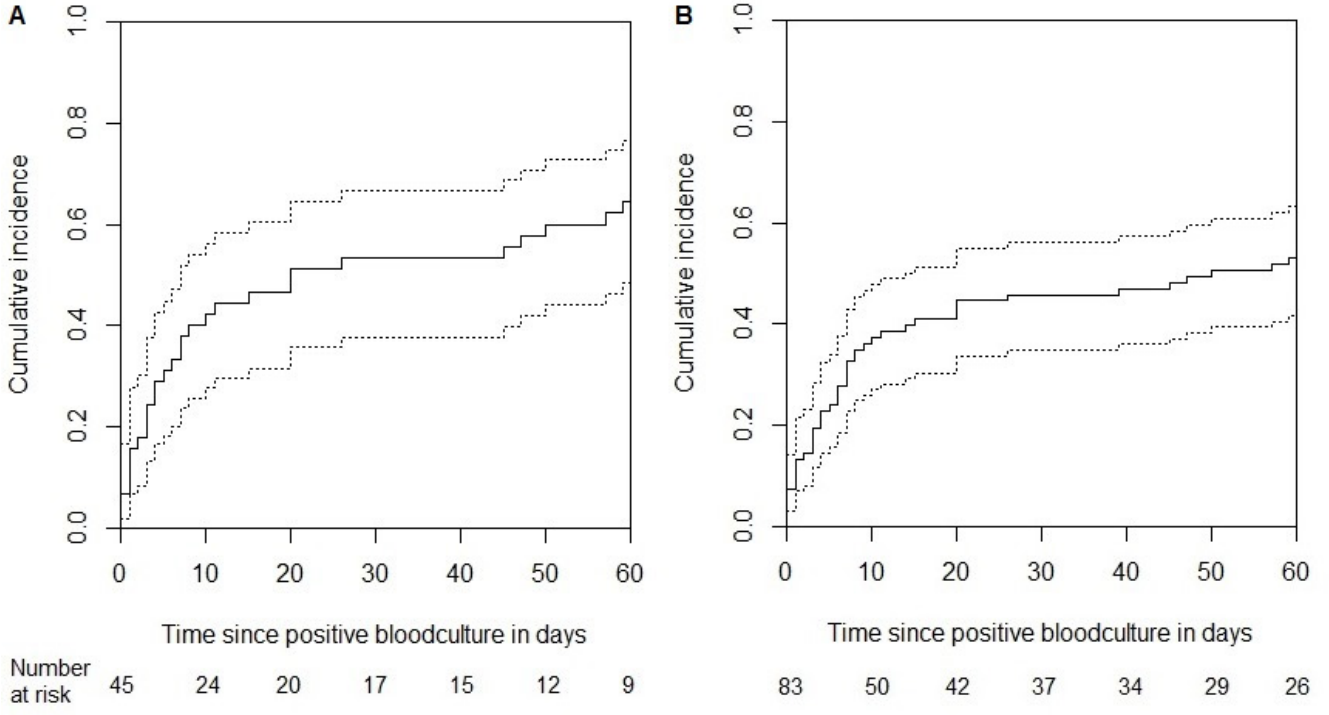
[a] During seven episodes, signs of a local infection were observed, but following the CLABSI criteria an mucosal-barrier injury laboratory confirmed bloodstream infection was scored.

[b] Adequate empirical antibiotic treatment was defined as patients who received antibiotics directly after the start of the episode for which the Enterobacterales that was eventually identified was susceptible

Escherichia coli (37%), *Enterobacter cloacae complex* (17%), and *Klebsiella pneumoniae* (12%) were the most commonly cultured isolates (see **Supplementary Digital Content 1**)

The cumulative incidence of the primary endpoint / events at 60 days was 64.4% (CI95% 48.3-76.7) for CLABSIs (**Figure 2A**) and 53.0% (CI95% 41.7-63.1) for BSIs (**Figure 2B**).

Figure 2 Cumulative incidence of an event from *Enterobacterales* blood culture collection for patients receiving salvage treatment for (A) an *Enterobacterales* CLABSI, and (B) an *Enterobacterales* BSI.



CLABSI; Central Line Associated Bloodstream Infection, BSI; Bloodstream Infection. Day 0 represents positive blood culture collection followed by the start of salvage treatment. Event = removal, intensive care unit admission, or death related to the primary CLABSI/BSI. Three events occurred directly after blood culture collection for CLABSIs, these episodes all concerned direct intensive care unit admissions. Six events occurred directly after blood culture collection for BSIs, these episodes all concerned direct intensive care unit admissions.

Intensive care unit admission or death related to the primary BSI was not observed after the episodes where the CVC was immediately removed. After CLABSI *Enterobacterales* episodes where salvage treatment (N=45) was attempted, the following events related to the primary episode were observed: 27 (60%) CVC removals, 7 (16%) PICU admissions, and one (2%) death. Furthermore, 6 (13%) relapses and 2 (4%) re-infections were observed, which in all cases required CVC removal. No children were admitted to the pediatric intensive care unit or died due to relapses or re-infections. Of all CLABSI *Enterobacterales* events (N=29), 11 (35%) events occurred more than 10 days after the start of the primary episode. Of these 11 events, 9 (82%) occurred after adequate antibiotic treatment for the primary episode was stopped, one (9%) occurred during adequate antibiotic treatment for the primary episode and one (9%) occurred after a primary episode that was never adequately treated. Symptoms of these events were observed after a median of 8 (Q1-Q3: 1-32) days after adequate treatment for the primary episode was stopped. These results are described for all and CLABSI *Enterobacterales* episodes where salvage treatment was given in **Table 2**. Including also the 12 immediate removal patients (N CLABSI=56 and N BSI=95) and counting these removals as an event, 40 (71.4%) and 56 (58.9%) events occurred during the follow-up in the *Enterobacterales* CLABSI and BSI group, respectively.

No notable difference in the presence of a thrombosis or local infection during episodes with and without a BSI-related event were observed (see **Supplementary Digital Content 2**).

No risk factors were significantly associated to the hazard for both CLABSIs and BSIs (see **Table 3** and **Supplementary Digital Content 3**, respectively).

