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# Central Lines in

# Preterm Newborn Infants

## Retrospective Study

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## ABSTRACT

**BACKGROUND** Central lines (CL) are often used in the care of preterm newborn infants. However, they are associated with a number of possible complications including infections. Therefore, benefits must be weighed against risks when considering placement of a CL.
**AIM** To provide data on the use of Umbilical artery catheters (UACs), Umbilical vein catheters (UVCs) and Peripheral inserted central catheters (PICCs) in preterm newborn infants admitted to our Neonatal intensive care unit (NICU).
**METHODS** We identified infants with a CL admitted to our NICU at Karolinska University Hospital, Danderyd from January 1, 2010 to December 31, 2012. The CLs studied were UACs, UVCs and PICCs. Clinical data and complications including Central line – associated blood stream infection (CLABSI) were studied retrospectively.
**RESULT** A total of 192 CLs, including 76 UACs, 51 UVCs and 65 PICCs were placed in 104 infants. 6 cases of CLABSI occurred (6,5 per 1000 catheter – days). An independent predictor of CLABSI was prolonged duration of CL use. No other potential risk factors showed any correlation with the development of CLABSI.
**CONCLUTION** Prolonged duration of catheter use is an important predictor of CLABSI in preterm newborn infants. Clinicians should be aware of this risk when placing a CL and in timing the removal of a CL.


| ABBREVIATIONS | |
|---|---|
| BSI | Blood Stream Infection |
| BW | Birth Weight |
| CDC | Centers for Disease Control |
| CL | Central Line |
| CLABSI | Central Line – Associated Blood Stream Infection |
| CoNS | Coagulase – Negative Staphylococcus |
| CRBSI | Catheter – Related Blood Stream Infection |
| CRP | C – Reactive Protein |
| GA | Gestational Age |
| NICU | Neonatal Instensive Care Unit |
| PICC | Peripherally Inserted Central Catheter |
| TPN | Total Parenteral Nutrition |
| UAC | Umbilical Artery Catheter |
| UVC | Umbilical Vein Catheter |
| WBC | White Blood Cell Count |

# INTRODUCTION

CLs including UACs, UVCs and PICCs are often used in the care of preterm newborn infants to provide arterial and venous access. However, the use of CLs is associated with several complications including infection (1, 2). For this reason, the decision to insert a CL should always be carefully considered for every patient individually, and the benefits must be weighed against the risks. A CL should only be inserted when clearly necessary and should be removed when no longer essential (3).

**INFECTION** Newborn and especially preterm infants are naturally more vulnerable to infections. When inserting and using CLs it is important to minimize the risk of infection. Therefore, an aseptic technique is required when inserting and using intravascular catheters (3, 4).
The most commonly reported pathogens which cause CLABSI are Coagulase – negative staphylococci (CoNS) (1, 2, 5 - 9), followed by Staphylococcus Aureus, Enterococci and Candida (4, 3). The CL can be contaminated through organisms on the skin which migrate from the site of insertion along the surface of the catheter to the catheter tip, direct contamination of the catheter through contact with hands or devices, through an infection at another site that reaches the CL hematogenously, and by infusion of contaminated fluids (3). Also, the characteristics of the material from which the CL is made contribute to the vulnerability to microbial colonization and subsequent CLABSI. The same is true of virulence factors of the pathogen and host factors in the infant (3).

**INSERTION AND MAINTENANCE** The umbilical vessels are preferred for intravenous and intraarterial access during the first days after birth. The umbilical vein is available for catheterization up to seven days after birth, while the umbilical arteries will usually not be accessible for more than a couple of days (10). However, by using the alternative technique of lateral cut – down, this period may possibly be extended.
Aseptic conditions during catheter insertion and management are vital for prevention of infectious complications (3, 10, 11). It has been shown that the incidence of CLABSI can be reduced by education and training for care providers who insert and maintain catheters (3, 11, 12). In an effort to develop best practices and reduce the rate of complications, a PICC – team was formed in our NICU consisting of specialized nurses who provide PICC care.
**Insertion** In our NICU the insertion procedures for UACs, UVCs and PICCs are quite similar. They are bedside procedures. The skin is cleansed with chlorhexidine solution (0,5 mg/ml for infants with a birth weight (BW) < 1200 grams and at an age < 1 week, and 5 mg/ml for infants with a BW > 1200 grams or at an age > 1 week), and sterile drapes are placed prior to insertion. ECG or pulse oximetry monitoring is used during the procedure. When the catheter is in place, it is flushed with 0.9% NaCl and a continuous infusion is started. The catheter position is confirmed by X – ray (10). Umbilical catheterization is performed by a physican in sterile gown and gloves and with a nurse assisting, while PICC insertion is most commonly performed by a specialized PICC nurse.
**Maintenance** The catheter should be manipulated as little as possible. The site of insertion is inspected several times a day. Daily review of the catheter is essential to ensure removal at the earliest time feasible. Because of the risk for bleeding, the infant is observed for at least 4 hours after umbilical catheter removal (10). In our NICU, UVCs and UACs are removed at the age of 7 days, exceptionally they are used up to ten days. However, when central vascular access is needed beyond 7 days, a umbilical catheter is often replaced by a PICC (10).

