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VENOUS THROMBOSIS IN CHILDREN; THE ROLES OF VASCULAR ACCESS AND CRITICAL ILLNESS

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Venous thrombosis in children; the roles of vascular access and critical illness

THESIS FOR DOCTORAL DEGREE (PH.D.)

By: Åsa Östlund

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To all children in need of medical care and venous access.

Popular science summary of the thesis

The focus of this thesis was venous thrombosis (VT) in children. VT can lead to occlusion of the vein. Moreover, thrombi can migrate and cause severe morbidity. In pediatric health care, the need for secure access to the vein is often imperative. Children's veins are small which means that intravenous access is more difficult. Compared to adults children are less prone to let you hurt them by puncturing the skin repeatedly when the peripheral intravenous catheters (PIVC) stop working. One way to solve the problem is to place a catheter in one of the bigger veins, a central venous catheter (CVC). A CVC can be used for several weeks if properly maintained. In contrast to the PIVC, CVCs can also be used for cytostatics and intravenous nutrition. So why not always place a CVC?

The major risk factor for venous thrombosis in children is the presence of a CVC. Previous studies have shown that many CVC-related venous thromboses are asymptomatic. Symptoms of thrombosis include swelling of the extremity, discoloration, and pain for example.

In paper I we investigated the rate of and risk factors for VT related to pediatric CVCs. We found CVC-related venous thrombosis in 30% of pediatric CVCs. Some thrombi were very small, while some totally occluded the vein. The risk for venous thrombosis was increased if the CVC was placed in the internal jugular vein, for double-lumen CVCs, and if the patient was male. However, when considering only symptomatic and occlusive thrombosis the risk factors were young age, PICU admission, CVC located in the femoral vein, and a ratio between catheter and vein diameter >0.33.

Continuous renal replacement therapy (CRRT) is used in the pediatric intensive care unit (PICU) to treat severely ill children with renal failure. CRRT requires a large-bore central venous catheter. There were no pediatric data on the risk for venous thrombosis related to vascular catheters used for CRRT. In paper II, we found that six out of 105 vascular catheters used for CRRT in the PICU were complicated by venous thrombosis.

Critically ill children in the PICU are considered to be at increased risk of VT. Most pediatric VTs are related to CVCs, and in PICU patients there are very limited data describing the risk of VTs that are not related to a CVC.

In study III, the incidence of VTs not related to a vascular catheter was investigated in 70 PICU patients considered to be at high risk of VT. Patients admitted to the PICU for ≥72 hours and with at least two risk factors for VT could be included in the study. We did not find any VT not related to the presence of a CVC.

One way to decrease the risk of CVC-related VT is to avoid inserting a CVC. Another option for venous access is a midline catheter which is longer and usually inserted in deeper veins in comparison to a PIVC. However, the safety and durability of midline catheters are not well documented in children. In paper IV we investigated the rate of VT related to pediatric midline catheters. We found that 30% of the midlines were complicated by thrombosis. This incidence is similar to the incidence of CVC-related venous thrombosis found in paper I, but all VTs found in paper IV occurred in peripheral veins. Few patients needed therapy for their midline-related VT. 78% of patients could complete short-term iv therapy with the midline catheter, without the need for additional venous access.

The conclusions of this thesis are:

- VT is a common complication of pediatric CVCs.
- VT is a clinically relevant complication of pediatric CRRT.
- VT that is not related to CVCs is uncommon in PICU patients.
- Midline catheters could be an alternative to a CVC in selected patients.

Abstract

Venous thromboembolism (VT) is a rare event in the general pediatric population. However, the incidence in hospitalized children is higher and has increased dramatically reaching 58 per 10 000 children. The single most important risk factor for pediatric VT is the presence of a central venous catheter. The overall aim of this thesis was to achieve a better knowledge and understanding of risk factors for VT in children, specifically related to the use of vascular catheters and to critical illness

The studies in this thesis were performed at the department of Pediatric Perioperative Medicine and Intensive care at Karolinska University Hospital, Stockholm. All patients studied were under 18 years of age.

In study I the incidence of CVC-related VT was prospectively investigated in 211 non-tunneled pediatric CVCs using doppler ultrasonography. CVC-related VT occurred in 30% of cases. Risk factors for any CVC-related VT were internal jugular vein insertion, multiple lumen CVCs and male sex. However, risk factors for small asymptomatic VTs differed from risk factors for VTs with larger thrombotic mass that were symptomatic and/or occluded vein blood flow. Symptomatic and/or occlusive VT was more likely to occur with femoral vein insertion, a catheter/vein diameter ratio >0.33, PICU admission, and young age.

In study II, the risk for VT related to vascular access catheters used for pediatric CRRT was retrospectively evaluated. Patients with vascular access used for CRRT for at least 48 hours were included. In this study, 5.7% (95% CI: 2-12%) of vascular catheters used for CRRT were complicated by a VT event. Five out of six patients with thromboembolic complications were neonates.

In study III, the incidence of VTs not related to a vascular catheter was prospectively investigated in 70 PICU patients considered to be at high risk of VT. Patients admitted to PICU for ≥72 hours and with at least two risk factors for VT were eligible for inclusion. The incidence of symptomatic VT or asymptomatic not related to a vascular catheter was 0% (95% CI: 0-5.1%). This corresponds to a VT incidence of 0% (95% CI: 0–5.1%).

In study IV the frequency of catheter-related VT and other complications related to the use of pediatric midline catheters was prospectively evaluated. One hundred patients who received a midline catheter at Astrid Lindgren Children´s Hospital were included. Midline catheter-related VT was found in 30% (95% CI 21-40%) of catheters. Mechanical complications occurred in 33 (33%, 95% CI 24-43%) midline catheters but no midline-related bloodstream infection was found. 78% of patients completed iv therapy without the need for additional iv access.

The main conclusions of this thesis are:

- VT is a common complication of pediatric CVCs. Risk factors for smaller, asymptomatic VTs are different from risk factors for VTs with larger thrombotic mass
- VT is a clinically relevant complication of pediatric CRRT. Neonates seem to be at the highest risk for this complication.
- The risk for VT not related to a venous catheter is low in PICU patients.
- Based on the incidences of clinical complications and the observed dwell-time, midline catheters could be alternative to CVCs for short-term iv therapy inselected patients.

Keywords: *central venous catheters, complications, continuous renal replacement therapy, midline catheter, pediatric, risk factors, PICU, venous thromboembolism.*

List of scientific papers

I. *Incidence of and risk factors for venous thrombosis in children with percutaneous non-tunnelled central venous catheters*
Åsa Östlund, Urban Fläring, Åke Norberg, Ann Dahlberg, Jonas Berner, Sylvie Kaiser, Lena Vermin, Anna Svenningsson, Tony Frisk, Peter Larsson, Andreas Andersson
British Journal of Anaesthesia, 123(3):316-324(2019)

II. *Thromboembolic complications of vascular catheters used for pediatric continuous renal replacement therapy; prevalence in a single-center, retrospective cohort*
Isabelle Szeps, **Åsa Östlund**, Åke Norberg, Urban Fläring, Andreas Andersson
Pediatric Critical Care Medicine, 8(22):743-752(2021)

III. *Incidence of thromboembolic events not related to vascular catheters in a prospective cohort of critically ill children*
Åsa Östlund, Urban Fläring, Peter Larsson, Sylvie Kaiser, Lena Vermin, Tony Frisk, Ann Dahlberg, Jonas Berner, Åke Norberg, Andreas Andersson
European Journal of Pediatrics, 181(8):3031-3038(2022)

IV. *A prospective study on complications of pediatric midline catheters*
Åsa Östlund, Urban Fläring, Åke Norberg, Sylvie Kaiser, Tony Frisk, Peter, Larsson, Andreas Andersson
A revised version of this manuscript has been accepted for publication in Anesthesia & Analgesia.

Contents

List of abbreviations

AKI	Acute kidney injury
ANZCRT	Australian New Zealand Clinical Trial Registry
ANO	asymptomatic non-occlusive
aPTT	activated partial thromboplastin time
ATIII	Antithrombin III
CRRT	Continuous Renal Replacement Therapy
CVC	Central Venous Catheter
DOAC	direct oral anticoagulants
ECMO	Extracorporeal Membrane Oxygenation
INR	International Normalized Ratio
Iv	intravenous
IQR	Interquartile Range
MC	Midline Catheter
MRI	Magnetic resonance imaging
MV	Mechanical Ventilation
PDR	Predicted Death Rate
PICU	Pediatric Intensive Care Unit
PIM	Pediatric Index of Mortality
PIVC	Peripheral intravenous catheter
pTP	pharmacologic thromboprophylaxis
SO	symptomatic and/or occlusive
US	Ultrasonography
VT	Venous thromboembolism
WMA	World Medical Association

1. Introduction

In recent years, there has been a substantial increase in the diagnosis of venous thrombosis (VT) in children[1]. The strongest risk factor for the development of VT in children is the presence of a central venous catheter (CVC). CVC-related VT is often asymptomatic in children[2], and requires diagnostic screening to be found. No evidence-based guidelines currently exist on how to prevent the development of CVC-related VT in children. Also, the existing data regarding risk factors for pediatric CVC-related VT are incomplete.

In adults, midline catheters can be used as an alternative to a CVC in suitable patients. Possibly, the use of midline catheters in children could be an approach to reduce the numbers of CVC-related VTs. However, there is only very limited data on the use of midline catheters in children, and more knowledge is needed both regarding the clinical effectiveness and potential complications.

Venous thrombosis in relation to vascular catheters used for CRRT has not been studied in the pediatric population. Catheters used for CRRT need to be large-bore, hence occluding the vessel to a high degree and thereby potentially increasing the risk of venous thromboembolism. But the frequency of these events needs to be clarified.