Table 2 Events, relapses and re-infections

		Salvage treatment (n=83)	
		Total BSI (n=83)	**CLABSI (n=45)**
		N (%) or median (Q1-Q3)	**N (%) or median (Q1-Q3)**
CLABSI/BSI-related events	No	39 (47.0%)	16 (35.6%)
	Yes	44 (53.0%)	29 (64.4%)
	Days until	6 (2-15)	6 (2-20)
CVC removal related to BSI	Yes	39 (47.0%)	27 (60.0%)
	Days until	7 (3-20)	7 (3-20)
PICU admission related to BSI	Yes	13 (15.7%)	7 (15.6%)
	Days until	1 (0-1)	1 (0-1)
Death related to BSI	Yes	4 (4.8%)	1 (2.2%)
	Days until	3 (1-6)	1 (1-1)
CLABSI/BSI-related events 10 days after start primary episode	Yes	14[a] (16.8%)	11[a] (24.4%)
	Days from stop primary antibiotics until first symptoms of event	8 (1-32)	8 (1-32)
Relapse of primary infection	Yes	6 (7.2%)	6 (13.3%)
	Days until	20 (18-44)	20 (18-44)
	Requiring CVC removal	6 (7.2%)	6 (13.3%)
Re-infection after primary infection	Yes	5 (6.0%)	2 (4.4%)
	Days until	32 (32-43)	45 (43-47)
	Requiring CVC removal	4 (4.8%)	2 (4.4%)

CLABSI; central line-associated bloodstream infection, BSI; bloodstream infection, CVC; central venous catheter, PICU; paediatric intensive care unit, Q1; first quartile, Q3; third quartile. Bloodstream infection related events, relapses and re-infections during a 60-day follow-up period.

During one episode no adequate antibiotics were given for the primary episode, and during another episode antibiotics for the primary episode were still continuously given during the start of the symptoms of the event after 10 days.

Table 3 Estimated cause-specific hazard ratio (HR) along with the 95% confidence interval (CI) from a Cox model for all CLABSIs

	Salvage treatment episodes that met CLABSI criteria (n=45)
	Risk of event
Risk factors	HR (CI95%)
Diagnosis	
Hematologic malignancy / Lymphoma	1
Solid tumor	0.60 (0.12-3.12)
Benign stem cell recipient	1.16 (0.24-5.72)
CVC type	
Tunneled external CVCs	1
TIVAP	1.12 (0.23-5.50)
Non-tunneled CVCs	1.42 (0.26-7.69)
Neutropenia at BSI onset	
No	1
Yes	1.09 (0.28-4.29)
Empirical antibiotics adequate	
Yes	1
No	1.86 (0.41-8.35)

CLABSI; central line-associated bloodstream infection, TIVAD; totally implantable venous access device, BSI; bloodstream infection, PICC; Peripherally Inserted Central Catheter, HR; hazard ratio, CI; confidence interval.
Event = removal, intensive care unit admission, or death related to the primary CLABSI.
Non-tunneled CVCs = PICC and non-tunneled CVCs.

DISCUSSION

In this study, the cumulative incidence of an event at 60 days after salvage with antibiotics for the treatment of *Enterobacterales* CLABSIs and BSIs in pediatric oncology patients is high. Furthermore, severe sepsis requiring PICU admission appeared to be a common complication of *Enterobacterales* CLABSIs.

The IDSA guidelines only recommend CVC removal for CLABSIs caused by *Enterobacterales* in case of severe sepsis or persisting infections.(8) Benefits of CVC salvage are continuity of care, and avoidance of general anesthesia and vascular damage. However, the results of this study suggest that, in the majority of the cases, CVC removal at a certain point was unavoidable. Delaying the decision to remove

the CVC, can have significant consequences regarding the clinical status of the children; i.e. severe sepsis requiring PICU admission and possibly even resulting in death. PICU admission and death were in this study not observed in the patients where the CVC was immediately removed, which further suggests that this might be avoidable by immediately removing the CVC upon *Enterobacterales* CLABSI diagnosis.

When only *Enterobacterales* CLABSIs were included in the analyses, the cumulative incidence at 60 days increased from 53.0% (CI95% 41.7-63.1) to 64.4% (CI95% 48.3-76.7). This difference can be explained by the inclusion of BSIs originating from other sources than the CVC (e.g. *Escherichia coli* from the urinary tract or translocation due to a weakened mucosal barrier in the gut), in which the CVC may not have become colonized or infected.

Previously performed comparable studies investigating the safety and efficacy of salvage treatment in pediatric oncology patients for *Enterobacterales* bloodstream infections were not identified. Nazemi et al. (2003) reported an unsuccessful salvage rate of 55% for *Enterobacterales* BSIs in neonates with mostly peripherally inserted central catheters.(12) Furthermore, a meta-analysis from 2022 including seven studies, reported a pooled unsuccessful salvage rate of 53% for gram-negative CLABSIs.(20) However, the results were highly heterogeneous (I^2 95%), a variety of patient groups and CVC types were included, some studies used ALT as treatment, and the definition of catheter salvage and which gram-negative bacteria were included was unclear.(13-20) Finally, Ashkenzani-Hoffnung et al. (2020) reported an unsuccessful salvage rate of 0% (N=16) for *Enterobacterales* CLABSIs in pediatric oncology patients with the additional use of ALT.(21) Comparable relapse and/or re-infections rates of 7-14% have been reported previously for gram-negative CLABSIs.(12, 20) No studies investigating the incidence rate of intensive care unit

admission after salvage treatment due to *Enterobacterales* CVC related bloodstream infections were identified. Comparable mortality rates of 4-7% after salvage treatment (with/without ALT) for *Enterobacterales* CVC related bloodstream infections were reported in previous studies.(12, 17)

The cumulative incidence estimated in this study is higher than the one expected by clinicians based on the scarce previously published literature.(12-20) Differences with previous literature can be explained by multiple reasons. First, successful salvage was defined taking into account the clinical status of the patient and not solely CVC removal or reinfections as done by previous studies.(12-20) Second, this study used the CLABSI criteria, whereas other studies included all positive blood culture episodes.(12) Third, this study focused on *Enterobacterales* only; including other gram-negative micro-organisms might have resulted in higher success rates, due to a lower pathogenicity of the micro-organisms.(13-20) Fourth, some of the previously performed studies used ALT in addition to CVC salvage treatment. ALT seems promising in improving the successfulness of CVC salvage treatment in pediatric oncology patients but further research is needed to determine its safety and efficacy.(9, 10, 17, 20, 21)

Strengths of this study are the relatively large sample size for a study in paediatric oncology, the use of a comprehensive definition of treatment failure (i.e. taking into account the clinical status of patients and including also late treatment failure), and the strict inclusion and excluding criteria used. Limitations of this study are the retrospective study design, and the small sample size due to which comparisons between groups based on risk factors was difficult. Furthermore, CVC removal might have been avoidable in some cases where the CVC was extracted immediately, since the decision to remove the CVC was made based on the discretion of the infectiologist, oncologist and/or surgeon. Finally, the CLABSI criteria might result in

an under- or overestimation of the actual bloodstream infections caused by the CVC. For pediatric oncology patients however, the CLABSI-criteria are currently the most suitable criteria since it does not require the results of peripheral blood cultures (which are rarely obtained in children).(32) In conclusion, salvage treatment with systemic antibiotics alone for *Enterobacterales* CLABSIs in pediatric oncology patients results in a high event rate. Immediate CVC removal appears recommendable for this patient group.