**UAC** The umbilical artery catheter can be placed either in a high or a low position.

- High: On X – ray the catheter tip is projected at the level of vertebrae T6 – 10 (4, 10, 13).
- Low: On X – ray the catheter tip is projected at the level of vertebrae L4 – 5 (4, 10, 13).

The catheter position is always checked on X – ray (4, 10). A catheter tip position between vertebrae T11 and L2 should be avoided, as the blood vessels to the abdomen and kidneys originate in this area and their blood supply should not be impeded (4).

**Anatomy** The umbilical arteries connect to the internal iliac arteries. Therefore a catheter introduced into the umbilical artery usually passes from the internal iliac artery into the aorta.

**Indications** Frequent blood sampling, measurement of pH and arterial blood gases, continuous monitoring of arterial blood pressure and infusion therapy (Vaminolac) (4, 10, 14).

The UAC is not used for infusion of drugs used for resuscitation. Blood products, vasoactive medications and calcium should not be given through a UAC (10). Hyperosmolar glucose should never be given through a UAC because of the risk for potent insulin release and hypoglycemia (10).

**Complications** Catheter dislocation, hemorrhage, perforation, extravasation, occlusion, arterial vasospasm, thromboembolism, renal artery thrombosis, infections (local or systemic) (10, 14).

**UVC** The optimal position for the catheter tip is in the inferior vena cava (1, 10). Intrahepatic and portal vein positions should prompt catheter removal. When used for continuous infusions, the catheter position is always confirmed by X – ray (10).

**Anatomy** The umbilical vein goes from the umbilicus and to the right where it gives off several large intrahepatic branches that are distributed directly to the liver tissue. It joins the left branch of the portal vein and continues into the ductus venosus, which terminates in the inferior vena cava (13).

**Indications** Exchange and dilution transfusions, intravenous drug therapy, infusion therapy, infusion of vessel – irritating and potentially tissue – damaging substances, blood sampling, nutrition (intravenous hyperalimenation), central venous pressure monitoring and achieving venous access when the options are limited (1, 10).

All types of infusions and medications can be given through the UVC (10), assuming that the tip is correctly positioned. The UVC is not used for infusion of drugs used for resuscitation (10).

**Complications** Catheter dislocation, hemorrhage, perforation, extravasation, occlusion, broken catheter, embolization, air embolization, thrombosis (including the portal vein), liver damage, infections (local or systemic), thrombophlebitis, myocardial rupture, cardiac tamponade, arrhythmias, portal hypertension and pleural effusion (1, 4, 10). Infusion of hyperosmolar solutions in the liver may lead to development of liver damage and portal vein thrombosis (10).

**PICC** PICCs offer an alternative to surgically placed Central venous catheters. It avoids the need for sedation and surgical insertion in the operating room (11). (Figure 1 shows a PICC placed in the left arm).

The ideal position for the tip of the PICC is in the inferior or superior vena cava (1, 11, 15). The position is always confirmed by X – ray (Figure 2).

There are two types of PICCs, made of silicone and polyurethane respectively.

**Anatomy** The peripheral veins of first choice are the veins of the antecubital fossa, the basilic and cephalic veins, as well as the axillary veins. Other vessels used are the femoral and

saphenous veins of the leg, the external jugular vein of the neck and the temporal vein of the scalp (4).

**Indications** Drug administration, parenteral nutrition, fluid therapy, infusions, and hemodynamic monitoring (6, 10, 11), although given the small bore of the catheters used, the latter is usually not possible in the smaller infants.

Almost all types of infusions and medications can be administered through a PICC (10), but drug incompatibility is often a limitation. Drug incompatibility is a frequent cause of line occlusion (16). Given the risk of occlusion, blood products should only be given exceptionally (10). Venous blood sampling is not taken through a PICC given the risk of occlusion and thrombosis. Injections and temporary infusions should be avoided given the risk of infection.

**Complications** Catheter dislocation, hemorrhage, perforation, extravasation, occlusion, breakage and leakage of the catheter, formation of venous thrombi, embolization, infections (local or systemic), thrombophlebitis, arrhythmias, myocardial lesion including perforation, pneumothorax, hydrothorax, and pleural effusion (1, 5, 10 - 12).

## AIM

To provide data on the use of UACs, UVCs and PICCs in preterm newborn infants admitted to our unit. Several aspects were considered, presented in the table below.

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|---|
| CL use |
| Duration of CL use |
| Cause of CL removal |
| Incidence of CL – associated mechanical complications<br>- Dislodgement<br>- Reduced peripheral circulation<br>- Hemorrhage<br>- Thrombophlebitis<br>- Occlusion<br>- Inapproppriate placement of the tip requiring catheter removal<br>- Extravasation<br>- Perforation |
| Incidence of CL – associated infectious complications<br>- CLABSI<br>- Clinical sepsis<br>- Contamination |
| Causative pathogen of infection |

## METHODS

**SETTING AND DESIGN** This was a retrospective study which covered the period from January 1, 2010 to December 31, 2012 in the Neonatal Intensive Care Unit at Karolinska University Hospital, Danderyd, Stockholm.
Infants who fulfilled the following criteria were included:

- Infants born during the above mentioned period.
- CL placed or in place in our NICU.
- Gestational age week $32^{6}$ or less.