In adults, critical illness is a risk factor for venous thrombosis, and adult intensive care unit patients normally receive pharmacological thromboprophylaxis. Admission to the pediatric intensive care unit (PICU) is a significant risk factor for VT in children[3], but pharmacological thromboprophylaxis is not routinely used in PICU patients. However, so far there are no prospective studies investigating the incidence of and risk factors for PICU-related VT. More data is needed to evaluate current guidelines and practices regarding thromboprophylaxis in the PICU.

2. Literature review

2.1 CENTRAL VENOUS CATHETERS

A CVC is a vascular catheter with the tip positioned in a large central vein. The main indications for the insertion of a CVC are irritant drugs that require central vein delivery, hemodynamic monitoring, the need for repeated blood sampling, and difficulties with peripheral venous access[4]. Examples of drugs that require central vein delivery include parenteral nutrition, vasoactive drugs, and chemotherapy. For CRRT a central catheter is needed for both in- and outflow. In children, non-tunneled CVCs are often used to avoid repeated puncture of veins.

There are several different types of CVC, with somewhat different characteristics:

- Non-tunneled CVCs: Percutaneously inserted catheters. Shorter intended use, normally not more than three weeks.
- Tunneled CVCs: The catheter is tunneled under the skin from the insertion site to a separate exit site. A tunneled catheter can be used for several months.
- Implantable ports: The catheter is tunneled, and the entire line and port lie subcutaneously. An implanted port can be used for years, and patient comfort is good.
- Peripherally inserted central catheter (PICC): PICCs are inserted percutaneously through a peripheral vein and the catheter tip is then advanced to a central position. Common veins used are the basilic, brachial, or saphenous veins. PICCs are used for short to intermediate (several months) duration.

Sites most often used for non-tunneled CVCs in children are the internal jugular, the subclavian, and the femoral vein. Tunneled CVCs and implantable ports are commonly placed in the internal jugular or subclavian veins.

There are several complications associated with the use of CVCs. Immediate complications to insertion include bleeding, hematoma, arterial puncture, pneumothorax, and arrhythmia. Among the delayed catheter-related complications are infection, VT and post-thrombotic syndrome.

2.2 VENOUS THROMBOSIS

2.2.1 Venous thrombosis - pathophysiology

Thrombosis is the homeostatic mechanism whereby blood clots, a physiological process central to the process of hemostasis. However, VT is also a pathological process where blood clots form in the deep veins of the body. The three main factors that are central to the development of VT are venous stasis, hypercoagulability, and vein injury with endothelial activation. These factors were described by Rudolf Virchow in 1856, and are known as Virchow's triad. The insertion of a CVC increases the risk of VT in all three factors. The process involves endothelial disruption and damage, the catheter itself disturbs venous flow causing venous stasis, the foreign material in the catheter activates the coagulation system and additionally infused substances can cause further vascular irritation.

2.2.2 Venous thrombosis in children

The overall incidence of VT in children is low, reported being 0.07 to 0.14 in 10 000 children annually[5] , compared to 10 in 10 000 adults[6]. However, in hospitalized children, the incidence is higher. From 2001-2007 the rate of VT in hospitalized children increased dramatically by 70 %, reaching 58 per 10 000 children in the USA[1]. The incidence rates vary in different reports, due to different study designs and inclusion criteria, but the increase in the rate of pediatric VT is consistent[7]. This increase is likely due to the increased availability of supportive care and treatment for children with complex medical conditions and improved clinical outcomes in previously fatal conditions. Increased awareness of the problem and improved diagnostics could also contribute to the described increase in the incidence of pediatric VT.

2.2.3 Risk factors for VT in children

The presence of a central venous catheter is the single most important risk factor for venous thromboembolism in children[8,9]. In neonates, 90% of VT is CVC-related, and in older children > 60% of VT are CVC-related. The incidence of VT in children seems to have a bimodal association with age, with an increased risk of VT for children <1 year and >13 years[8]. The increased risk of VT seen in adolescents could be related to physiologic changes in the coagulation system as well as the use of oral contraceptives in females. Moreover, comorbidities associated with VT (trauma, smoking, malignancies, renal disease) are more frequently seen in older children.

Several other risk factors for pediatric VT have been described in the literature. In 2015, a meta-analysis of published studies on risk factors for VT in hospitalized pediatric patients found that increased length of stay, intubation, and ICU admissions were associated with an increased risk of hospital-associated VT[3]. Medical conditions that have been associated with pediatric VT include active malignancy, systemic infection, congenital cardiac disease, renal disease, and rheumatologic disorders. Surgical procedures and certain drugs, such as asparaginase treatment for cancer and oral contraceptives, are other acquired risk factors for VT in children[10-12].

Endogenous prothrombotic conditions have been associated with an increased risk of VT in both children and adults. However, the KIDCAT study demonstrated that the impact of prothrombotic conditions on the risk of VT was limited for pediatric short-term CVCs, and that screening for prothrombotic conditions was not justified for short-term CVCs[13].

2.2.4 Pediatric CVC-related VT

Although the use of CVCs is necessary, the presence of a CVC is also the strongest risk factor for VT in children[3,14], and CVC-related VT has been increasingly recognized as a clinical problem.

The reported incidence of pediatric CVC-related VT varies considerably, between 2-81% in different studies[15], in a more recent review 4-50% in different studies[16]. This variation is related to differences in study design, CVC indication and types, study population, and most importantly mode of diagnosis and whether diagnostic screening for asymptomatic VT was used. The suggested risk factors for CVC-related VT can be divided into intrinsic

factors related to the CVC, and factors related to the patient's characteristics. However, risk factors are incompletely understood, and there are no evidence-based guidelines on which insertion site or central venous catheter size and type should be used to avoid CVC-related VT. Many previous studies have limitations, including small sample sizes, retrospective design, and differences in definitions and procedures. Moreover, no evidence-based pharmacological strategies for the prevention of CVC-related VT in children currently exist[2,17].

2.2.5 Asymptomatic and symptomatic VT

Since the majority of CVC-related VT are asymptomatic[2], a main factor explaining the varying rates of VT is whether the incidence of CVC-related VT was determined using prospective screening or extracted from retrospective data on symptomatic VT. The rates of CVC-related VT in children identified through clinical diagnosis were 4–13%[18-20], and for ultrasonographic and venography screening 1-44% [20] and 13–50%[18,19,21], respectively.

Guidelines state that both symptomatic and asymptomatic VT should be included in the primary outcome of studies on pediatric VT[22], but the clinical significance of asymptomatic CVC-related VT is controversial[23]. Asymptomatic CVC-related VT seems to be more common in children compared to adults. Symptoms can be transient and easily overlooked, and small children may not be able to communicate symptoms.

2.2.6 VT and the type of central venous catheter

Among factors potentially affecting the incidence of CVC-related VT is the type of CVC used. Besides short-term non-tunneled percutaneous CVCs, other types of CVCs include tunneled CVCs, peripherally inserted central catheter (PICC) lines, umbilical vein CVCs, and implanted ports. Different types of CVCs have distinct features and indications, possibly affecting the risk of CVC-related VT.

In a meta-analysis by Vidal et al, tunneled CVCs had a higher frequency of CVC-related VT compared to non-tunneled CVCs, PICC lines, and umbilical catheters. However, in a systematic review from 2015, tunneled CVCs had the lowest incidence rate of thrombotic complications[24]. In conclusion, the risk of CVC-related VT could be affected by the type of CVC used, but data are limited and somewhat conflicting[25].

2.2.7 VT and CVC insertion site

The choice of insertion site for the CVC could potentially influence the rate of CVC-related VT. Some previous studies have indicated that a majority of symptomatic CVC-related VTs occur in the femoral vein[26-28]. However, it is not clear whether femoral vein placement reflects a true increase in the risk for VT, or whether this merely reflects that femoral vein VTs are more likely to cause recognizable symptoms compared to VTs in the internal jugular vein or subclavian vein.

Male et al found an increased risk of VT with placement in the femoral or subclavian vein compared to the internal jugular vein using venography screening[29] but since venography is insensitive for internal jugular vein thrombosis[30] the incidence is likely underestimated using this method. In a study on PICU patients, asymptomatic CVC-related VT was found to be more frequent with catheter placement in the internal jugular vein[27]. A meta-analysis including 32 studies did not find any significant difference in the incidence of CVC-related VT between the upper and lower body half. The impact of the choice of insertion site on the risk for CVC-related VT remains unclear[2].

2.2.8 Other risk factors for CVC-related VT in children

The use of multi-lumen catheters has been identified as a risk factor for CVC-related VT in previous studies[26,31]. A possible explanation for this finding is the increase in catheter size seen with multi-lumen catheters. Since obstruction of venous blood flow from the CVC is considered to be an important pathogenic mechanism for the development of VT[32], a high ratio between catheter size and vein diameter could be a risk factor for CVC-related VT. International recommendations from 2012 regarding pediatric CVC insertion suggest that the ratio between the external diameter of the catheter and the diameter of the cannulated vein should not exceed 0.33[33]. This suggestion was based on the expert's opinion and, to our knowledge, no previous clinical data exist to support this recommendation. In an adult study on PICC lines a cut-off of 0.45 found higher rates of VT in patients with malignancy[34,35].

Among patient-related risk factors for CVC-related VT in children described in the literature are malignancy, young age, adolescence, and thrombophilia[36, 37, 27, 38].

2.3 PHARMACOLOGIC THROMBOPROPHYLAXIS FOR PEDIATRIC CVC-RELATED VT

Several randomized controlled trials evaluating pharmacological interventions to prevent CVC-related VT have been performed in children. However, no intervention has so far been proven to be effective in preventing pediatric CVC-related VT. Among interventions evaluated are unfractioned heparin[39], heparin-bonded CVCs[40-42], low molecular weight heparin[43,44], antithrombin III concentrate [45], and warfarin[46]. There are ongoing trails with rivoxaban and dabigatran to elucidate if thromboprophylaxis is effective in the pediatric population[47].