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SUPPLEMENTARY FILES

Supplemental Digital Content 1 Enterobacterales isolates

Micro-organisms	**Salvage treatment (n=83)**				**Immediate removal (n=12)**	
	Total (n=83)		**CLABSI (n=45)**			
Citrobacter braakii	1	1.2%	1	2.2%	0	0.0%
Citrobacter freundii (incl.1 ESBL+)	2	2.4%	1	2.2%	0	0.0%
Enterobacter cloacae complex (incl. 6 ESBL+)	15	18.1%	10	22.2%	1	8.3%
Escherichia coli (incl. 9 ESBL+)	30	36.1%	10	22.2%	5	41.7%
Escherichia vulneris	0	0.0%	0	0.0%	1	8.3%
Hafnia alvei	1	1.2%	0	0.0%	0	0.0%
Klebsiella oxytoca	3	3.6%	2	4.4%	0	0.0%
Klebsiella pneumoniae (incl. 5 ESBL+)	9	10.8%	3	6.7%	2	16.7%
Pantoea agglomerans	4	4.8%	3	6.7%	0	0.0%
Pantoea eucrina	1	1.2%	1	2.2%	0	0.0%
Pantoea septica	7	8.4%	6	13.3%	0	0.0%
Raoultella species	1	1.2%	1	2.2%	0	0.0%
Serratia marcescens	2	2.4%	1	2.2%	0	0.0%
Enterobacterales unspecified	1	1.2%	0	0.0%	0	0.0%
Mixed	6	7.2%	6	13.3%	3	25.0%

CLABSI; central line-associated bloodstream infection, BSI; bloodstream infection, mixed; poly-microbial infection with more than one *Enterobacterales* bacteria cultured in initial blood culture at bloodstream infection diagnosis.

Supplemental Digital Content 2 Signs of local infection or thrombosis

		Total (N=95)		**CLABSI (N=45)**	
		Event (N=44)	No event (N=39)	Event (N=16)	No event (N=29)
Signs of local infection, n (%)	No	30 (68.2%)	32 (82.1%)	20 (69.0%)	12 (75.0%)
	Yes	13 (29.5%)	7 (17.9%)	9 (31.0%)	4 (25.0%
	Missing	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Signs of thrombosis, n (%)	No	6 (13.6%)	4 (10.3%)	3 (10.3%)	2 (12.5%)
	Yes	3 (6.8%)	1 (2.6%)	2 (6.9%)	1 (6.3%)
	No radiological imaging	35 (79.5%)	34 (87.2%)	24 (82.8%)	13 (81.3%)

CLABSI; central line-associated bloodstream infection

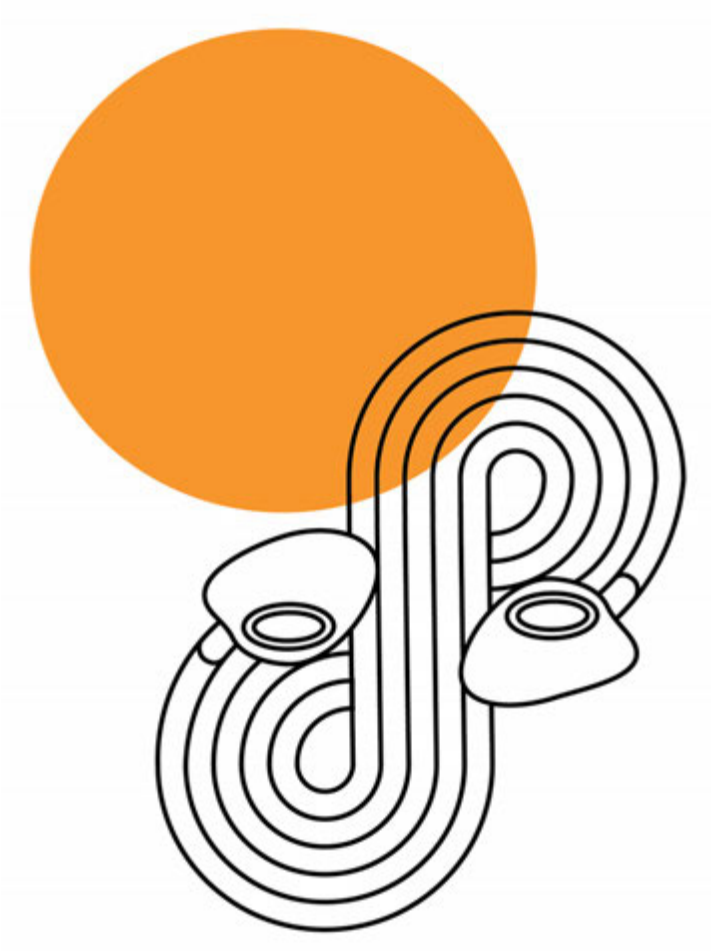
Supplemental Digital Content 3 Estimated cause-specific hazard ratio (HR) along with the 95% confidence interval (CI) form a Cox model for all bloodstream infections.

	Salvage treatment episodes (n=83)
	Risk of event
Risk factors	HR (CI95%)
Diagnosis	
Solid malignancy	1
Hematologic malignancy / lymphoma	0.80 (0.42-1.52)
Benign stem cell recipient	0.74 (0.16-3.38)
CVC type	
Tunneled CVCs	1
Non-tunneled CVC and PICC	1.27 (0.28-5.68)
Neutropenia at BSI onset	
No	1
Yes	0.66 (0.34-1.25)

TIVAD; totally implantable venous access device, BSI; bloodstream infection, HR; hazard ratio, CI; confidence interval.
Event = removal, intensive care unit admission, or death related to the primary CLABSI.
Tunneled CVCs = TIVAD and tunneled external CVC.

CHAPTER 13

Summary and general discussion
Future perspectives



SUMMARY AND GENERAL DISCUSSION

Over the years, central venous catheters (CVC) became more popular in the field of paediatric oncology since they provide a reliable long-term venous access route, without the need for repeated venous punctures. Although the implantation of a CVC provides many benefits for patients as compared to peripheral infusion, CVCs can also cause adverse events that can have a serious impact on patients and their caregivers. Paediatric oncology patients mostly receive long-term treatment via totally implantable venous access ports (TIVAP) and have many co-morbidities (e.g., thrombocytopenia, thrombogenicity, neutropenia and mucositis), that can make the insertion period very challenging in terms of CVC-related complications. (1) This patient group will therefore benefit from more evidence-based guidelines, adapted to their specific needs. However, current evidence-based CVC guidelines, developed to minimize the negative burden of CVCs on the paediatric oncological care, are mostly based on adult literature or literature in children with other underlying diagnoses. (2-6) Well-designed studies with large sample sizes are required to create solid evidence where we can build proper guidelines on. The Princess Máxima Centre for paediatric oncology, the largest paediatric oncology centre in Europe, has an opportunity to take the lead in this. The groundwork to accomplish standardized evidence-based CVC care, was laid through the execution of the studies described in this thesis.