We were able to track hospitalizations which preceded as well as followed the stay in our NICU. The infants were included if the CL was present at any time during the infant´s stay in our NICU. Infants whose CLs were removed before arrival at or inserted after transfer from our NICU were excluded. Also, surgery prior to CL introduction or surgery while a CL was in place resulted in exclusion of the case. For infants with multiple CLs all CLs were taken into account.

**DEFINITIONS** A CL was defined as an intravascular catheter that terminated in one of the great vessels and close to, or inside the heart. We defined CLABSI as a primary BSI (sepsis) associated to the usage of a central line. The time of CLABSI onset and Clinical sepsis were defined as the first detected sign or symptom, arising ≥ 48 hours after CL introduction or within 24 hours after CL discontinuation and not secondary to an infection arising from other foci (1, 3, 17). (Tables 1, 2 and 3 show the definitions of infection, including BSI, clinical sepsis, and contamination used at our NICU).

**CASE ASCERTAINMENT** The study population was found through our administrative database named PNQn (*Perinatal Quality Register neonatal)*. Dates for PICC insertion and removal, as well as indications for PICC insertions were extracted from the PICC – team database. Patient characteristics were extracted from medical records found in our electronic medical chart (*Take Care)*. The medical records were reviewed to determine whether the infants met the inclusion criteria and if the CLABSI criteria were fulfilled. We also reviewed the results of each infant´s blood, urine and cerebrospinal fluid tests, as well as X – rays. We tracked the status of each infant until at least 48 hours after CL removal. For each infant we recorded clinical variables such as gestational age (GA), BW, clinical indication for CL placement, type of CL, age of infant at the time of CL placement, duration of catheter use, cause of catheter removal, CRP maximum, CL dwell time at the time of CRP maximum, antimicrobial therapy, complications (as mentioned in aims), CL dwell time on the day of that infection was diagnosed, and hospitalizations at other NICUs.

**STATISTICAL ANALYSIS** Descriptive characteristics were calculated separately for UACs, UVCs and PICCs, as well as for the whole population. All data were expressed as numbers and percentages, or as mean, SD, maximum and minimum, and were calculated using Microsoft Excel™. Data were maintained in Microsoft Excel™ and were analyzed using IBM SPSS Statistic (version 20) and Statistica (version 10). P - values < 0.05 were considered statistically significant.
In order to give all CLs an equal probability for developing CL – associated infections such as CLABSI and clinical sepsis, all CLs with a dwell time < 48 hours were excluded (33 CLs) when considering these infectious complications. Therefore, statistical analysis considering CLABSI and clinical sepsis were performed on a subpopulation consisting of 159 CLs. Statistical analysis considering CL contamination were performed on the whole population, as contamination can appear at any time during CL use.

The incidence of CLABSI and complications were measured as episodes per 1000 catheter – days. To identify potential independent risk factors for CLABSI, the Fisher exact test and the Mann – Whitney U test were used. As potential risk factors the following were taken into account: UAC (yes/no), UVC (yes/no), PICC (yes/no), GA (weeks, numerical value), BW (grams, numerical value), administration of TPN (yes/no), antimicrobial therapy prior to CLABSI development (yes/no) and duration of CL use (days). Differences between UACs, UVCs and PICCs as regards time until occurrence of CLABSI were analyzed by using Kaplan – Meier survival curves and was subsequently compared with a Generalized Wilcoxon log – rank test. Further, Kaplan – Meier estimates were performed to show the duration of catheter use until occurrence of CLABSI and a Hazard – curve was constructed to estimate the risk of developing CLABSI as a function of duration of catheter use.

## RESULTS

During the study period 2754 infants were admitted to our NICU. Of these, 303 (11%) infants were born at week $32^{6}$ or earlier, of whom 109 (36%) had a CL placed. Five infants had surgery before the introduction of a CL or at the time of an indwelling CL and were excluded. Thus, 104 patients were eligible for our study. The total number of CLs included was 192.
60/104 (57,7%) infants received more than one CL. 34/104 (32,7%) patients who had CLs also had these in place at the time of transfer into or out of our NICU.
The mean GA among the infants was 29,6 ± 1,8 weeks, with a range from 25,1 to 32,9. The mean BW was 1325 ± 351 grams, ranging from 720 to 2406. (Demographic characteristics of the study population are shown in Table 4).
The mean duration of catheter use was 4,9 ± 3,7 days, ranging from 0 to 23. The mean age of the infant at the time of catheter insertion was 2,2 ± 4,9 days, ranging from 0 to 38. (See table 5).

UACs were placed in 76/104 (73,1%) infants, of which 68 were placed in a high position and 8 in a low position. UVCs were placed in 51/104 (49%) infants. PICCs were placed in 65/104 (62,5%) infants, including 28/65 (43,1%) introduced in the right arm, 29/65 (44,6%) introduced in the left arm, 2/65 (3,1%) introduced in the left leg and 6/65 (9,2%) introduced in the right leg.

152/192 (79,2%) CLs were removed electively, as they were no longer needed, while 16/192 (8,3%) were removed because of inappropriate placement of the tip, 15/192 (7,8%) were removed because of mechanical complications, and 4/192 (2,1%) were removed because of suspected local or systemic infection. 4/192 (2,1%) of the CLs were dislodged.
In 17/65 (26%) cases of PICC placements the tip was initially placed in an incorrect position requiring correction. Of these, in one case the catheter tip was placed in a small peripheral vessel, in another the tip was placed in the internal jugular vein and in fifteen cases the tip was placed in the heart.