2.4 COMPLICATIONS TO VENOUS THROMBOSIS

VT can lead to several severe complications. Pulmonary embolism (PE) can be life-threatening. PE is believed to be a rare event in children, but since the incidence of VT is increasing the incidence of PE is also expected to increase. The incidence of PE among hospitalized children has been found to be of 8.6 to 57 per 100 000. Overall mortality of PE is 10%[48]. In children with intracardial shunts there is also a risk of paradoxical cerebral embolism. In PICU-patients, symptomatic VT has been associated with longer PICU length-of-stay and fewer ventilator-free days[18]. Loss of venous access can also be a severe complication both short and long term.

Post-thrombotic syndrome (PTS) is a long-term complication with an incidence of between 3-70% in children with VT[49]. CVC-related VT, complete occlusion of the vein and incomplete VT resolution were found to be prognostic factors for PTS in a recent meta-analysis[50]. Clinical symptoms of PTS include swelling of the affected limb, pain, discoloration, and decreased tolerance of exercise. PTS has been shown to affect quality of life and to increase the health economic burden on society[51]. The assessment tools for children with PTS is based on adult tools. The Manco-Johnson is both modified and validated whereas the Villalta tool is only modified for pediatric use[49]. Both tools are good in detecting PTS[52], however, there is a significant inconsistency between the two tools regarding moderate to severe PTS.

2.5 DIAGNOSIS OF VT IN CHILDREN

2.5.1 Clinical signs

Clinical suspicion of VT is based on the presence of swelling, tenderness, erythema, skin discoloration, pain, presence of collateral veins, and/or loss of CVC function. These symptoms are insensitive, non-specific, and could very well be transient enough to go unrecognized. Collaterals seem to develop rapidly in children, and especially small children are not capable of communicating symptoms. Moreover, VTs in the central venous system do not always lead to classic symptoms such as swelling and erythema. The majority of pediatric VTs are asymptomatic[2], and in these cases diagnostic imaging is required.

2.5.2 Ultrasonography

Ultrasonography (US) has been proven to be a highly sensitive and specific modality for diagnosing deep vein thrombosis without the need for radiation or contrast media exposure. Two distinct protocols have been developed for the sonographic evaluation; limited / simplified compression US and duplex sonography. The latter involves B-mode or gray-scale imaging with transducer compression maneuvers as well as color-flow Doppler imaging and spectral Doppler waveform analysis. The diagnosis of venous thrombosis is made on the basis of direct and indirect signs[17]. The diagnostic criteria are listed in methods Table 4.2.

Ultrasonography has very good sensitivity for the diagnosis of VT in the internal jugular vein and lower extremities. The main drawback is the low sensitivity in detecting VT in central veins, where compressibility cannot be assessed. The PAARKA study found an overall sensitivity of ultrasound for VT in the upper venous system of only 37%, reflecting the problems with detecting intrathoracic VT with ultrasonography[22]. Other limitations include disturbances from the bowels when examining iliac veins, and the fact that dressings and casts can impede ultrasound access.

2.5.3 Venography and CT venography

Venography has traditionally been seen as the gold standard for VT diagnosis. However, venography has several disadvantages including the invasive nature, radiation exposure, the use of contrast media, and significant

consumption of resources. Moreover, venography has a very low sensitivity for VT in the internal jugular vein[53]. This has been explained by insufficient retrograde filling of jugular veins with contrast agent injected into the arms and washout from the jugular veins. Due to these disadvantages venography is not commonly used today. In addition there is an inadequate or inconclusive rate of 10-20% and interobserver disagreement of 12-16%[30].

Spiral-CT venography has similar drawbacks as conventional venography, but higher sensitivity for VT in the internal jugular vein. CT venography is often used for the diagnosis of VT when ultrasonography results are unclear or when venous thrombosis in the central veins is suspected.

2.5.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) can also be used for the diagnosis of VT, with a high specificity and sensitivity[54]. However, MRI is costly, the availability is generally low and children often need sedation or anesthesia to remain immobile during the procedure.

2.6 MIDLINE CATHETERS

Midline catheters are inserted percutaneously through a peripheral vein. The midline catheter is longer than the routinely used peripheral venous catheter, but the catheter tip does not reach the central veins. There is no need for radiographic confirmation of tip position. In adults, midlines are often inserted in a vein in the antecubital fossa or upper arm, with the tip located at or below the axillary vein. In the adult population, midlines are used when there is a need for the infusion of non–peripherally compatible infusions for 2-4 weeks. Advantages of midlines compared to CVCs include low cost, less radiation exposure, no risk of bleeding or pneumothorax, and improved patient comfort. The risk of catheter-related infection is also considered to be lower with midlines compared to CVCs[55,56]. In a recent retrospective study, midlines were found to be a safer option compared to CVCs using a composite endpoint of mortality, catheter-related infection, mechanical issues, thrombosis, and readmission because of a line-related complication[55].

Children generally need anesthesia or sedation for the insertion of CVCs, but midline catheters can often be inserted in the awake child[57]. Compared to traditional peripheral venous catheters, midlines have a longer dwell time[58].

One drawback of midlines compared to CVCs is a higher risk for mechanical complications such as leakage, dislodging, infiltration and occlusion[55,59].

Most of the current data on the use of midline catheters come from the adult population, and data on pediatric use is very scarce. A recent small study including 18 patients found that midlines could be a valid option for medium-term intravenous access in children undergoing surgery[60]. In a retrospective study from 2016 the median dwell-time for pediatric midline catheters was found to be 8 days[59]. Midline catheters could be an attractive alternative to a CVC or repeated peripheral cannulations in suitable children. However, there is a need of further data on the frequency of complications when using midline catheters in children. Also, to find suitable indications for pediatric midline catheters, the expected dwell-time needs to be clarified.

2.7 VENOUS THROMBOSIS IN THE PICU

Critically ill children in the PICU are considered to be at higher risk of VT than other hospitalized children[61]. Often these children have multiple risk factors for the development of VT, including CVCs, surgery, malignancy, immobilization, and systemic inflammation.

In adult ICU patients, pharmacologic thromboprophylaxis is considered the standard of care, but in critically ill children pharmacologic thromboprophylaxis is infrequently used. In a recent multi-national study investigating the use of thromboprophylaxis in PICUs 12,4% of patients received some sort of pharmacologic thromboprophylaxis[62]. This study also highlighted a high variability in thromboprophylaxis routines between different PICUs.

Data regarding the incidence of PICU-related VT mostly come from retrospective studies on subgroups of patients or from studies on CVC-related VT in the PICU. Prospective data from general pediatric populations are scarce. A prospective observational multi-center study from the US found

an incidence rate for VT of 0.74% with a point prevalence of 0.93%[14]. However, this study included only symptomatic cases and did not prospectively screen for VTs, and possibly the true incidence of VTs in PICU patients was underestimated. The rate of diagnosis of VT was higher in infants younger than 1 year, and patients with a CVC had a nine-fold increased risk of developing VT.

In recent years, the awareness of CVC-related VT in children has increased. Many of these VTs are asymptomatic and require diagnostic screening to be found. Currently, there are no prospective studies screening for VT in PICU-patients. Prospective screening is necessary to diagnose asymptomatic VT, and it is unclear to what extent PICU-patients develop asymptomatic VT.

There is a lack of pediatric specific guidelines regarding pharmacologic thromboprophylaxis in the PICU. More data on the risk of PICU-related VT are necessary to adequately assess the relationship between risk and benefit when using pharmacologic thromboprophylaxis in PICU patients. To obtain data on the true incidence of PICU-related VT prospective studies using screening for VT are necessary.

2.8 PEDIATRIC CRRT

Acute kidney injury (61%), fluid overload (29%) and inborn error of metabolism (4%) are the three most important indications for continuous renal replacement therapy in the pediatric setting[63,64]. Cardiopulmonary bypass, sepsis and heart failure are some of the most common causes of AKI in the industrialized world[65].

Vascular access

A functional vascular catheter allowing adequate blood flow is a cornerstone of pediatric CRRT. To accomplish a high blood flow rate the vascular access needs to be wide and short. The use of larger sized catheters has been correlated to an increased circuit survival[66]. Even in neonates and small children, 6 or 7 French double lumen catheters are commonly used. The use of two smaller single lumen catheters inserted in different vein has been described[67 63], but the success of this method as compared to larger double lumen catheters is unclear. Circuit survival is also associated to the insertion

site for the vascular access. Using the right internal jugular vein for vascular access has been associated with an increased circuit lifespan[66]. The risk for VT related to vascular access used for CRRT in children is not known.

Anticoagulation

Effective circuit anticoagulation is another key aspect in order to prevent filter clotting and improve circuit lifespan. Systemic anticoagulation with unfractionated heparin or regional anticoagulation with sodium citrate are most frequently used. Anticoagulation using prostacyclin infusion has also been described in children[68]. Recent data indicate that regional citrate anticoagulation could be more effective in prolonging circuit lifespan as compared to heparin[69,70]. Potential adverse effects of citrate include citrate overload as well as electrolyte disturbances and acid-base derangements. The risk of bleeding complications is higher with heparin, and there is also a risk of heparin induced thrombocytopenia[71]. Both heparin and citrate anticoagulation needs close monitoring to maintain patient safety.

3 Research aims

The overall aim of this thesis was to achieve a better knowledge and understanding of risk factors for venous thromboembolism in children, specifically related to the use of vascular catheters and to critical illness.

The specific aims were:

- To determine the frequency of and risk factors for CVC-related venous thrombosis in children.
- To descibe the risk of venous thromboembolic events related to vascular catheters used for CRRT in children.
- To determine the frequency of PICU-related venous thrombosis in a PICU population considered to be at high risk of venous thromboembolic complications.
- To describe the frequency of venous thrombosis and other complications related to the use of pediatric midline catheters.
- To investigate the success rate when using midline catheters for short-term peripheral iv therapy in children.

