The Pennsylvania State University

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CONTINUOUS LOW-DOSE HEPARIN INFUSION FOR CATHETER-RELATED THROMBOSIS PROPHYLAXIS IN CRITICALLY-ILL CHILDREN

A Thesis in

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by

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Abstract

Background: Central venous catheters (CVC) are often required in critical care settings to provide a secure point of access for life-sustaining care. Clinical studies identify CVC presence as the single greatest risk factor for deep vein thrombosis (DVT) in children. Venous thromboembolic events (VTE) incidence rates range of critically ill children with a CVC range from 0.3-18% and 0.06-32.5/1000 catheter days depending on the population studied. Per unit protocol, the Penn State Health Children's Hospital PICU (Hershey, PA) utilizes a low dose continuous infusion of unfractionated heparin (LDUFHI) at 10 units/kg/hr as prophylaxis against CVC-related VTE and to maintain line patency. The efficacy of this approach has never been evaluated.

Objectives: To determine if LDUFH for prophylaxis results in lower incidence of CVC-related VTE, catheter dysfunction and central line-associated blood stream infection (CLABSI).

Design/Methods: To determine if the incidence of catheter-related VTE is lower than published data, a retrospective chart review was conducted utilizing the institutional electronic medical record for all patients in 2015, aged 0-17.99 years, who had a CVC during a PICU admission. Secondary objectives such as the incidence of catheter dysfunction, CLABSI, and any associated bleeding complications were analyzed.

Results: Three hundred and sixty three eligible subjects resulted in 483 central lines. Subjects who received LDUFHI has longer PICU and hospital durations with temporary catheters and femoral location being the most commonly placed. Incidence rates of VTE and CLABSI were higher in LDUFHI lines in comparison to non-LDUFHI lines (2.17 vs. 1.96 per 1000 catheter days [p=0.9], 2.48 vs. 1.96 per 1000 catheter days [p=0.77]). A subset analysis of all non-cardiothoracic surgery subjects, there were lower VTE, CLABSI and catheter dysfunction incidence rates in CVCs receiving LDUFHI (2.73 vs.4.28 per 1000 catheter days [p=0.48], 1.43 vs. 4.28 per 1000 catheter days [p=0.23], 16.67 vs 19.27 per 1000 catheter days [p=0.7]). There were no major bleeding events.

Conclusion: LDUFHI is a safe practice and does show some benefit in decreasing the incidence of catheter related VTE, CLABSIs, and catheter dysfunction. This practice should be further investigated in a multicenter, randomized clinical trial with systematic screening to fully determine if the practice is beneficial to all critically ill pediatric patients

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Acknowledgements

I owe a tremendous amount of gratitude to my beautiful and amazing wife, Laura, for it is with her unwavering support I have been able to achieve my dreams.

Continuous Low-Dose Heparin Infusion for Catheter-Related Thrombosis Prophylaxis in Critically-Ill Children

Background

Central venous catheters (CVC) are often required in critical care settings to provide essential antibiotics, blood products, total paternal nutrition, various life-sustaining medications, and hemodynamic monitoring. Their usage has improved the quality of care in pediatric patients by providing a secure point of access and minimizes the number of peripheral needle sticks. However, CVC usage is not without risks. Children can experience acute CVC-related complications such as deep venous thrombosis, pulmonary embolism, stroke or infection and chronic complications such as post-thrombotic syndrome [1-5]. Venous thromboembolic events (VTE) in pediatric patients are rare with incidence rates ranges from 0.07-0.49 per 10,000 children and are higher in hospitalized children and patients with a CVC [6-13]. Over the past 20 years, its incidence is increasing [14-16] and these complications result in increased lengths of stay (LOS) and hospital costs [17, 18]. Mortality rates from CVC-related VTE are unclear as studies reporting mortality are limited [19].

Thrombosis formation involves a combination of or all three factors of Virchow's triad (hypercoagulability, hemostasis, endothelial injury). Catheter insertion, placement, and the patient's underlying disease process produce a hypercoagulable state which contributes to Virchow's triad as follows: (1) The venous endothelial layer is directing damaged during catheter insertion exposing von Willebrand factor and triggering the clotting cascade along platelet activation and adhesion (2) the presence of the catheter creates decreased local velocity (3) increased turbulent blood flow at the site of insertion. In addition, catheter composition can contribute to the propensity of VTE formation [19].