PART 1 – COMPREHENSIVE ANALYSIS OF CENTRAL VENOUS ACCESS CARE

Summary

In this part of the thesis, we performed a comprehensive analysis of the central venous access care for paediatric oncology patients in the Netherlands. A paediatric oncology specific surgical CVC implantation guideline was developed, and CVC complication rates were evaluated. This guideline aligned the surgical CVC

implantation method (incl. port localization based on the SPACE-study and CVC choice implications for Hodgkin lymphoma patients based on our retrospective study) within our hospital. The proposed guideline may provide additional information to institutions lacking dedicated guidelines and can serve as reference for comparison with other institutions' guidelines. Furthermore, central line associated bloodstream infections (CLABSI) were identified as posing the highest burden on patients, their caregivers, and the health care system, making the prevention CLABSIs the primary focus for further research within our department.

Strengths

This part of the thesis gave us a comprehensive overview of our current CVC practice by considering the experience of surgeons, satisfaction of patients, caregivers, survivors and nurses, and complication rates. This resulted in a paediatric oncology specific CVC implantation guideline, provided baseline complication rates for this population for future reference, and key areas of focus for future research were defined.

Limitations

The studies included in this part of the thesis were mostly retrospective from the period before centralization of the paediatric oncology care in the Netherlands in 2018. The centralization led to an increase of the number of CVCs implanted from approximately 120 to 700 per year in the Princess Máxima Centre. The data was therefore still limited as compared to the currently available data. Additionally, the data may overestimate the current burden that CVCs pose on this patient group since 1) CVC protocols were aligned in the Netherlands during the centralization, 2) the medical staff was trained extensively on the new protocols and 3) information sheets and videos on CVC care became available for patients and caregivers. On the other hand, the data from the retrospective parts of this thesis might have underestimated

the current burden since the data exchange between shared care centres improved over time resulting in less missing data. Furthermore, late-effects data was used, providing information on long-term effects, however, this data describes the results of the practice from the past and is therefore not completely representative of our current practice.

PART II – CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING PREVENTION

Summary

Since we identified CLABSIs as posing a high burden of disease on patients and caregivers, we dedicated the second part of this thesis to the optimization of CLABSI prevention in children with cancer. We identified that antimicrobial lock solutions, and specifically taurolidine containing lock solutions, are a promising strategy for the prevention of CLABSIs. The evidence in paediatric oncology patients, however, was scarce and a large-scale randomized controlled trial in this patient group was needed. Before we wanted to design such a trial, we deemed it important to investigate two limitations of previous studies that are important to accurately interpret study results: (1) the impact of taurolidine on blood culture results and (2) the applicability of the CLABSI definition in children with cancer. We observed in a laboratory setting that taurolidine could delay the time-to-detection of blood cultures considerably, which could have serious clinical implications (i.e., treatment delays resulting in severe sepsis) in the future. The effect on study results (i.e., CLABSI yes or no) however, was deemed minimal since all vials in the laboratory setting eventually did became positive. The CLABSI criteria appeared to be applicable for the paediatric oncology population but may lead to an overestimation of bloodstream infections truly caused by the CVC. These findings were used for the interpretation of results from previous studies and the randomized controlled trial described in this thesis (the CATERPILLAR-study). The CATERPILLAR-study was designed and performed to investigate the effect of taurolidine locks as compared to heparin locks

for the prevention of CLABSIs in children with cancer. No difference was detected in the incidence of CLABSIs for taurolidine and heparin locks in paediatric oncology patients within the setting of our randomized controlled trial.

Strengths

This part of the thesis describes the largest randomized controlled trial investigating the efficacy of taurolidine locks in all patient populations. (7) The CATERPILLAR-study used an assessor-blinded design, very strict inclusion and exclusion criteria creating a homogenous group, stratification for two important risk factors during randomization, and three experts to evaluate the primary outcome following the CLABSI criteria. Furthermore, as stated above, we performed two additional studies to investigate the influence of two potential limitations (i.e., taurolidine in blood culture vial and applicability of the CLABSI definition) on the trial results. This way, we performed a comprehensive trial that provides high quality evidence that taurolidine locks do not differ from heparin locks in the prevention of CLABSI in the paediatric oncology population.

Limitations

Even though we became aware of the flaws of the CLABSI criteria in the paediatric oncology population, these criteria were used in most studies described in this thesis. These criteria were used since it is currently the only internationally recognizable and most applicable definition for this patient group, remaining one of the major limitations of studies being performed investigating CLABSIs in paediatric oncology patients. Future technologies must be developed to better identify the cause of a bacteraemia, as will be discussed under future perspectives.

The sample size of the CATERPILLAR-study was based on our retrospective study investigating the incidence of CLABSI and the available evidence from the literature

as we evaluated in our systematic review and meta-analysis investigating the efficacy of taurolidine. The possible overestimation of the true CLABSI incidence due to the applicability of the CLABSI criteria, might have resulted in an inaccurate sample size analysis (i.e., inclusion of CLABSIs that were not caused by the CVC and are therefore not preventable by a lock solution). Additionally, the effect size appeared to be smaller than the one used for computing the sample-size, which was based on previously performed studies in the meta-analysis. This might have been caused by the frequency in which locks were given as compared to other studies and/or the delay in the timing of the first lock instillation.

During the CATERPILLAR-study, the goal was to insert the first lock solution as soon as possible after the CVC was connected. This ensured the lock was inserted before the formation of the intraluminal biofilm. However, this meant that patients and caregivers needed to be informed and give their consent directly after the diagnosis was given. Logically, due to psychosocial circumstances, this was not possible and desirable in many cases. This limitation is difficult to overcome and will always play a role in future research in this patient group.

Lock solutions are developed to prevent infections that originate from the inside of the catheter lumen. Various other contamination routes can cause a CLABSI, i.e., haematogenous seeding from distant sites, contaminated hubs, or transcutaneous migration of micro-organisms. Locks could therefore only be a part of the solution. Thereby, we would like to underline the importance of implementing CVC care bundles (i.e., especially focusing on simple hygiene practices such as hand washing and cleaning of the exit-site) and training health care workers, children, and caregivers according to these.

PART III CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING TREATMENT

Summary

In this part of the thesis, we focussed on the optimization of CLABSI treatment, with the goal to reduce the number of CLABSI-related (serious) adverse events such as CVC removal, intensive care unit admission and death due to severe sepsis. We specifically studied *Enterobacterales* CLABSIs since health care professionals are often in doubt if salvage treatment with antibiotics should be attempted in these cases. Our retrospective study showed that the incidence of CLABSI-related events was very high and therefore we concluded that immediate CVC removal after an *Enterobacterales* CLABSI is recommended for this patient group. This was implemented in the CVC guidelines of our hospital.