4 Materials and methods

4.1 ETHICAL CONSIDERATIONS

All four studies were approved by the Regional Ethics Review Board in Stockholm.

Research involving children are ethically more complex than in adults. Ethical Principles for Medical Research Involving Human Subjects, Helsinki Declaration 1964 by World Medical Association (WMA) states that a key factor in all research is informed consent. This is naturally problematic with children and infants, and in many cases impossible. Even older children have a limited ability to comprehend risks and foresee consequences. It is not until 15 years of age that children, if able, are allowed to consent to research on their own. The Helsinki Declaration widened the concept of the Nuremberg Code[72], making it possible for guardians to give permission to conduct research on their child. During our research we followed the Helsinki Declaration[73].

The legal guardians for all children who met the inclusion criteria in study I, III and IV were asked for consent to participate. If the child was considered mature enough and able to understand the benefits and risks of the study, informed consent was also obtained from the child. No child, regardless of age, was subject to examination if unwilling to. Guardians and children were informed that consent could be withdrawn at any time, without any explanation and that it would not affect the care or treatment delivered. Patients where death was deemed imminent were not included in the study. Also, children were not included if we due to language barriers, could not be sure that guardians and/or children fully comprehended all aspects of the study.

The intervention we exposed the children for in study I, III and IV was ultrasonography, an investigation that is not painful but sometimes time consuming. In study III the ultrasonography protocol was comprehensive, lasting about 20 minutes. In a few cases this led to some distress for patients, mainly infants. If there was only slight distress the investigation proceeded as planned, but the investigation was cancelled if the child displayed obvious discomfort. In these cases, the distress for the individual child needs to be weighed against the opportunity to gain knowledge that will benefit fu-

ture patients. During the course of the study, we improved our information regarding the time aspect of the ultrasound investigation, so that guardians could prepare and support their child better.

As stated earlier, research on children requires consent from guardians, but how do we know that guardians make ethically correct decision for their child? Decisions made by guardians are affected by his/her own altruistic motives, or just the desire to do good. There is also an imbalance in power between guardians, children and health care workers that needs to be taken in to account.

When a catheter-related VT was diagnosed, management strategy and the follow-up plan were decided after consultation with the pediatric coagulation unit. In a few cases patients with asymptomatic VT, which would not have been found without the study protocol, were considered to need treatment. The treatment of choice was often low molecular weight heparin administered subcutaneously. Adverse effects of the treatment include discomfort and pain due to subcutaneous drug administration and the risk of bleeding. If they would not have been included in the study, the individual child would not have been exposed to the treatment. Since there is little data supporting treatment strategies for asymptomatic VTs, each case was disscused with the pediatric coagulation unit. More data regarding outcome and treatment after CVC-related VT are needed, and further research in this area is vital.

A constant ethical reflection is needed, and it becomes apparent that the regulations that we as researcher need to consider is necessary and helpful in reminding us of respect, benefit and justice for all our patients. Even future ones.

4.2 STUDY DESIGN

Table 4.1 Schematic of study design included in the studies.

	Study I	**Study II**	**Study III**	**Study IV**
Design	Prospective observational study	Retrospective cohort study	Prospective observational study	Prospective observational study
Study period	April 2015-June 2016	January 2009-December 2016	April 2015-November 2016	May 2019-June 2021
Number of study objects	211 pediatric non-tunneled CVCs	105 vascular catheters used for pediatric CRRT	70 PICU patients	100 pediatric midline catheters
Intervention	Ultrasonography of the cannulated vein	None	Ultrasonography of the great veins	Ultrasonography of the cannulated vein
Primary outcome	CVC-related VT	VT related to the vascular catheter	VT not related to a vascular catheter	MC-related VT
Analyses	Mann-Whitney U test, Fisher's exact test, logistic regression	Mann-Whitney U test, Fisher's exact test	Wilcoxon signed-rank test	Mann-Whitney U test, Fisher's exact test

Quantitative methods were used during all four studies. Study I, III, and IV were registered in Australian New Zealand Clinical Trail Registry (ANZCTR). To be included in study I, III and IV, written consent had to be given from legal guardians and, when possible, from the child. Informed consent was waived for study II in accordance with the Regional Ethics committee.

4.3 PARTICIPANTS

Patients included in these studies were children (<18 years). Data regarding medical history, pharmacological treatment and laboratory tests was obtained from the patient's medical record (Take Care) and from the electronic patient data management system (Centricity Critical Care). In study I, III and IV a standardized report form was used to prospectively collect patient data, including risk factors for VT and catheter characteristics. In study II, data were retrospectively collected from Take Care and Clinisoft.

In study I all patients receiving a non-tunneled CVC at Astrid Lindgren Children´s Hospital were eligible for inclusion. Patients with body weight <1250 g or with a previous VT in the cannulated vein were excluded from the study. Patients were also excluded if death was deemed imminent and unavoidable or if the CVC was inserted in the ECMO department.

In study II, patients in the PICU with a vascular access used for CRRT for at least 48 hours were included. The patients were identified in electronic patient data management system and medical record.

In study III, patients admitted to PICU for ≥72 hours and with at least two risk factors for VT were eligible for inclusion. Patients receiving anticoagulation therapy or prophylaxis during the entire PICU stay were excluded from the study. Exclusion criteria also included body weight <1250g and if death was deemed imminent and unavoidable.

In study IV, all patients receiving a midline catheter at Astrid Lindgren Children´s Hospital were eligible for inclusion. Patients with a previous VT in the cannulated vein were excluded.

4.4 STUDY PROCEDURE

Study I

All CVCs were inserted under sterile conditions using the Seldinger technique. Ultrasound guidance was almost always used. If clinical conditions permitted, the diameter of the vein to be cannulated was measured. Vein diameter was measured with the patient in the supine horizontal position and while avoiding compression of the vein. This was done in order to be able to calculate the ratio between the external diameter of the CVC and the vein diameter. Difficult insertion was defined as more than two attempts at insertion.

Patients were prospectively followed daily for clinical signs of CVC-related VT. The decision to remove the catheter was made by the physician responsible for the patient.

The primary outcome of the study was the frequency of CVC-related VT. Compression US with color Doppler was used to diagnose CVC-related VT at the time of catheter removal or when CVC-related VT was suspected by the clinical team. US was performed either by a sonographer (specialist technician) or by a pediatric radiologist, using a linear array vascular transducer of 5-12 MHz and a width of 6 – 8 cm. The US equipment used in a vast majority of patients was Siemens Acuson S 2000, while a small number of patients were examined with a Philips EPIQ 7. Duplex sonography was the technique of first choice. However, since some patients either were unable to cooperate or had obscuring bandages, the two US techniques were combined. The diagnosis of thrombosis was made on the basis of previously described direct and indirect signs[17,74], and the diagnostic criteria are listed in Table 4.2. The finding of a direct sign gave a definite diagnosis of VT, while the presence of indirect signs only was rated as suspected thrombosis. After a VT had been diagnosed, the extent was evaluated, and the proximal and distal ends defined. The features of thrombi were evaluated as either occlusive or non-occlusive, and a comment was made on floating nature, if present.

All CVC-related VTs were classified as occlusive or non-occlusive based on vein blood flow, and symptomatic or asymptomatic based on clinical findings. This classification was done to identify a group of VTs with larger thrombotic mass (occlusion to vein blood flow or causing clinical symptoms) indicating an increased risk of complications. Catheters with occlusive and/or symptomatic VT were compared to catheters with VTs that were asymptomatic and non-occlusive.

The management strategy and follow-up plan after a diagnosis of VT was decided by the clinical team responsible for the patient after consultation with the pediatric coagulation unit.

In patients with CVC-related VT the therapeutic strategy, treatment effect and follow-up time were prospectively recorded.

Direct signs	Indirect signs
Intraluminal thrombus (echogenic clot)	Loss of phasic flow on Valsalva maneuver
Lack of compressibility	- Proximal thrombosis
Increased vein diameter	
No flow in pulsed Doppler	Loss of flow augmentation (of calf squeeze)
No flow in color Doppler	- Distal thrombosis

Table 4.2 US diagnostic criteria for VT.

Study II

All data in study II were retrospectively collected. The primary outcome was the rate of VT related to the vascular catheter used for CRRT.

Patient demographics, reason for PICU admission and severity of illness at admission according to Pediatric Index of Mortality (PIM)-3 score were recorded. Catheter-related data and CRRT data was registered, including venous thromboembolic events during CRRT. In order to assess severity of the VT, all symptoms of VT were registered. Data regarding length of hospital stay, PICU stay, duration of mechanical ventilation and the need for ECMO- treatment were also collected. The patient's medical record was followed until discharge, or in the case of catheter-related VT until the final follow-up.

Study III

Patient characteristics and risk factors for VT were recorded for all patients. Risk factors for VT included the presence of av CVC, congenital heart disease, trauma, sepsis, cancer, previous VT, perioperative patient, renal failure, mechanical ventilation, age <1year or >12 years, oral contraceptives, active inflammatory disease and antiphospholipid syndrome. All anticoagulation therapies prescribed during the PICU stay were recorded. Pediatric Index of Mortality (PIM)-2 score at admission was noted.

PICU length of stay, duration and need for MV and CRRT as well as need for ECMO treatment were recorded. Laboratory results for platelet count, activated partial thromboplastin time (aPTT), international normalized ratio (INR), antithrombin III, fibrinogen and D-dimer at admission and discharge were recorded if available.

Patients were followed for clinical signs of VT during their PICU stay. At discharge from PICU an extensive compression US with color Doppler screening for VT was performed using the same methods as previously described in study I. Veins included in the screening were lower extremity (popliteal, superficial femoral, common femoral), upper extremity (subclavian, internal jugular, brachiocephalic) and intraabdominal (external iliac, common iliac, inferior caval, portal, renal) veins.