The most frequently used infusion was Total parenteral nutrition (TPN), which was administered in 151/192 (78,6%) of all CLs. (Table 6 shows the infusions administered in UACs, UVCs, PICCs and in total).

**COMPLICATIONS** were calculated based on the whole population, which included 192 CLs. Of these 192, 41 (21,4%) were associated with a complication. Overall, the rate of CL – associated complications was 43,7 instances per 1000 catheter days. 4/192 (2,1%) were accidentally dislodged, 3/192 (1,6%) developed reduced peripheral circulation, 1/192 (0,5%)

developed hemorrhage, 2/192 (1,0%) developed thrombophlebitis, 12/192 (6,3%) were occluded, 16/192 (8,3%) had an inappropriate placement of the tip and 3/192 (1,6%) were contaminated. Extravasation or perforation did not occur in any of our patients.
Among the 76 UACs, 17/76 (22,4%) were associated with a complication, and the rate of UAC – associated complications was 52,1 instances per 1000 catheter days. Among the 51 UVCs, 17/51 (33,3%) were associated with a complication, and the rate of UVC – associated complications was 131,8 instances per 1000 catheter days. Among the 65 PICCs, 7/65 (10,8%) were associated with a complication, and the rate of PICC – associated complications was 14,5 instances per 1000 catheter days. (Table 7 shows the distribution of complications in the three catheter groups).

Rates of CLABSI and Clinical sepsis were calculated based on the subpopulation, which included 159 CLs (67 UACs, 30 UVCs and 62 PICCs). During the study period we observed 6/159 (3,8%) instances of CLABSI. The rate of CLABSI was 6,5 instances per 1000 catheter days. CLABSI occurred in 3/67 (4,5%) of the UACs, 1/30 (3,3%) of the UVCs and 2/62 (3,2%) of the PICCs. (See table 8). In the 6 patients with CLABSI the mean GA was 29,5 ± 1,4 weeks, the mean BW was 1176 ± 149 g, the mean duration of CL use was 8,3 ± 2,2 days, 100% recieved TPN and 50% received antimicrobial therapy prior to developing CLABSI. (Table 9 summarizes the characteristics of the infants with and without CLABSI).

In our study the infants appeared to develop CLABSI from UACs more frequently (4,5%) than from UVCs (3,3%) and PICCs (3,2%), but this difference was not statistically significant. When evaluating CLABSI in relation to potential risk factors, neither the use of UACs (p = 0,699), UVCs (p = 1,0), or PICCs (p = 1,0) showed any statistically significant association with the development of CLABSI. Nor was there any statistically significant association between CLABSI and GA (p = 0,982), BW (p = 0.614), administration of TPN (p = 1,0) or having received antimicrobial therapy prior to developing CLABSI (p = 0,689).

There was no statistically significant difference between the three catheter groups in time to development of CLABSI using a Kaplan – Meier survival curve (p = 0,156). (Figure 3).
The risk for developing CLABSI was analyzed as a function of increasing duration of catheter use in a hazard curve. The risk was 0.005 at day 5, 0.08 at day 10 and 0.3 at day 15. This apparent relationship failed to reach statistical significance. However, this may be due to the small sample size and does not rule out the possibility that the risk of developing CLABSI increases with increasing duration of catheter use (Figure 4).

Overall, clinical sepsis occurred in relation to 3/159 (1,9%) CLs, of which 1/67 (1,5%) in a UAC, 1/30 (3,3%) in a UVC and 1/62 (1,6%) in a PICC.

The incidence of contamination was calculated on the whole population consisting of 192 CLs. The overall incidence of CL contamination was 3/192 (1,6%), all UAC related, including 3/76 (3,9%) of the UACs in total.

The most common causative pathogens were CoNS and S. Aureus, both causing 3/6 cases of the CLABSIs each, and 1/3 cases of contamination each. The remaining 1/3 case of contamination was caused by a Group A Streptococcus.

## DISCUSSION

We report results from a retrospective study of neonates with central lines, UACs, UVCs and PICCs. The CLs were used in selected cases, in infants with a low GA and a low BW.
CLABSI has become a major concern in neonates. A retrospective cohort study performed by Odetola et al. (18) at a Pediatric intensive care unit suggested that 90% of nosocomial BSIs were related to intravascular catheter devices.
Our main finding was a low incidence of CLABSI. We observed 6 cases of CLABSI among 159 catheters in a high risk population consisting of preterm newborn infants born at gestational week $32^{6}$ or earlier.

It was difficult to compare studies because of the heterogeneity in context and study population, as well as the different definitions of CLABSI.
Some of the studies we compared our study result with used the definition Catheter – Related Blood Stream Infection (CRBSI) instead of CLABSI. CRBSI identifies the catheter as the source of the BSI more thoroughly, and requires more specific laboratory testing compared to CLABSI (3). The CDC´s Guidelines for the Prevention of Intravascular Catheter – Related Infections (3) suggests that CLABSI may overestimate the true incidence of CRBSI.