Strengths and limitations

The large sample size allowed for analyses per micro-organism, resulting in a clinical recommendation and change in the guideline. As a result of the CVC complication database built in the Princess Máxima Centre, conducting comparable studies has become considerably more straightforward, offering promising prospects for future research projects.

However, the retrospective data collection makes the database prone to bias. On the other hand, prospective studies investigating vulnerable immunocompromised paediatric patients at risk of severe CLABSI-related sepsis are often ethically difficult or impossible to design. Moreover, the sample sizes of these studies were currently relatively small. In future perspectives, the importance of surveillance will be discussed besides the possibility of using this database to perform large studies.

FUTURE PERSPECTIVES

Despite the efforts made in this thesis to reduce the impact of CVCs on children, their caregivers, and survivors, the rates of CVC-related complications and the incidence of associated sequelae remains high. Therefore, it is of the utmost importance to further optimize prevention and treatment strategies. In this part of the thesis, we will discuss ideas for future developments and research projects to decrease the negative impact of CVCs on children with cancer. An overview of these ideas is described in **Table 1**.

PART 1 – COMPREHENSIVE ANALYSIS OF CENTRAL VENOUS ACCESS CARE

CVC-complication surveillance system

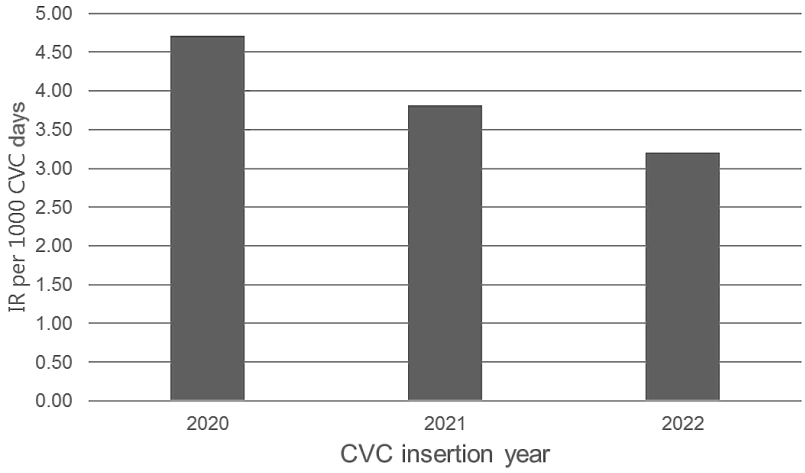
The creation of a CVC-related complication surveillance system is of great importance. The data from these databases should be used to detect peaks in the incidence of complications and to identify their root causes. Moreover, conducting multi-variate risk factor analyses is essential to pinpoint the most significant risk factors and prioritize preventive strategies targeted at addressing these factors. In collaboration with the central venous access working group of the Princess Máxima Centre for paediatric oncology, the department of medical microbiology of the University Medical Centre Utrecht, infectiologists of the Wilhelmina Children's Hospital Utrecht and the author of this thesis (CvdB), we started with the development of such a system, which has been kept up to date since 2020. This surveillance database contains CLABSI-related data from the 700 CVCs implanted annually in the Princess Máxima Centre for paediatric oncology. (8) Since 2020, the CLABSI incidence has been monitored each quartile by the central venous access working group, see **Figure 1**. This has led to various improvements and research projects, including some studies described in this thesis. Overall, the incidence rate of CLABSI decreased between 2020 and 2023 (3.05 to 2.15 CLABSIs per 1.000 CVC-days), this might be the result of the various improvements that have been

implemented so far (i.e., alignment of protocols, training of health care professionals, improved CVC type indication and the (re-)start of antibiotic prophylaxis in some haematological patient groups) but also due to more accurate and strict registration of the events. Continuation of this CLABSI surveillance system in the future is highly recommended so that the CLABSI incidence can be closely monitored and acted upon if needed. Other hospitals may also benefit from the set-up of our CLABSI surveillance system, therefore in the future, publishing our set-up might be useful for them.

A second complication database for non-CLABSI CVC-related complications was created by the surgeons at the Princess Máxima Centre for paediatric oncology and the author of this thesis (CvdB). This database currently contains data from the period 2015-2018, of which data has been used for various research projects in the past, including studies described in this thesis. Continuation of the data-collection for CVCs implanted from 2018 onwards and ideally creating an up-to-date CVC-related complication surveillance database would be useful to monitor and further optimize the quality of CVC care by identifying and tackling the root-causes of CVC-related complications.

Keeping surveillance systems up to date is time demanding and methods for semi-automation of these systems should be further investigated. (9) However, due to the shared care construction of the Princess Máxima Centre for paediatric oncology, (semi-)automation will currently be very challenging since each hospital uses its own electronic patient file system. Centralizing health records in the Netherlands would therefore be a goal for the future.

Figure 1 CLABSI incidence per 1,000 CVC-days in the Princess Máxima Centre for paediatric oncology per year using data from the CLABSI surveillance database. (8)



IR; Incidence rate, CVC; Central Venous Catheter

CVC implantation

In the future, research projects aiming to further optimize CVC implantation should focus on the following promising innovations and strategies.

Regarding CVC-type, the insertion of double lumen TIVAPs instead of double lumen external cuffed CVCs, might be beneficial, but its applicability has not yet been studied for the paediatric population. Furthermore, the risk of complications of long-term CVCs might differ between material types where the catheter is made of and should be studied. (10)

Regarding the localization of the TIVAP port, implantation in the arm might be useful in the paediatric population since the port can be punctured out of the patients view and the scar is less visible as compared to chest localization. (11) Additionally, our

hypothesis is that the scar of anterior thoracic chest wall ports becomes much broader as compared to lower lateral chest wall ports. During the SPACE-study, we decided not to further inspect the scar of the current patients, since the scar would still change over-time. However, scar differences could already be noticed in our current patients.

Regarding CVC-tip localization, the electrocardiogram (ECG)-guided technique might be quicker, more accurate and uses less radiation as compared to the current standard of care in our hospital with fluoroscopy. (12)

CVC management for the prevention of non-CLABSI complications

Regarding the prevention of non-CLABSI related CVC complications, the following innovations and strategies could be considered. Cyanoacrylate glue on the exit site of a CVC has been suggested as an effective strategy for dislodgement, local bleeding, and local infections. (13) Furthermore, a regular saline lock might be as effective as heparin for the prevention of CVC occlusions. (14) At last, direct oral anti-coagulants for the primary prevention of CVC-related central venous thrombosis (CVT) might be applicable for paediatric oncology patients with a peripherally inserted central catheter (PICC) and/or other CVT-related risk factors, but the evidence is still scarce. (15)

PART II – CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING PREVENTION

CLABSI diagnosis

We suggested a modification of the CLABSI definition to make it more applicable for paediatric oncology patients. However, by using an adjusted definition, it will make the data incomparable to data from other centres, preventing the execution of accurate meta-analyses. Therefore, we concluded that the current CLABSI criteria should be used in research and surveillance projects. However, to consider the

limitations of these criteria, it is recommendable to include multiple independent assessors and to let these assessors evaluate the bacteraemia episodes clinically as done during the CATERPILLAR-study, so that these results can be used in sub-analyses. Furthermore, future technologies might be developed which can be used to diagnose or classify the risk of a bloodstream infection using machine learning (9) or biomarkers (16) and should be studied.