Study IV

Midline catheters (MCs) were placed under sterile conditions, under US guidance. When clinical conditions allowed for it, vein diameter was measured in the supine horizontal position and while avoiding compression of the vein. Analgesia/anesthesia method and catheter characteristics were recorded.

Patients were followed daily for clinical signs and symptoms of VT and for catheter complications such as catheter occlusion, pain on injection, thrombophlebitis, edema, swelling of the extremity, leakage at the insertion site, infiltration and catheter-related bloodstream infection. If catheter-related VT was suspected by the clinical team before catheter removal, compression US with color Doppler was performed.

After catheter removal US screening was performed to diagnose asymptomatic VT in the cannulated vein. The US equipment used was Philips EPIQ 7, and US was performed as previously described in study I. Management strategy and follow-up plan for VTs were planned by the physician responsible for the patient after consultation with the pediatric coagulation unit. Type and duration of therapy were recorded.

4.5 STATISTICS

Nominal data are presented as frequencies and percentages. Continuous data are presented as median and IQR. Normality tested by D'Agostino Pearson omnibus test showed that no data were normally distributed in any of the papers, hence mean and standard deviation were not applicable.

$p<0.05$ was regarded as statistically significant in all tests.

Study I

The primary aim, the incidence of VT associated with percutaneous non-tunnelled CVCs in a general pediatric population, was presented as number, percentage and as the corresponding number per 1000 catheter days with 95% confidence interval (CI). Mann-Whitney U-test or Fisher's exact test were applied to continuous and dichotomized patient characteristics, respectively, comparing the no VT and VT groups (Table 5.1). The same two tests were used as appropriate to risk factors for VT.

The secondary aim, to find predictive factors for VT, was further investigated by univariate logistic regression presented as odds ratios and 95% CIs. Covariates with $p < 0.2$ were then included in the following stepwise backward multivariable logistic regression. A decrease of deviance by 3.84, corresponding to $p=0.05$, was needed for a factor to be included in the final predictive model (Table 5.2). Then, the predictive risk for VT and its 95% CI was calculated for the different possible combinations of the 3 significant risk factors (Table 5.3).

Study II

The primary aim, the incidence of venous thrombotic complications associated with catheters for CRRT in a PICU population, was presented as number and percentage with a 95% CI. To find factors associated with VTs was the secondary aim of the study, and baseline characteristics for the groups with or without VT were compared by Fisher's exact test or Mann-Whitney U-test as appropriate. Similar statistics were used for catheter and CRRT items, respectively.

Study III

In this study the primary study objective was to assess the incidence of VT that was not associated with a CVC in a PICU population. No such VT was found but a 95% CI was still calculated. Patient baseline data and risk factors for VT are presented as median (IQR) or numbers (%). Changes in coagulation parameters from PICU admission to discharge were compared by Wilcoxon sign rank test.

Study IV

In this study, the primary aim was to find the frequency of VTs associated with MCs in an unselected pediatric population. This was presented as number (percentage) and the corresponding number per 1000 catheter days and its 95% CI. This also applies to the main complications of the midline catheters, *i.e.* the secondary aim of the study. Baseline data for the groups with or without VT were compared by Mann-Whitney U-test or Fisher's exact test as appropriate, and so was the catheter properties.

5 Results

The most important results are presented here. All results are included in the individual articles enclosed at the end of this thesis.

5.1 STUDY I

This study investigated the incidence of and risk factors for pediatric CVC-related VT. In 211 CVCs ultrasound evaluations were performed according to protocol. Median patient age was 2.7 years and 40.8% of patients were female (Table 5.1). The internal jugular vein was the most common insertion site (52.6%), followed by the femoral vein (42.4%). Multiple lumen catheters were used in 64.9% of cases. In 64 catheters (30.3%), a CVC-related VT was found. This corresponds to an incidence rate of 29.6 (CI 22.5-36.9) cases per 1000 CVC days. Most VTs were asymptomatic and did not occlude vein blood flow (49 cases, 76,6%).

When analyzing risk factors for CVC-related VT, multiple lumen CVCs, upper body insertion site and male sex were found to be significantly and independently associated with the development of CVC-related VT in multivariate regression analysis (Table 5.2) The predicted probability of a CVC-related VT in relation to these three risk factors are displayed in table 5.3. None of the other risk factors analyzed had any impact on the risk of CVC-related VT in this study.

To identify risk factors for developing VTs with larger thrombotic mass, we compared catheters with symptomatic and/or occlusive (SO) VT to catheters with VTs that were asymptomatic and non-occlusive (ANO). The risk for a VT with larger thrombotic mass was significantly higher with CVC placement in the femoral vein, young age, PICU admission, mechanical ventilation, and a CVC/vein diameter >1/3 (Table 5.4).

In 45.3% of the CVC-related VTs anticoagulation therapy was prescribed.

Variable	All CVCs n=211	No VT n=147 (69.7%)	VT n=64 (30.3%)	p-value
Age, years, median (IQR)	2.7 (0.2-7.8)	2.7 (0.2-7.7)	2.0 (0.1-7.8)	0.933
Weight, kg, median (IQR)	11.4 (4.8-25.5)	11.6 (5.0-25.5)	10.3 (4.3-26.9)	0.781
Gender, female, n (%)	86 (40.8)	65 (44.2)	21 (32.8)	0.130
PICU, n (%)	115 (54.5)	83 (56.4)	32 (50.0)	0.453

Table 5.1 Patient characteristics in study I.

Lumina	CVC insertion site	Sex	Predicted % of CVC-related VT	95% CI
>1	Upper body	Male	50.2	38.0-62.3
>1	Lower body	Male	42.3	31.3-54.1
>1	Upper body	Female	41.2	31.2-52.1
1	Upper body	Male	37.1	26.2-49.6
>1	Lower body	Female	33.8	25.8-42.8
1	Lower body	Male	30.0	21.7-40.0
1	Upper body	Female	29.1	21.1-38.6
1	Lower body	Female	23.0	16.9-30.5

Table 5.2 Predicted probability of developing CVC-related VT for different risk groups according to the model in table 5.2.

Variable	All VT n=64	ANO n=49 (76.6%)	SO n=15 (23.4%)	p-value
Age, years, median (IQR)	2.0 (0.1-7.8)	4.6 (0.3-9.3)	0.3 (0.02-1.2)	0.011
CVC insertion site Internal jugular vein n (%) Femoral vein n (%)	 45 (70.3) 19 (29.7)	 42 (85.7) 7 (14.3)	 3 (20) 12 (80)	 <0.001
PICU, n (%)	32 (50.0)	18 (36.7)	14 (93.3)	<0.001
MV, n (%)	18 (28.1)	10 (20.4)	8 (53.3)	0.021
CVC/vein diameter >0.33 n (%)	10 (18.5)	4 (9.5)	6 (50.0)	0.005

Table 5.3 Risk factors for larger thrombotic mass.

Study II

This retrospective observational study aimed to determine the risk of catheter-related VT in vascular catheters used for pediatric CRRT.

One hundred and five catheters used for CRRT, in 80 patients, were included. Most patients were infants or neonates (n=53, 50.5%), and median patient age was 10 months. The most common indication for CRRT was acute kidney injury/fluid overload (n=72, 68.8%). Most catheters were double lumen catheters (n=94, 89.5%) and inserted in the internal jugular vein (n=74, 70.5%).

Variable	**All catheters n=105**	**No VT n=99**	**VT n=6**	**p-value**
Neonates, age <1 mo	33 (31.4)	28 (28.3)	5 (83.3)	
Infants, age 1-12 mo	20 (19)	20 (20.2)	0 (0)	
Children, age > 12mo	52 (49.5)	51 (51.5)	1 (16.7)	
Age, mo, median (IQR)	10 (0-73)	14 (0-75)	0 (0-28.5)	0.05
Reasons for CRRT -AKI/fluid overload -Chronic renal failure -Metabolic disorder/liver disease	 72 (68.6) 22 (21) 11 (10.5)	 69 (69.7) 20 (20.2) 10 (10.1)	 3 (50) 2 (33.3) 1 (16.7)	
Number of lumens -One -Two	 11 (10.5) 94 (89.5)	 11 (11.1) 88 (88.9)	 0 (0) 6 (100)	>0.99
Site -Internal jugular vein -Subclavia vein -Femoral vein -Extrernal jugular vein	 74 (70.5) 1 (1) 28 (26.7) 2 (2.9)	 71 (71.7) 1 (1) 25 (25.3) 2 (2)	 3 (50) 0 (0) 3 (50) 0 (0)	0.34*

Table 5.4 Patient and catheter characteristics. Upper body vs lower body*

Six catheters (5.7%) were diagnosed with catheter-related VT. Five out of six VTs were symptomatic. Symptoms included life-threatening pulmonary embolism and superior vena cava syndrome.

Five of the patients with a VT were neonates ≤1 month, and all VTs occurred in patients with double lumen catheters. No differences in catheter size were found between the groups, but the ratio between catheter size in mm and body weight was greater in catheters complicated by VT (p = 0.02). The need for local therapy with alteplase instillation due to catheter dysfunction was significantly increased in the group with catheter related VT (p <0.01). PICU stay, hospital length of stay, CRRT and mechanical ventilation duration were longer in patients with VT, Table 5.5.

Variable	**All catheters n=105**	**No VT n=99**	**VT n=6**	**p-value**
PICU, days median (IQR)	16 (8-39)	15 (8-33)	54 (41-65)	< 0.01
Mechanical ventilation, days, median (IQR)	10 (4-27)	10 (4-27)	26 (18-56)	0.03
Hospital LOS, days, median (IQR)	44 (21-61)	43 (20-58)	60 (57-101)	0.02

Table 5.5 Patient characteristics in study II.