In the present study the incidence of UVC – associated CLABSI was 3,3% and the risk expressed as instances per 1000 catheter – days was 8,1. This is lower than the rate of CLABSI reported from a NICU in China, where the incidence of UVC – related septicemia was 9,5%, with a rate of 13,6 per 1000 catheter – days (8).
Compared with a study performed by Advani et al. (5) on children and full term infants at a Children´s Center at The John Hopkins Hospital, who reported a rate of PICC – associated CLABSI of 2,58 instances per 1000 catheter – days, our rate of PICC – associated CLABSI of 4,1 instances per 1000 catheter – days is high. However, because of differences in immunocompetence and underlying conditions, neonates may not be directly comparable with older children. The same study also reported that the incidence of PICC – associated CLABSI was higher in children of less than one year of age (5). Therefore, this comparison may not be reliable.
A prospective cohort study performed at a NICU by Chien and coworkers (2) reported 7,2 instances of CL – related BSI per 1000 UVC – days and 13,1 instances of CL – related BSI per 1000 PICC – days. The occurrence of UVC – associated CLABSI was slightly higher in our NICU, and the occurrence of PICC – associated CLABSI was lower. Chien´s study had a much larger study population, 19 507 infants, compared with our study population of only 104 infants. It is interesting that our study, based on a small population, finds results very similar to those in the larger studies, such as the results reported by Chien´s group (2).

In agreement with previous studies (1, 2, 5 - 9), we found that CoNS is a major causative pathogen for development of CLABSI.

The main purpose of our study was to determine potential risk factors for development of CLABSI. The causes of nosocomial bloodstream infections are multifactorial (9). In addition to CL exposure there are many other factors, especially in the NICU environment, that can contribute to the development of a BSI. Therefore, it is difficult to pinpoint a true independent contribution to the development of CLABSI.
Several factors have been noted in earlier studies to have a role in the development of CLABSI. These include low GA (19), low BW (2, 20), administration of parenteral nutrition (3, 5, 11) and prolonged duration of catheter use (3, 5, 6, 12).

Stoll et al. (21) suggested an increase in CL – related BSI as GA and BW decreased. These factors did not have a significant effect on CLABSI in our study. However, because our study population had a limited range of GA and BW, we may not have had sufficient statistical power to address this particular question.

Previous studies have demonstrated an association between administration of parenteral nutrition and CLABSI (3, 5, 11). A similar relationship was not shown in our study. However, this might be explained by the predominant use of TPN in our study population as 143/159 (90%) received TPN. All the infants who developed CLABSI received TPN, and this might indicate an association with CLABSI at first sight. However, as almost all infants who did not develop CLABSI also received TPN, lack of statistical power may have prevented us from finding the putative association between TPN and development of CLABSI.

Several studies have evaluated the effect of increased duration of catheter use on the incidence of CLABSI. Consistent with previous studies, our study suggests that prolonged duration of catheter use might be an important predictor of CLABSI. However, we did not have a sufficient number of CLABSIs for analysis. Thus, any single event could have a large impact on the outcome. However, many other studies with a higher power have suggested a correlation between increasing duration of catheter use and the rate of CLABSI (3, 5, 6, 12).
The CDC´s Guidelines for the Prevention of Intravascular Catheter – Related Infections recommends a duration of UAC use of less than 5 days and an duration of UVC use of less than 14 days to reduce the incidence of CRBSIs (3).
Butler – O´Hara et al. (12) found an accelerating risk of UVC – related CLABSI after 7 days of use and a stable rate of PICC – related CLABSI for a up to 14 days of use. This study also reported that replacement of a UVC with a PICC when central venous access remains essential after 7 days, may reduce the incidence of CLABSI (12).
Our data showed that there is an increased risk for developing CLABSI that rises 16 – fold from day 5 to day 10. This was not significant but supports data presented in the literature and suggests that the risk of CLABSI increases with prolonged duration of CL use. This may warrant considering CL removal after 5 to 10 days of catheter use in effort to reduce the incidence of CLABSI. However, considering the low risk presented in our study, the need for a CL some times might be more important than the concern for development of an infection.

In our study the PICCs remained *in situ* longer compared with UACs and UVCs. Also, the PICCs only contributed 1/3 of the cases of CLABSI. A study performed by Sengupta et al. (6) showed an increase in the risk of PICC – associated CLABSI that warranted PICC replacement after 35 days of duration. Therefore, our results, suggesting CL removal after 5 to 10 days of duration may not include PICCs. Hence, additional studies are needed to identify a threshold for catheter dwell time with these three catheters individually.

Several limitations should be considered when interpreting our data. First, our study had a small sample size (n = 192). The study was conducted over a three year period, but despite this we only captured 6 events of CLABSI. Thus, we did not have a sufficient number of CLABSIs to achieve valid outcomes. Second, we included infants with multiple catheters and with multiple catheters at the same time. Hence, some infants were counted several times and the infant´s individual risk for developing CLABSI was not taken into account. Third, we did not control for other potentially confounding factors that may contribute to the development of CLABSI. These factors can be patient – related such as underlying health state, environmental such as hospitalization and intubation, and CL – related such as line material

and position. Finally, we did not have a control group. Clearly, it would have been valuable to compare the occurrence of BSIs with a population without any CL.

Our study contributes to increased knowledge of the use of CLs in a very selected population of preterm infants born at or below week $32^{6}$ of gestation. Our data confirm that CLABSI is mainly caused by CoNS and that the risk of CLABSI onset drastic increases after 5 to 10 days of CL use. Further studies on preterm infants are needed to provide better understanding of CLABSI to improve clinical practices.