CLABSI prevention

Many innovative strategies have been studied and suggested for the prevention of CLABSIs, however, in our opinion, using accurate hygiene practices is key. Therefore, we would like to underline the importance of education on hygiene practices to health care personnel, patients, and caregivers. Further innovative preventative strategies that might be promising to combat CLABSIs are alcohol/chlorhexidine-impregnated caps, antimicrobial bathing, and nasal mucopuricin ointment. (17) Additionally, taurolidine locks might still be beneficial if administered more frequently, for specific patient groups, for patients with a history of multiple CLABSIs, or for CVC salvage during a CLABSI. The efficacy of these strategies can be assessed by using the surveillance data collected. Moreover, before a strategy is implemented, researchers should make sure that accurate cost-effectiveness analyses have been performed.

PART III CENTRAL VENOUS ACCESS INFECTIONS: OPTIMISING TREATMENT

CLABSI treatment

Regarding CLABSI treatment, antimicrobial locks might be promising for the treatment of CLABSIs. Research in paediatric oncology patients is scarce but promising and should be further explored. (18) Furthermore, the most optimal CVC free interval after CVC removal due to a CLABSI should be defined. The current guidelines are based on very limited research. (2)

Table 1 Suggestions for future developments and research.

Part I	CVC-complication surveillance system	• Continuation of CVC complication surveillance system to: o Detect peaks in the incidence of complications and identify their root causes. o Perform multi-variate risk-factor analyses to prioritize preventative strategies. • Publication of the surveillance system set-up to guide other hospitals in the creation of such a system. • Evolution to (semi-)automatic surveillance system. • Centralizing health records for better surveillance.
	CVC implantation	• Applicability of double lumen TIVAPs. • Safety of polyurethane versus silicone catheters. • Applicability of arm TIVAPs. • Scar appearance of anterior versus lower lateral port scars. • Accuracy and usability of ECG-guided catheter tip localization.
	CVC management for the prevention of non-CLABSI complications	• Efficacy of exit-site glue for the prevention of dislodgement, local bleeding, and infections. • Non-inferiority of saline lock versus heparin lock for the prevention of occlusions. • Efficacy and safety of direct oral anti-coagulants for the primary prevention of CVT in patients with a PICC and/or other CVT-related risk factors.
Part II	CLABSI diagnosis	• Adjustment or considering an altered CLABSI definition which is more applicable for paediatric oncology patients. • Machine learning for the diagnosis of CLABSI. • Biomarkers (e.g., citrulline) for the diagnosis of CLABSI. • Use of multiple independent assessors of CLABSIs in surveillance and research projects. • Let assessors in research projects also evaluate the episodes clinically and perform sub-analyses with these data.
	CLABSI prevention	• Focus on simple preventative methods such as education on hygiene. • Other promising strategies are alcohol/chlorhexidine-impregnated caps, antimicrobial bathing, and nasal mucopuricin ointment. • Cost-effectiveness analysis of CLABSI prevention strategies.
Part III	CLABSI treatment	• Antimicrobial locks for the treatment of CLABSI. • Benefit of CVC free interval.

CVC; Central Venous Catheter, TIVAP; Totally Implantable Venous Access Port, ECG; Electro-Cardiogram, PICC; Peripherally Inserted Central Catheter, CLABSI; Central Line Associated-Bloodstream Infection, CVT; Central Venous Thrombosis.

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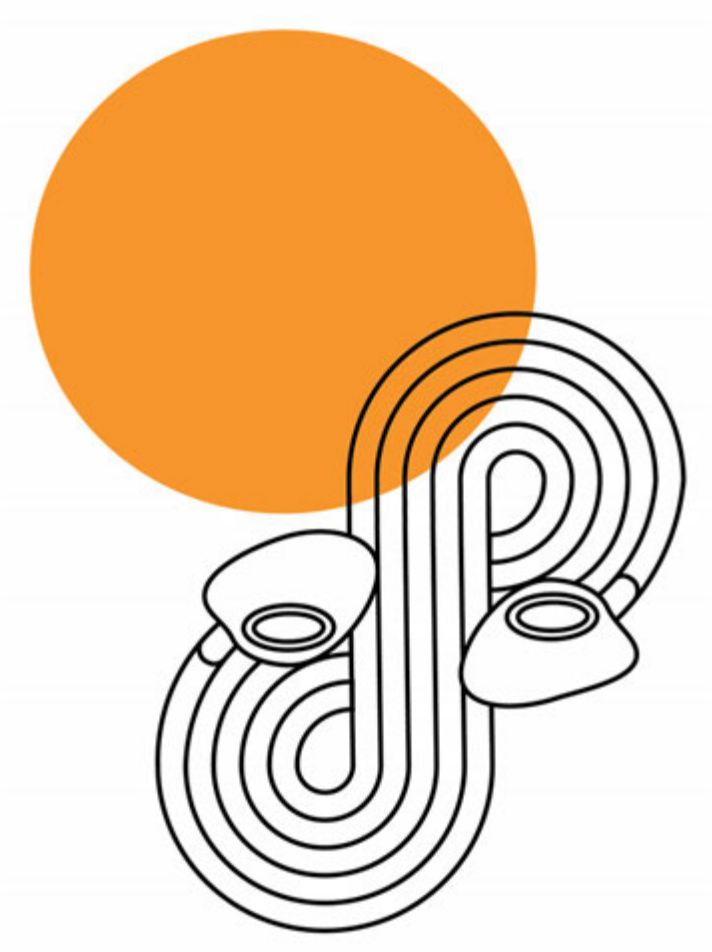
ADDENDUM