None of the eleven single lumen catheters were complicated by VT. In catheters complicated by VT the ratio between catheter size in mm and body weight was significantly increased compared to catheters with no VT. However, there were no significant differences between the groups regarding catheter diameter. The need for alteplase instillation due to catheter dysfunction was significantly increased in catheters with VT (10.1% vs 83.3%, p<0.01).

Study III

This study described the incidence of VT not related to a vascular access in a cohort of PICU patients considered to be at high risk for VT.

All included patients (n=121) were followed for symptoms of VT. In 46 cases a complete ultrasound evaluation could not be performed at discharge, and five patients were excluded since they received anticoagulation therapy or prophylaxis during their entire PICU stay. In 70 patients, extensive ultrasonography screening for VT was performed according to protocol at PICU discharge.

Most patients (n=46, 65.7%) were < 1 year of age. PICU admission was most commonly due to respiratory failure, surgery for congenital abnormalities, sepsis and seizures in descending order. Median length of PICU stay was 9 days, and patients had a median of three risk factors for VT. The most common risk factors were the presence of a CVC (n=60, 85.7%), the need for mechanical ventilation (n=51, 72.9%), and age less than 1 year (53, 50.4%). The median PIM-2 score of the patients was 4.6%.

Regarding the primary outcome, VTs not related to a vascular catheter, we did not find any symptomatic or asymptomatic VT in the 70 patients who underwent a complete ultrasound screening. This corresponds to a VT incidence of 0% (95% CI: 0–5.1%).

Including the 46 patients that were followed for symptomatic VT but where ultrasound screening was not performed, 116 patients were followed for symptomatic VT not related to a vascular catheter. No symptomatic VT not related to a vascular catheter were found in these 46 patients, resulting in an incidence of symptomatic non-CVC related VT of 0% (95% CI: 0–3.1%) in the total cohort of 116 patients. Eight patients were diagnosed with CVC-related VT during their PICU stay.

Variable	All patients n=70
Age, years, median (IQR)	0.3 (0-4.3)
Neonates, age <1 mo	24 (34.3)
Infants, age 1-12 mo	18 (25.7)
Children, age 1-12 yrs	22 (31.4)
Children, age >12 yrs	6 (8.6)
Weight, kg, median (IQR)	5.2 (3.3-15.1)
PICU, days median (IQR)	9 (5-17)
Mechanical ventilation, days, median (IQR)	8 (4-14)
Hospital LOS, days, median (IQR)	22 (11-50.2)
ECMO	6 (8.6)
CRRT	4 (5.7)

Table 5.6 Patient characteristics in study III.

Study IV

The primary outcome of this study was the incidence of MC-related VT in children. Ultrasound evaluation was performed after catheter removal in 100 midline catheters. Median age of the patients were 5.7 years (IQR 1.8-8.9). Most MCs (58%) were inserted in the perioperative period. The most common insertion site was the basilic vein (58%).

MC-related VT was found in 30 catheters (30%), corresponding to an incidence rate of 39 (95% CI: 25-53) cases per 1000 MC days. The risk for

MC-related VT was significantly increased with placement in the saphenous vein compared to upper extremity veins (p=0.03) and with a shorter catheter length (p=0.04).

Eleven (36.7%) MC-related VTs were symptomatic. Pain on MC injection (p<0.01), thrombophlebitis (p<0.01) and swelling of the extremity (p<0.01) were all significantly more common in MCs complicated by VT. Seventeen VTs completely occluded vein blood flow, but only five of these were symptomatic. No MC-related central vein thrombosis was found. Anticoagulation therapy was given to five patients with MC-related VT, but in only two cases were MC-related VT the reason for anticoagulation therapy.

We did not find any case of MC-related bloodstream infection. No difference in catheter dwell-time or failure rate were found between catheters with and without VT. Mechanical complications occurred in 36 catheters, with no significant difference between the groups. Seventy catheters were electively removed, and in 78 catheters no additional venous access was needed to complete iv therapy.

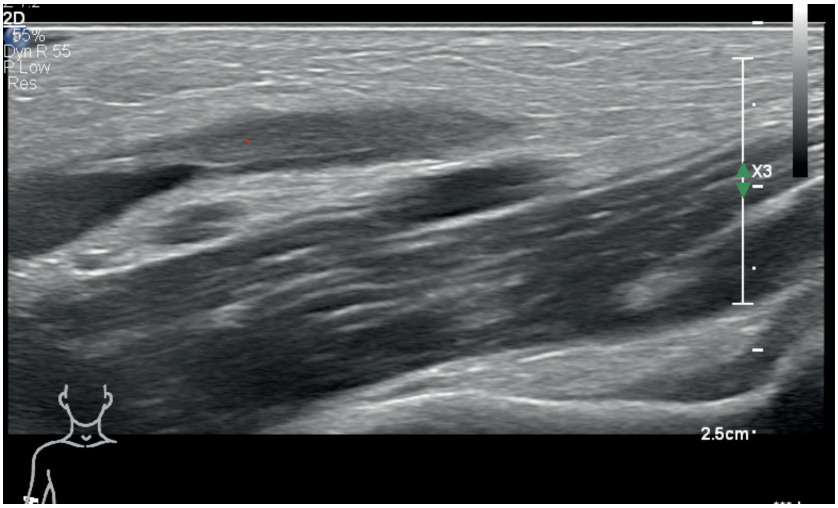

Figure 5.1 Ultrasonography of basilic vein with a thrombosis.

Variable	All MCs n=100	No VT n=70 (70%)	VT n=30 (30%)	p-value
Pain on injection n (%)	14 (14)	4 (5.7)	10 (33.3)	0.0007
Leakage at insertion site n (%)	9 (9)	7 (10)	2 (6.7)	0.72
Swelling of extremity n (%)	6 (6)	0 (0)	6 (20)	0.0005
Thrombophlebitis n (%)	4 (4)	0 (0)	4 (13.3)	0.007
Erythema n (%)	2 (2)	0 (0)	2 (6.7)	0.09
MC-related bloodstream infection n (%)	0	0 (0)	0 (0)	
Catheter occlusion n (%)	8 (8)	7 (10)	1 (3.3)	>0.99
Infiltration n (%)	5 (5)	3 (4.3)	2 (6.7)	0.64
Accidental extraction n (%)	1 (1)	1 (1.4)	0 (0)	>0.99
MCs with any complication n (%)	51(51)	21 (30)	30 (100)	<0.0001
MCs with mechanical complications n (%)	33 (33)	21 (30)	12 (40)	0.36

Table 5.7 Complications related to MC in study IV.

6 Discussion

The main focus of this thesis is pediatric venous thrombosis, an increasing clinical problem in pediatric medical care. The rise in the rate of pediatric venous thrombotic events has several reasons. Most pediatric VTs are catheter-related, and advancements in pediatric care has led to an increased use of CVCs. Moreover, technical and medical development have improved treatment and supportive care for severely ill children who previously would not have survived. An increased awareness of the risk for pediatric VT and improvements in diagnostic methods are also factors contributing to the increased rate of VT in children.

CVC-related VT (paper I)

In paper I, we demonstrated that CVC-related VT occurred in 30% of non-tunneled CVCs in a general pediatric population. The incidence of VT found in our study is similar or somewhat higher than the incidence found in previous studies[20,29,53,75]. However, previous data are mainly from groups of patients considered to be at an increased risk for CVC-related VT. This could indicate that catheter related risk factors are the most important factor in the development of CVC-related VT. This is interesting, since many catheter-related risk factors are under the control of the physician inserting the catheter.

Using multivariate analysis, number of lumina, insertion site and male sex were identified as independent risk factors for developing CVC-related VT. An increased risk for VT with multi-lumen catheters has been shown in previous studies[26,31]. This could be explained by the increase in catheter diameter seen with multi-lumen catheters. However, the fact that a CVC/vein diameter ratio >0.33 did not significantly increase the overall risk for CVC-related VT in our study would suggest another reason for this finding. Another possible explanation could be that the openings along the catheter in a multi-lumen CVC might generate a more turbulent blood flow[76]. The explanation behind the increased risk for CVC-related VT seen in male patients in this population of mainly prepubertal children is unclear.

Previous data indicate that the risk of CVC-related VT is increased with insertion in the femoral vein[29]. However, most previous reports are retro-

spective, describing the rate of symptomatic cases of CVC-related VT, and femoral vein VTs are more likely to cause recognizable symptoms compared to VTs in upper body veins. In paper I, we used prospective ultrasonography screening to reliably diagnose all VTs, including asymptomatic cases. Moreover, we classified all VTs as being:

1. symptomatic and/or occluding vein flow
or
2. asymptomatic and non-occlusive to vein flow.

The reason for this was that we wanted to identify risk factors for VTs with a larger thrombotic mass and presumably with clinical significance regarding patient morbidity.

Interestingly, the risk factors for VTs with larger thrombotic burden differed from the identified risk factors for any CVC-related VT. The overall risk of VT was increased with internal jugular vein CVC location, but VTs in the femoral vein were more likely to be symptomatic and/or occlusive. Obstruction of venous blood flow by the CVC, is considered an important mechanism for the development of VT. In our study, vein diameter was measured before CVC insertion in approximately 75% of cases. Based on previously published guidelines, a cut-off value for CVC-vein diameter ratio of 0.33 was used [33] for analysis. A CVC/vein diameter ratio >0.33 was found to be a risk factor for symptomatic and/or occlusive CVC-related VT. The fact that catheter size and site of insertion were significantly associated with the development of VTs with larger thrombotic burden is interesting, since both these factors are under the control of the physician treating the patient. PICU admission and young age were also significant risk factors for symptomatic and/or occlusive CVC-related VT.

Risk factors for CVC-related VT	Risk factors for symptomatic and/or occlusive CVC-related VT
Multiple lumina	CVC/vein >0.33
IJV/Upper body insertion site	Femoral vein
Male sex	Young age
	PICU admission

Figure 6.1 Risk factors for any CVC-related VT versus risk factors for a CVC-related VT with a larger thrombotic mass.