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## APPENDIX

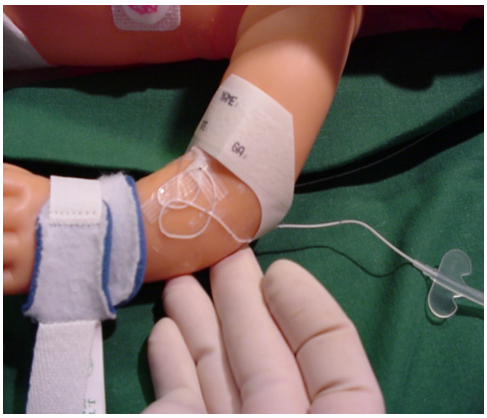
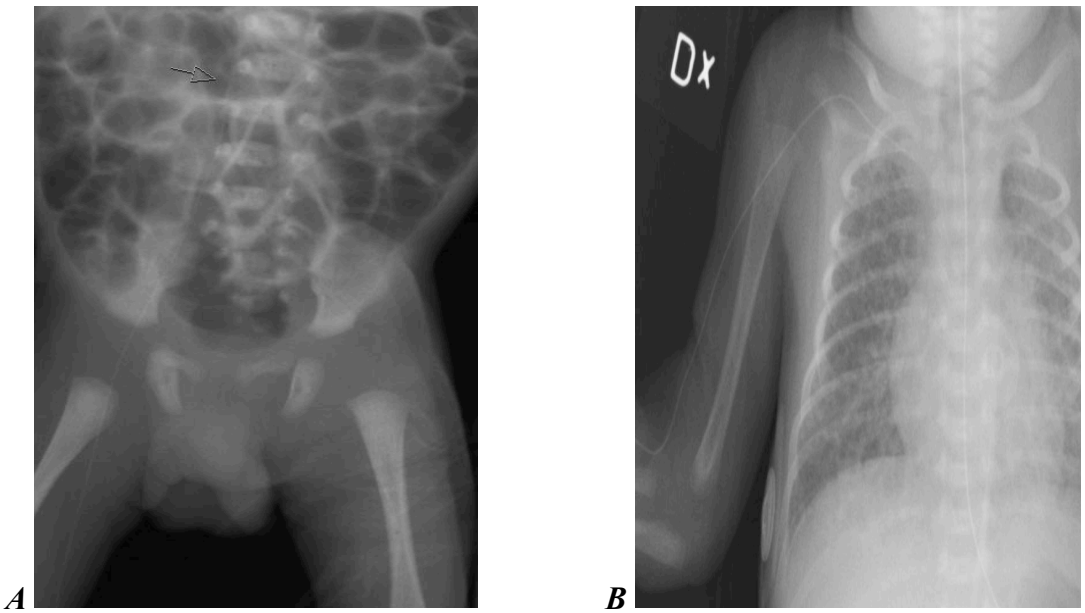


**Figure 1** A PICC placed in the left arm to show the dressing technique which allows inspection of the insertion site.




***A*** ***B***

**Figure 2** X – ray showing PICCs placed in the right leg (A) and in the right arm (B).

**Table 1** Definition of infection.

| | |
|---|---|
| Blood stream infection (sepsis) | a. ≥ 3 clinical symptoms (table 2)<br>b. 1 positive blood culture<br>c. ≥ 1 positive laboratory finding (table 3) |
| Contamination | a. 1 positive blood culture |
| Clinical sepsis | a. ≥ 2 clinical symptoms (table 2)<br>b. At least 1 positive laboratory finding (table 3)<br>c. No growth on blood culture<br>d. Treatment is introduced<br>e. No focus of infection is found |

**Table 2** Clinical symptoms of BSI (sepsis).

| | |
|---|---|
| Breathing | Breathing difficulties (grunting, flaring, retracting, tachypnea), increasing need for oxygen (desaturations), possible need for ventilatory support |
| CNS | New or increased apnea with or without bradycardia, lethargy, irritability, seizures, temperature instability |
| Circulation | Impaired peripheral circulation, hypotension, bleeding tendency |
| Gastrointestinal tract | Feeding intolerance, retentions, distended abdomen |

**Table 3** Laboratory findings of BSI (sepsis).

| | |
|---|---|
| WBC | ≤ 5 or ≥ $20 \times 10^9$/L |
| Neutrophils | < $1,5 \times 10^9$/L |
| Platelets | ≤ $100 \times 10^9$/L |
| CRP | ≥ 15 or rising |
| Blood glucose | Elevated |
| Blood gas | Metabolic acidosis (BE < − 7 mmol/L) |
| X-ray | New infiltrates |
| Cultures | Bacterial growth in blood, urine, or cerebrospinal fluid |
| Cerebrospinal fluid | Leukocytes > $30 \times 10^6$/L, or > 1 leukocyte /500 erytrocytes, glucose < 1 or < 1/3 of the blood glucose level |

**Table 4** Demographic characteristics of the study population (n = 192).

| | UAC | UVC | PICC | Total |
|---|---|---|---|---|
| Number | 76 (39,6) | 51 (26,6) | 65 (33,8) | 192 |
| GA, weeks | | | | |
| Mean ± SD | 29,6 ± 1,6 | 29,7 ± 1,6 | 28,9 ± 1,8 | 29,6 ± 1,8 |
| Maximum | 32,9 | 32,7 | 32,9 | 32,9 |
| Minimum | 26,6 | 26,9 | 25,1 | 25,1 |
| BW, grams | | | | |
| Mean ± SD | 1347 ± 348 | 1352 ± 330 | 1212 ± 320 | 1325 ± 351 |
| Maximum | 2406 | 2406 | 2274 | 2406 |
| Minimum | 720 | 913 | 733 | 720 |

Data presented as no (%) or mean, SD, maximum and minimum.