DUTCH SUMMARY

Door de jaren heen, zijn centrale lijnen steeds populairder geworden binnen de kinderoncologie. Centrale lijnen zorgen ervoor dat kinderen een betrouwbare toegang hebben tot hun vaten, zonder dat regelmatig venapuncties nodig zijn. Hoewel het inbrengen van een centrale lijn veel voordelen heeft voor patiënten ten opzichte van een perifeer infuus, zien we alsnog veel nadelige effecten die een grote impact kunnen hebben op patiënten en hun ouders/verzorgers. Centrale lijn richtlijnen die ontwikkeld zijn om deze nadelige effecten zoveel als mogelijk tegen te gaan, zijn echter vooral gebaseerd op studies in volwassenen of studies in kinderen met andere aandoeningen. Kinderoncologie patiënten zijn moeilijk te vergelijken met deze groepen omdat ze vaak langer behandeld worden via een ander type lijn en veel co-morbiditeiten hebben (i.e., trombocytopenie, thrombogeniciteit, neutropenie en mucositis). Deze co-morbiditeiten liggen vaak ten grondslag aan de centrale lijn complicaties die we zien. Deze patiëntengroep heeft daarom behoefte aan specifieke kinderoncologie richtlijnen. De kinderoncologische richtlijnen moeten onderbouwd worden door grote goed ontworpen studies. Het Prinses Maxima Centrum voor kinderoncologie, het grootste kinderoncologie ziekenhuis van Europa, heeft de kans om hierin het voortouw te trekken. De eerste stappen om dit te bereiken, zijn gelegd door de uitvoering van de studies in deze thesis.

In het eerste deel van de thesis, hebben we een uitgebreide analyse gedaan van de status van de centrale lijn zorg van kinderoncologie patiënten in Nederland. We hebben gekeken naar verschillende facetten: hoe brengen wij lijnen in, hoeveel complicaties zien we, en hoe tevreden zijn patiënten, ouders, survivors en verpleegkundigen met de lijnen. We zagen dat patiënten gediagnosticeerd met Hodgkin een lager risico hebben op een centrale lijn trombose als ze een port-a-cath® krijgen in plaats van een perifeer ingebrachte centrale katheter. Daarnaast

zagen we patiënten, ouders, survivors en verpleegkundigen erg tevreden waren met het gebruikt van de centrale lijnen. De locatie waar de lijn geplaatst wordt heeft echter wel verschillende voor- en nadelen, waar rekening mee gehouden dient te worden bij het informatiegesprek voorafgaand aan de operatie. Daarnaast zagen we een hoge incidentie van centrale lijn infecties in onze patiëntenpopulatie met vervelende gevolgen. Gemiddeld maakt een op de drie kinderoncologie patiënten een of meerdere centrale lijn infecties door gedurende zijn/haar behandelperiode en in ongeveer de helft van deze gevallen moet de centrale lijn verwijderd worden. Daarnaast komt, door een ernstige centrale lijn gerelateerde sepsis, 5% van de kinderen met een centrale lijn uiteindelijk op de intensive care terecht. Het doel was daarom om ons in de komende jaren te focussen op het voorkomen van centrale lijn infecties in kinderen met kanker. Op basis van deze informatie hebben we een chirurgische centrale lijn richtlijn gemaakt die gebruikt kan worden als leidraad voor andere kinderoncologische ziekenhuizen en voor het vergelijken van chirurgische methodes.

In het tweede deel van de thesis zijn de eerste stappen gezet om het aantal centrale lijn infecties te verminderen. We identificeerde antimicrobiële locks, specifiek taurolidine bevattende locks, als een veelbelovende strategie voor de preventie van deze infecties. Er was echter nog weinig wetenschappelijk bewijs voor de effectiviteit van deze locks in de kinderoncologische populatie. Daarom zijn we gestart met de opzet van de tot nog toe grootste gerandomiseerde trial naar de effectiviteit van deze locks. Tevens waren wij van mening dat twee limitaties van eerdere studies goed onderzocht moesten worden om de uiteindelijke resultaten van de trial goed te kunnen interpreteren: (1) de impact van taurolidine op het resultaat van bloedkweken, en (2) de toepasbaarheid van de veel gebruikte central line-associated bloodstream infection (CLABSI) definitie in kinderen met kanker. We observeerden in het lab dat taurolidine de tijd-tot-detectie van bloedkweken aanzienlijk kan

verlengen, wat grote klinische gevolgen kan hebben (i.e., behandel vertraging resulterend in ernstige sepsis) in de toekomst. Het effect van taurolidine in bloedkweken op de resultaten van onderzoek zal minimaal zijn, aangezien alle bloedkweek flesjes uiteindelijk wel positief werden. De CLABSI-definitie bleek toepasbaar te zijn in de kinderoncologische populatie, maar zou kunnen leiden tot een overschatting van het aantal bloedbaan infecties dat veroorzaak wordt door de centrale lijn. Beiden zijn belangrijke bevindingen voor de interpretatie van de CATERPILLAR-studie resultaten. De CATERPILLAR-studie was ontworpen en uitgevoerd om uit te zoeken of taurolidine locks effectief zijn in het voorkomen van CLABSIs in vergelijking met heparine locks in kinderen met kanker. Taurolidine locks bleken niet effectiever te zijn dan heparine locks in het voorkomen van CLABSIs en het gebruik van deze locks en de inzet van deze locks wordt momenteel dus niet geadviseerd voor kinderoncologie patiënten. In de toekomst zal verder onderzoek moeten laten blijken of het vaker toedienen van deze locks, het toedienen van deze locks aan hoog risicopatiënten, of het gebruik van deze locks in de behandeling van CLABSIs wel effectief is.

In het laatste gedeelte van de thesis hebben we ons gefocust op het optimaliseren van de behandeling van CLABSIs. Het doel was om het aantal CLABSI-gerelateerde events zoals lijn verwijdering, intensive care opnames en overlijden door ernstige sepsis te voorkomen. We hebben specifiek gekeken naar *Enterobacterales* CLABSIs aangezien ziekenhuis professionals vaak twijfelen of behandeling met enkel antibiotica wel gepoogd moet worden in deze situaties. Onze retrospectieve studie liet zien dat de incidentie van CLABSI-gerelateerde events erg hoog was na het behandelen van deze CLABSIs met enkel antibiotica, en dat directe lijn verwijdering in deze gevallen dus aangeraden wordt. De guidelines in ons ziekenhuis werden hierop aangepast.

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LIST OF PUBLICATIONS

Publications in this thesis

van den Bosch CH, Loeffen Y, van der Steeg AFW, van der Bruggen JT, Frakking FNJ, Fiocco M, van de Ven CP, Wijnen MHWA, van de Wetering MD. The CATERPILLAR-study: An assessor blinded randomized controlled trial comparing a taurolidine-citrate-heparin lock solution to a heparin-only lock solution for the prevention of central-line associated bloodstream infections in paediatric oncology patients. J Hosp Infect. 2024 Jul;S0195-6701(24)00228-7

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van den Bosch CH, Frakking FNJ, Loeffen YGT, van Tinteren H, van der Steeg AFW, Wijnen MHWA, van de Wetering MD, van der Bruggen JT. The applicability of the central line-associated bloodstream infection (CLABSI) criteria for the evaluation of bacteraemia episodes in paediatric oncology patients. Eur J Haematol. 2024 May;112(5):832-839.