The clinical importance of asymptomatic CVC-related VT is controversial, but guidelines recommend that both symptomatic and asymptomatic VT should be included in the primary outcome in pediatric VT studies[77]. Recent prospective data indicate that asymptomatic CVC-related VT carries a low risk of long-term complications even without anticoagulation therapy[23]. In line with this, symptomatic CVC-related VT has been associated with fewer ventilator-free and ICU-free days in children, but asymptomatic CVC-related VT did not impact these outcomes. On the other hand, pulmonary embolism[78] , as well as post thrombotic syndrome[79], can occur as a complication to asymptomatic CVC-related VT. Moreover, the distinction between symptomatic and asymptomatic VT is not always clear-cut. Small children and infants cannot always communicate symptoms, and symptoms of VT can be transient and overlooked in children. Even VT with a larger thrombotic mass can present with subtle or no symptoms. Our data indicate that asymptomatic VT can be clinically relevant, since we found four asymptomatic VTs that completely occluded vein blood flow. However, the risk of clinically relevant complications of asymptomatic VTs is likely small compared to symptomatic VTs.

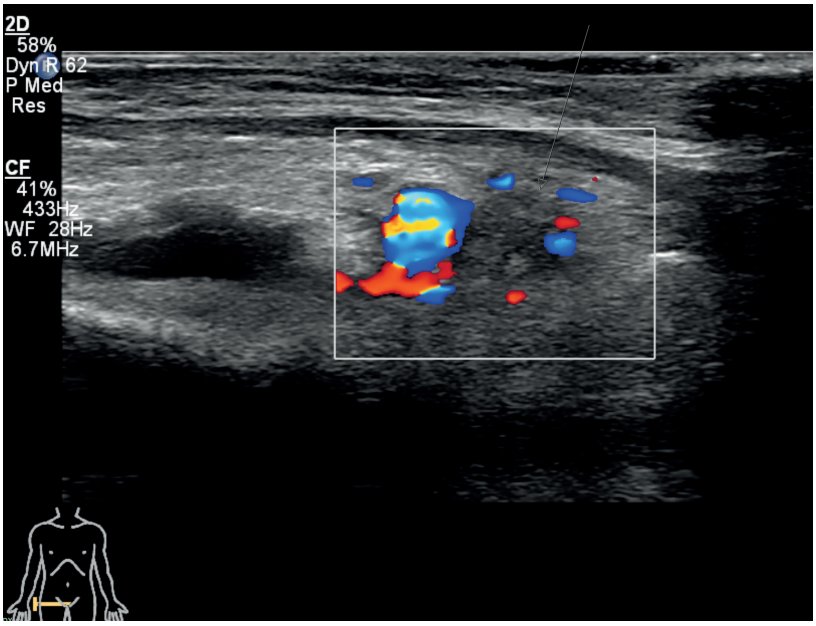

Figure 6.2 Ultrasonography of femoral vein with a thrombosis.

Venous thrombosis and vascular catheters used for CRRT (paper II)

In paper II we retrospectively found that 5.7% (95%CI, 2-12%) of vascular catheters used for pediatric CRRT were complicated by a VT. The risk for venous thrombotic events related to pediatric CRRT catheters has not previously been described.

In patients on CRRT there are many factors influencing the risk of venous thrombosis. Vascular access for CRRT are large-bore catheters, thereby occluding a large part of the vein. This could potentially increase the risk for VT. However, patients on CRRT often receive systemic anticoagulation with heparin to prevent filter and circuit clotting. Previous data indicate that low dose heparin is not an effective prophylaxis for the prevention of CVC-related VT [39], but in CRRT anticoagulation higher doses of heparin is normally used. Also, renal disease can significantly affect the coagulation system[80,81].

The risk for VT found in paper II is similar to the risk for symptomatic CVC-related VT in the PICU described in previous studies[36,82] and in the general pediatric population studied in paper I (11/211, 5.2%). This could

indicate that either the effect of catheter size is smaller than expected or that the effect of catheter size and heparin coagulation neutralizes each other.

Most of the VTs found in paper II led to clinically relevant complications. One patient suffered from a life-threatening pulmonary embolism necessitating prompt systemic thrombolysis with alteplase. Other complications included two cases of superior vena cava syndrome. This underscores that clinicians caring for children on CRRT need to be aware of the risk for venous thrombotic complication sin order to recognize symptoms and initiate swift treatment.

Five VTs out of 6 occurred in infants ≤ 1 month of age, indicating that infants are at greater risk of this complication. This could be due to the fact that in infants the catheter diameter will be larger in relation to the vein diameter. In support of this, patients with VT had a significantly higher ratio between catheter diameter to body weight. However, no significant differences between the groups regarding catheter diameter in mm or French were found. None of the smaller single lumen catheters were complicated by a VT, but the limited number of single lumen catheters and the retrospective study design precludes any firm conclusion regarding the risk of VT related to single lumen catheters.

Although smaller sized catheters might reduce the risk for catheter-related VT, smaller gauged CRRT vascular catheters has also been associated to an increased risk of filter clotting and a shorter circuit life [66]. Clotting of the CRRT filter leads to inefficient dialysis and causes significant blood loss. Failure to achieve prescribed CRRT doses and satisfactory fluid removal can have a substantial impact on patient outcome. In children receiving CRRT due to a combination of AKI and fluid overload, mortality was significantly lower in group of patients where a negative fluid balance was achieved within three days of CRRT initiation [83]. A reliable vascular access is a key factor to achieve efficient CRRT delivery, and the potential benefit of choosing a smaller sized vascular access must be balanced against the risk of negative effects on patient morbidity and mortality due to shorter circuit lifespan.

Venous thrombotic events in the PICU (Paper III)

The incidence of pediatric VT has increased dramatically in recent decades[1]. Still, the overall risk of VT in children is low, and VT is mainly considered to be a complication affecting severely ill children. The existing data regarding incidence of and risk factors for VT in critically ill children is very limited. Due to the lack of data, no evidence-based guidelines regarding when to use pharmacological thromboprophylaxis in critically ill children exist, and current guidelines are mainly based on experts' opinion. The American College of Chest Physicians guidelines do not recommend universal adoption of pharmacological thromboprophylaxis (pTP) in the general PICU population[84], but recently published recommendations suggested that PICU patients with two or more risk factors for VT might benefit from pTP[85]. In clinical practice, there is a large variation in the routines for prescribing pharmacological thromboprophylaxis for PICU patients.

As demonstrated in paper I, most CVC-related venous thrombotic events are asymptomatic in children. It is unclear whether this is also true for VTs that are not CVC-related. Previous data on the incidence of VTs in the PICU are mainly retrospective and includes symptomatic cases. This carries the risk of underestimating the true incidence of VTs in the PICU.

In paper III we performed a comprehensive ultrasonography screening of all the great veins in the body in 70 PICU patients. Since previous data indicate that the incidence of VT not related to a CVC is low in the general PICU population, we chose to study a group of PICU patients considered to be at high-risk of VT. Using ultrasonography screening in this high-risk cohort, we did not find any VTs that were not CVC-related, resulting in an incidence of 0% (95% CI: 0–5.1%). Additionally, no symptomatic VT was found in the 46 patients where ultrasound screening could not be performed, resulting in an incidence of symptomatic non-CVC related VT of 0% (0–3.1%) in this group of 116 patients.

Our main aim was to describe the true incidence of VTs not related to a CVC in a PICU population considered to be at high risk of VTs. The potential benefit of using pTP in this group of patients must be weighed against definitive and potential harm. Side-effects of pTP include bleeding, heparin-induced thrombocytopenia and neonatal osteopenia. Injection of LMWH also causes pain and discomfort. To make well-founded decisions

regarding the overall effect of using pTP it is crucial to know the true risk of VT. The fact that we did not find any VTs in our study supports the notion that pTP should not be regularly prescribed even in a general PICU population considered to be a high risk of VT. Still, our study was small and larger studies are needed before firm conclusions can be drawn. It should also be kept in mind that our cohort consisted of mainly prepubertal children, and the results should not be extrapolated to adolescents.

VTs not related to a CVC was chosen as the primary outcome of the study. A major reason for this is that CVC-related VT has distinct pathophysiological features, including endothelial damage, partial occlusion of the vein, and the presence of foreign material. LMWH is often used as pTP to prevent VT in the ICU, but previous data indicate that LMWH is not effective in preventing CVC-related VT. Moreover, incidence of and risk factors for CVC-related VT has previously been extensively described, whereas the data on VTs not related to a CVC are very sparse.

Pediatric midline catheters (Paper IV)

One way of avoiding CVC-related VT is to insert fewer CVCs. MCs could be an option to CVCs in selected pediatric patients, but the safety data on the use of pediatric MCs are very sparse. In paper IV, we investigated the rate of complications to pediatric MCs. We also wanted to investigate the success rate when using MCs for pediatric short-term iv therapy. The incidence of MC-related VT was chosen as the primary outcome of paper IV.

Midline-related VT occurred in 30% of cases. This is similar to the rate of CVC-related VT found in paper I. However, none of the MC-related VTs affected central veins. Also, only few patients with MC-related VT were considered to need anticoagulation therapy. In paper I, 45% of patients with CVC-related VT were prescribed anticoagulation therapy. Our data indicates that MC-related VT affects peripheral veins and are less likely to require anticoagulation compared to CVC-related VT. However, it should be kept in mind that no data exist on how to manage MC-related VT, and the management strategy and follow-up plan in paper IV were decided after consultation with the pediatric coagulation unit.