**Table 5** Duration of CL use and infant age at the time of CL insertion (n = 192)

| | UAC | UVC | PICC | Total |
|---|---|---|---|---|
| Duration of CL use, days | | | | |
| Mean ± SD | 4,3 ± 2,5 | 2,5 ± 2,5 | 7,5 ± 4,1 | 4,9 ± 3,7 |
| Maximum | 10 | 9 | 23 | 23 |
| Minimum | 0 | 0 | 0 | 0 |
| Infant age at CL insertion, days | | | | |
| Mean ± SD | 0,3 ± 0,9 | 0,1 ± 0,3 | 6,2 ± 6,8 | 2,2 ± 4,9 |
| Maximum | 5 | 1 | 38 | 38 |
| Minimum | 0 | 0 | 0 | 0 |

Data presented as mean, SD, maximum and minimum.

**Table 6** Infusions administered in UAC, UVC, PICC and in total (n = 192).

| | UAC | UVC | PICC | Total |
|---|---|---|---|---|
| TPN | 61 (80,3) | 29 (56,9) | 61 (93,8) | 151 (78,6) |
| Antibiotics (Vancomycin, Aminoglycoside, Benzyl penicillin) | 9 (11,8) | 15 (29,4) | 15 (23,1) | 39 (20) |
| Erythrocytes | 2 (2,6) | 4 (7,8) | 0 | 6 (3,1) |
| Plasma | 7 (9,2) | 3 (5,9) | 1 (1,5) | 11 (5,7) |
| Glucose (with heparin 20 U/ 100 ml) | 33 (43,4) | 24 (47,1) | 44 (67,7) | 101 (52,6) |
| NaCl (with heparin 20 U/ 100 ml) | 34 (44,7) | 5 (9,8) | 3 (4,6) | 42 (21,9) |
| Calcium | 3 (3,9) | 3 (5,9) | 0 | 6 (3,1) |
| Bicarbonate | 2 (2,6) | 1 (2,0) | 0 | 3 (1,6) |
| Isotonic amino acid solution | 7 (9,2) | 0 | 2 (3,1) | 9 (4,7) |
| Succinyl choline | 0 | 1 (2,0) | 0 | 1 (0,52) |
| Thiopental | 0 | 1 (2,0) | 0 | 1 (0,52) |
| Caffeine citrate | 0 | 0 | 2 (3,1) | 2 (1,0) |

Data presented as number (%).

**Table 7** Catheter – associated complications (n = 192).

| | UAC | UVC | PICC | Total |
|---|---|---|---|---|
| Total | 17 (22,4) | 17 (33,3) | 7 (10,8) | 41 (21,4) |
| Complications per 1000 catheter days | 55,2 | 131,8 | 14,5 | 43,7 |
| Dislodgement | 0 | 3 (5,9) | 1 (1,5) | 4 (2,1) |
| Reduced peripheral circulation | 3 (3,9) | 0 | 0 | 3 (1,6) |
| Hemorrhage | 1 (1,3) | 0 | 0 | 1 (0,5) |
| Thrombophlebitis | 1 (1,3) | 0 | 1 (1,5) | 2 (1,0) |
| Catheter occlusion | 7 (9,2) | 1 (2,0) | 4 (6,2) | 12 (6,3) |
| Inappropriate placement of the tip | 2 (2,6) | 13 (25,5) | 1 (1,5) | 16 (8,3) |
| Extravasation | 0 | 0 | 0 | 0 |
| Perforation | 0 | 0 | 0 | 0 |
| Contamination | 3 (3,9) | 0 | 0 | 3 (1,6) |

Data are presented as number (%) or events per 1000 catheter – days.

**Table 8** CLABSI and Clinically suspected sepsis (n = 159).

| | UAC | UVC | PICC | Total |
|---|---|---|---|---|
| CLABSI | 3 (4,5) | 1 (3,3) | 2 (3,2) | 6 (3,8) |
| CLABSI per 1000 catheter days | 9,4 | 8,1 | 4,1 | 6,5 |
| Clinical sepsis | 1 (1,5) | 1 (3,3) | 1 (1,6) | 3 (1,9) |

Data presented as number (%) or events per 1000 catheter days.

**Table 9** Characteristics of infants with and without CLABSI (n = 159).

| | No (%) | GA (weeks) | BW (grams) | UAC (%) | UVC (%) | PICC (%) | Duration of CL use (days) | TPN (%) | Antimicrobial therapy prior to developing CLABSI (%) |
|---|---|---|---|---|---|---|---|---|---|
| CLABSI | 6 (3,8) | 29,5 ± 1,4 | 1176 ± 149 | 3 (50) | 1 (16,7) | 2 (33,3) | 8,3 ± 2,2 | 6 (100) | 3 (50) |
| No CLABSI | 153 (96,2) | 29,3 ± 1,7 | 1282 ± 330 | 64 (40,3) | 30 (18,9) | 62 (37,7) | 5,7 ± 3,3 | 133 (83,6) | 92 (57,9) |

Data presented as no (%) or mean and SD.