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Jeremiasse B, Hulsker CCC, **van den Bosch CH**, Buser MAD, van de Ven CP, Bökkerink GMJ, Wijnen MHWA, van der Steeg AFW. Pulmonary Osteosarcoma Metastasectomy in Paediatric Patients using Near-infrared Fluorescence Imaging with Indocyanine Green. EJC Paediatric Oncology. 2023 Jun; 2:100019.

Jeremiasse B, **van den Bosch CH**, Wijnen MHWA, Terwisscha van Scheltinga CEJ, Fiocco MF, van der Steeg AFW. Systematic review and meta-analysis concerning the efficacy and safety of near-infrared imaging with indocyanine green (ICG) to identify the sentinel node in oncology patients. Eur J Surg Oncol. 2020 Nov;46(11):2011-2022.

CURRICULUM VITAE

Ceder Hildegard van den Bosch was born in Willemstad on October 11th 1994. She graduated from the Norbertuscollege, Roosendaal in 2012. Afterwards, she took a gap year during which she worked as a dental assistant, followed art history and clay sculpture courses, and made a kayak out of cedar-wood together with her father.

She moved to Utrecht in 2013 to study Medicine at Utrecht University. During this period she developed an interest for research during her first research internship in 2016 at the surgical oncology group of Prof. Dr. Wijnen at the Princess Maxima Centre for paediatric oncology. Afterwards, she started working in the Wijnen group as a student researcher, where she wrote the grant application for the CATERPILLAR-study and started with building a central venous access associated infection surveillance system for the Princess Maxima Centre for paediatric oncology. The grant was honoured by the Dutch Cancer Society (project 12617) a few months before she graduated from medical school in 2020. Thereby her PhD track could directly start after her graduation. Her PhD focused on improving the quality of life of children with cancer by optimising the central venous access care with a specific focus on the prevention of central venous access associated infections. Thanks to the results of her research multiple clinical protocol changes were implemented. She was supervised by Prof. Dr. Wijnen, Dr. van de Wetering, Dr. van der Steeg and Prof. Dr. Fiocco.

Thanks to her years at the Princess Maxima Centre, her interest in research has grown further and a specific interest in global/public health research developed. To pursue this calling, she started with a Master of International Health at the Royal Tropical Institute in Amsterdam in 2023 and applied for a residency in family medicine in 2024. In the future, her aim is to combine her research skills together with a clinical job. Her ultimate goal is to identify root causes of health inequities and to target them on a research and clinical level.

PHD PORTFOLIO

PhD period: October 2020 – January 2024
Promotors: Prof. Dr. MHWA Wijnen and Prof. Dr. MF Fiocco
Copromotors: Dr. MD van de Wetering and Dr. AFW van der Steeg
Independent supervisor: Prof. Dr. Merks
Graduate school: Graduate School of Life Sciences (GSLS), Utrecht, the Netherlands
PhD program: Clincial and Translational Oncology (CTO)

Table 1 Overview of ECTS credits gained

Clinical and Translation Oncology (CTO) courses	**Year**	**ECTS**
Introduction Course	2021	1.5
Clinical Trial Development Course	2022	1.5
Peer-to-Peer sessions	2022	0.3
CTO PhD retreat	2022/23	0.5
Graduate School of Life Sciences (GSLS) generic courses		
Introductory Biostatistics for Researchers	2021	4.5
Responsible Conduct of Research	2021/22/23	0.45
Adobe Illustrator	2022	1.0
Other courses		
BROK® - Dutch Federation of University Medical Centres (NFU)	2018	1.5
Microbiology Lab Training – University Medical Centre Utrecht (UMCU)	2021	1.0
Informed Consent Training - Princess Máxima Centre	2021	0.1
Survival analysis - Princess Máxima Centre	2023	0.1
Course on Global Health and Tropical Medicine – Royal Tropical Institute (KIT)	2023	20.0
Symposia and Conferences		
49th Congress of SIOP - Washington, USA	2017	2.0*
50th Congress of SIOP - Kyoto, Japan	2018	
Research Day NVKC – Utrecht, the Netherlands	2020	
6th World Congress of Vascular Access Congress - Virtual	2021	
54th Congress of SIOP - Barcelona, Spain	2022	
55th Congress of SIOP - Ottawa, Canada	2023	
Scientific Symposium Princess Maxima Centre - Utrecht, the Netherlands	2018/23	
PhD retreat Princess Maxima Centre - Utrecht, the Netherlands	2017/21/22	
Meetings		
Biweekly research meetings of paediatric surgery research group	2020-2023	1.0*
Honoured Grants and Nominations		
Dutch Cancer Society - Project number: 12617 “the CATERPILLAR-study”	2019	
Nominated for Best Paediatric Surgery Publication - NVKC	2020	
Best Poster Award – International Society of Paediatric Surgical Oncology	2023	

Oral presentations

Research Day NVKC – Utrecht, the Netherlands	2020
6th World Congress of Vascular Access Congress - Virtual	2021
55th Congress of SIOP - Ottawa, Canada	2023
Research Meeting Princess Maxima Centre – Utrecht, the Netherlands	2023

Poster presentations

54th Congress of SIOP - Barcelona, Spain	2022
55th Congress of SIOP - Ottawa, Canada	2023
55th Congress of SIOP - Ottawa, Canada	2023
56th Congress of SIOP – Honolulu, Hawaii	2024

Supervision of students

Kyra Prinsze - Baseline measurement of the effect of the current pain relief policy on Port-A-Cath (PAC) implantations in paediatric oncology patients	2020
Aranka Kops - Central venous catheter-related bloodstream infections caused by Enterobacterales in paediatric oncology patients; catheter salvage or removal	2022
Lieke van Walstijn – Early removal of Peripherally Inserted Central Catheters (PICC) due to complications in paediatric oncology patients	2022
Valentino van der Vlugt - Central venous catheter-related bloodstream infections caused by Enterobacterales in paediatric oncology patients; catheter salvage or removal	2021

ECTS; European Credit Transfer and Accumulation System, n.a.; not applicable, SIOP; Congress of the International Society of Paediatric Oncology, NVKC; Nederlandse Vereniging voor Kinderchirurgie.
*Following the guidelines of the Clinical and Translational Oncology (CTO) PhD program: International oncology symposia 0.3 ECTS/day with a maximum of 2.0 ECTS, for research meetings a maximum of 1.0 ECTS.

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Drs. C.E.J. Terwisscha van Schelting, **Drs. C.C.C. Hulsker**, **Drs. G.M.J. Bökkerink**, lieve Sheila, Caroline, en Guus. Wat een toffe groep hebben jullie zo samen, ik heb veel met jullie gelachen en veel van jullie geleerd waarvoor heel veel dank. Door jullie zou ik bijna chirurg zijn geworden.

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