The overall rate of complications was rather high, 51% of MCs were subject to at least one complication. Mechanical complications were the most common problem, occurring in 33% of catheters. Thirty percent of

catheters were removed before completion of therapy, due to complications or unintentionally. This corresponds to an incidence rate for MC failure of 39 cases per 1000 catheter days. However, only 22 cases needed additional venous access, and 78 cases did not need additional venous access to complete the intended short-term iv therapy. Pediatric CVCs have a comparable failure rate, 25%[24], but since CVCs are generally used for longer periods of time, the incidence rate of CVC-failure per 1000 days will be lower than for MCs. We did not find any MC-related bloodstream infection. This is in line with previous adult data indicating that the risk of catheter-related infection is lower with MCs compared to CVCs.

Even though mechanical and thrombotic complications were common, our data indicate that pediatric MCs could be an alternative to CVCs for short-term (5-10 days) iv therapy. However, RCTs comparing MCs and CVCs are necessary to draw firm conclusions regarding the potential benefits of MCs. Also, even though most VTs found in paper IV was not considered severe enough to warrant anticoagulation therapy, there are no data describing the natural history and potential long-term consequences of MC-related VT.

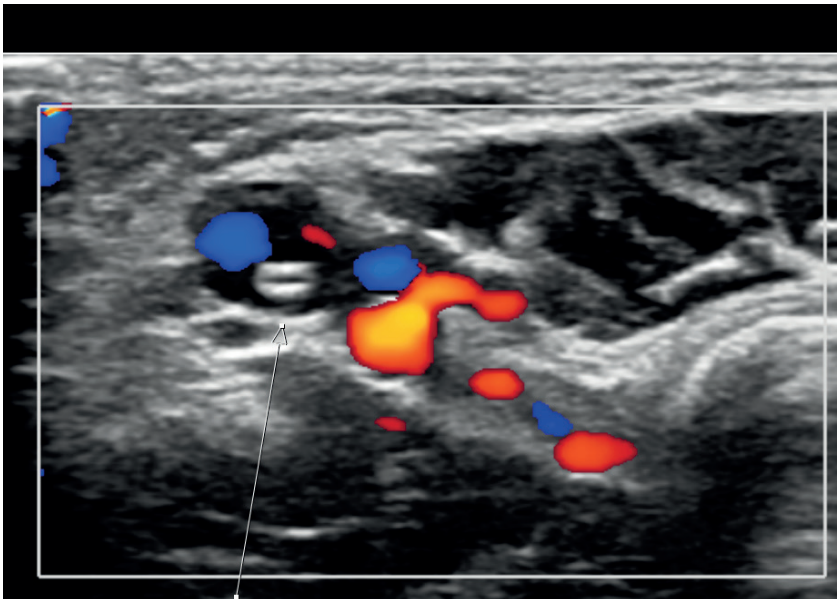

Figure 6.3 Ultrasonography of basilic vein with a midline catheter in place.

Clinical implications

Our data indicates that insertion site in the internal jugular vein leads to fewer clinically important thromboemobolic events compared to femoral vein insertion. The risk for symptomatic and/or occlusive CVC-related VT was also increased with PICU admission and young age. This indicates that the femoral vein should not be the first choice for CVC insertion site, especially in critically ill small children and neonates. Smaller size catheters and single lumen catheters also appear to reduce the risk of CVC-related VT, and this should be kept in mind when choosing catheter size and type.

In children, CVCs are often used if iv therapy exceeds 4-5 days and in cases of difficult venous access. However, the risk for severe complications is considerably higher for CVCs than for PIVCs. Thromboembolic complications to CVCs have important implications, including central vein depletion and post-thrombotic syndrome. One way of reducing the number of CVC-related VTs is to avoid using CVCs when possible. Our results indicates that MCs might be an alternative to CVCs for short-term (5-10 days) peripheral iv therapy. When choosing what catheter type to use, it is crucial to weigh risks and benefits of different catheters as well as for the individual patient. Data from study IV indicates that the risk of central vein thrombosis and catheter-related bloodstream infection are very low when using MCs. For patients considered to be at an increased risk of CVC-related VT or CVC-related bloodstream infection MCs could be an attractive option. On the other hand, for patients with chronic renal disease MCs should preferably be avoided due to the relatively high rate of peripheral vein thrombosis and occlusion. Also, 22% of patients with MCs needed more than one iv catheter to complete the intended therapy. A CVC is a more reliable option to complete short-term iv therapy without the need for additional catheters. For the individual patient, the risk of CVC-related complications must be weighed against the risk of MC failure and additional catheter insertions. Other factors that need to be considered are that MC insertion is less resource demanding and easier to perform with only local anesthesia and sedation compared to CVC-insertion.

In paper II we demonstrated that vascular access catheter-related VT is a clinically relevant complication to pediatric CRRT. Possibly, the risk could be reduced by using smaller sized catheters. However, this would also mean an increased risk of CRRT failure with significant negative consequences

for the patient. With the current knowledge, smaller sized catheters cannot be recommended. However, for the clinician caring for this group of children it is important to be aware of the risk of thromboembolic complications to recognize symptoms and initiate swift treatment.

Our results from paper III indicates that the risk of VT not related to a vascular catheter is low in prepubertal PICU patients. These data supports the current routine in our and many other PICUs of not routinely prescribing pTP to PICU patients. More data and larger studies are needed to understand more about the risk-benefit balance for pTP in PICU patients.

Methodological considerations

Doppler ultrasonography is the first-hand method to diagnose venous thrombosis in children. All examinations were performed by a pediatric radiologist or an experienced sonographer, and reviewed by a radiologist. There are very few side effects of ultrasonography. Ultrasonography is sensitive and specific[30,86], but has limitations when vein compression is difficult. The development of high resolution ultrasound equipment has led to excellent image quality, making visualization of even very small VTs with limited clinical relevance possible.

The previous golden-standard, contrast venography, is invasive, includes radiation exposure and is more resource demanding. Venography also has a low sensitivity for diagnosing VT in the internal jugular vein. Spiral CT has excellent accuracy and short examination time. However, drawbacks include iodine contrast media, radiation exposure, higher costs and sometimes a need for sedation. Ethically, it would have been difficult to defend venography or CT as the screening method in children due to exposure to radiation and contrast media and the need for vascular access. Another method used for VT diagnosis is MRI. The image quality is excellent, but MRI is time consuming, resource demanding, expensive and requires sedation or anesthesia. All these factors make MRI less favorable for screening purposes.

7 Conclusions

Conclusions from the studies comprising this thesis are:

- Incidence of non-tunneled CVC-related VT in our general pediatric population was 30%.
- The overall risk for CVC-related VT is increased with upper body CVCs, multiple lumen CVCs and male sex. However, risk factors for VTs with larger thrombotic mass is different, and includes insertion in the femoral vein, young age and PICU admission.
- Venous thrombosis is a clinically relevant complication to vascular access catheters used for pediatric CRRT, even if systemic heparin anticoagulation is used. 5.7% of vascular catheters used for CRRT were complicated by a VT. The risk is highest in neonates and small infants, possibly due to an increased catheter size in relation to vein size.
- In a cohort of PICU patients with a median of three risk factors for VT, we did not find any VT not related to a CVC, which indicates that VT is uncommon even in a selected group of severly ill children considered to be at high risk for VT.
- Venous thromboembolism and mechanical complications are common when using pediatric midline catheters. Still, 78% of patients do not need additional venous access to complete the short-term iv therapy. Midline catheters could be an option to CVCs for short-term peripheral iv therapy in selected children.

"Do not judge me by my successes, judge me by how many times I fell down and got up again." – Nelson Mandela

8 Points of perspective

Currently, no pharmacological prophylaxis has been proven effective as prevention for CVC-related VT. The main possibility for the clinician to reduce the risk of CVC-related VT lies in the choice of catheter size, insertion site and number of lumina. Our data indicate that smaller asymptomatic VTs are more common in the internal jugular vein, whereas use of the femoral vein is associated with VTs of greater clinical significance. To understand more regarding the effect of catheter insertion site in children, randomized controlled trials comparing CVC insertion in the femoral vein to the internal jugular vein are necessary.

The long-term consequences of asymptomatic non-occlusive CVC-related VT seems to be low[23]. However, more data on the long-term complications of asymptomatic VT are needed to determine how treatment strategies and follow-up for these patients are best designed. Large, prospective multi-center studies with strict surveillance protocols and long-term follow-up for PTS are needed. Also, it would be of interest to evaluate the patients from paper I in this respect[23,87].

The risk for clinically relevant thromboembolic complications to vascular access catheters used for pediatric CRRT was demonstrated in this thesis. The fact that these vascular catheters often are large bore double lumen catheters to maintain adequate blood flow increases the risk of VT. Single lumen catheters are smaller in size than double lumen catheters, and the risk of VT should be smaller. On the other hand, two catheters need to be inserted instead of one. Our data included eleven single lumen catheters used for pediatric CRRT, none of these were complicated by VT. Future studies investigating the rate of complications and the efficiency using two single lumen catheters for pediatric CRRT are needed to evaluate this strategy.

Several studies hade aimed to find an effective pharmacological prophylaxis for pediatric CVC-related VT, but so far without convincing results. There are ongoing trials on direct oral anticoagulants (DOAC) for VT prophylaxis in selected pediatric patient groups[47]. However, DOACs have so far not been evaluated as prophylaxis for CVC-related VT. Future RCTs are needed to establish the role of DOACs in prevention of pediatric CVC-related VT.

Or results from paper IV indicate that MCs could be an option to CVCs for short-term peripheral iv therapy in children. However, randomized controlled trials are needed to draw firm conclusions regarding potential benefits of MCs compared to CVCs. To clarify risks and benefits of different venous access catheters in children would have significant impact on clinical care for pediatric patients.

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"Well, Art is Art, isn't it? Still, on the other hand, water is water. And east is east and west is west and if you take cranberries and stew them like applesauce they taste much more like prunes than rhubarb does. Now you tell me what you know."
/ Groucho Marx

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