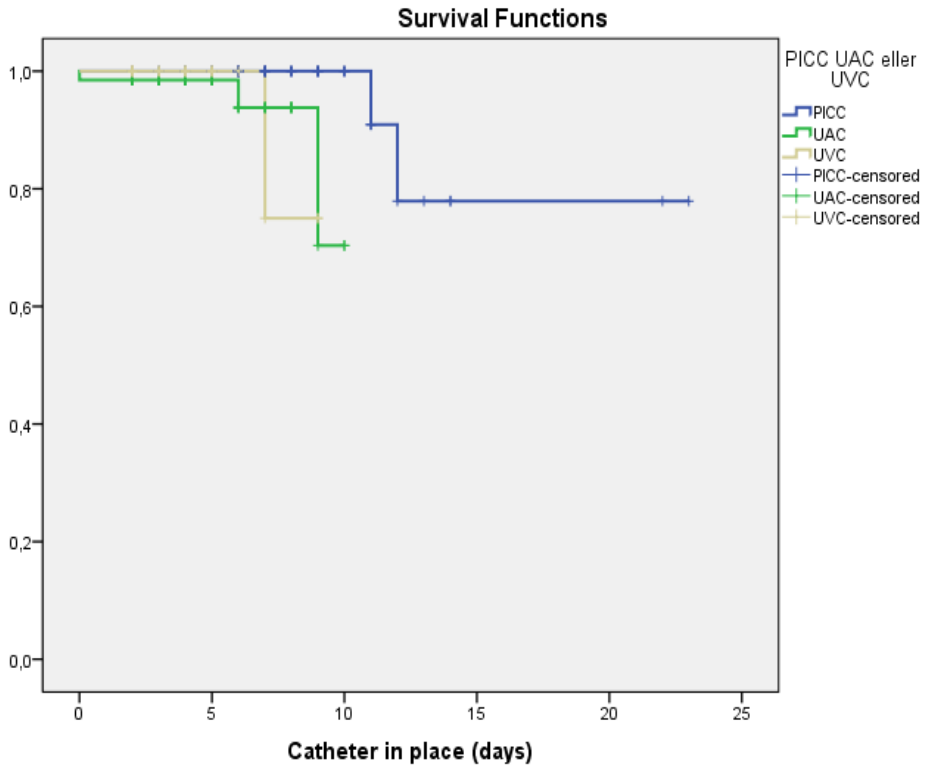



**Figure 3** Time until CLABSI in the three catheter groups UACs, UVCs and PICCs.

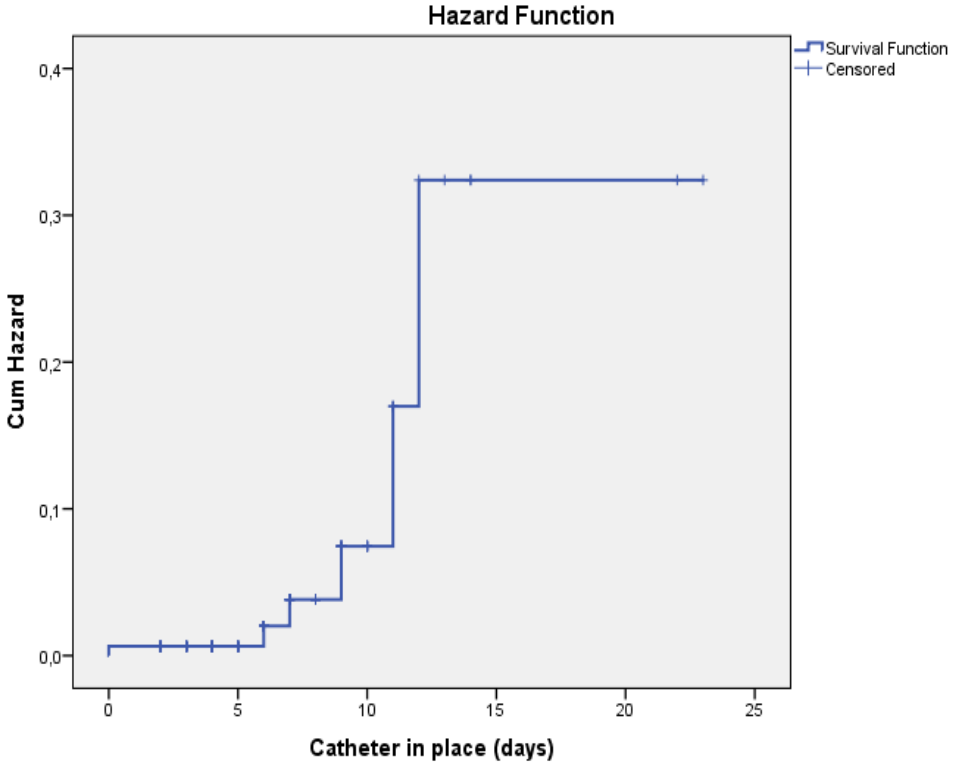



**Figure 4** The risk of developing CLABSI as a function of the duration of catheter use.