CVCs can include non-tunnel central venous catheters, peripherally inserted central catheters (PICCs), totally implantable devices (Mediport ™) or permanent tunneled central venous catheters (Broviac ™). An exact CVC-related VTE incidence is unknown as studies report widely divergent incidence rates based upon study design and specific populations [13, 19]. Clinical studies identify CVCs as the single most important risk for DVT in children [20] and incidence rates vary between types of CVCs [6, 10, 21-23]. Non-tunneled CVCs often have the highest reported incidence rates at 1.1-18.3 % and 0.6-32.5 per 1000 catheter days [8, 23, 24]. PICCs have a reported VTE incidence of 1.9-9.3% and 1-3.85 per 1000 catheter days [6, 23-25]. Totally implantable devices and permanent tunneled lines have lower incidence rate at 3.3% and 0.1 per 1000 catheter days and 2.3% and 0.3 per 1000 catheter days respectively [23].

Multiple factors can contribute to CVC-related thrombosis. These include, vein to catheter ratio [19, 26, 27], location of placement [28-30], solutions infused through the CVC [23], duration of use [31], and underlying hypercoagulability. While no studies have directly measured the role of ultrasound during CVC placement decreasing VTE risk, its use decreases number of attempts during placement [32] and could minimize endothelial injury.

Aside from CVC presence, specific pediatric populations, ages [23, 33, 34] or diagnoses are at increased risk for VTE [14, 15, 23, 28, 34-37]. Patients who require mechanical ventilation [12, 15] and longer PICU admission length of stays [38] are at increased risk also. Pediatric patients with prothrombotic conditions may be at increased risk for VTE in the presence of a CVC but studies are conflicting [39-41]. Studies have demonstrated that critically ill children are at a significantly increased risk for VTE [8, 42, 43]. Current incidence estimates for VTE in critically ill children range from 0.3-18% and 0.06-32.5 per 1000 catheter days [8, 31, 33, 38, 44-47].

Prevention of catheter-related thrombosis with prophylactic anticoagulants, such as unfractionated heparin, low molecular weight heparin or warfarin, have been tried in several studies and the majority of studies in pediatric populations do not demonstrate a benefit [9, 10, 48-52]. Several studies have shown anticoagulation prophylaxis to be beneficial in specific high risk populations [53-55]. These treatments can also have complications such as bleeding or heparin-induced thrombocytopenia (HIT). Therefore, the most recent CHEST guidelines do not recommend anticoagulation for line maintenance [20]. Despite this, *Clarke et al*. reported that nearly 50% of surveyed PICUs utilize heparin prophylaxis to prevent CVC-associated complications [56]. However, there is no standard of care across pediatric intensive care units (PICU) [57, 58].

VTE can clinically manifest as edema, erythema, warmth, pain or tenderness to palpitation or compression and can be diagnosed using a ultrasound. If a VTE is diagnosed, current consensus recommendations are for the CVC to be removed if nonfunctioning or no longer required [20]. Patients also require ongoing anticoagulation therapy with either low molecular weight heparin (LMWH) or vitamin K antagonist therapy for at least three months [20].

Besides VTE, fibrin sheaths or deposits cause catheter dysfunction rendering the line unusable [40, 59]. Both VTE and catheter dysfunction can lead to delays in patient care and could affect patient moridity and mortality. The most common complication associated with PICC use was obstruction with 6% (71/610) and 6.6/1000 catheter days and 52% received tPA [21]. Usage of tPA for catheter obstruction in critically ill children has limited reported data but it is estimated to occur in about 12% of CVCs [60, 61].

Central line associated bloodstream infections (CLABSIs) is a third complication of CVC use. Multiple factors place patients at risk for CLABSIs and include the following: catheter type, anatomical locations, usage of tPA, and placement at external facilities all which have different incidence rates [22, 61-63]. CVCs requiring tPA for obstruction were at higher risk for CLABSIs and episodes occur earlier in comparison to CVC not requiring tPA administration [61]. *Abdelkefi et al*. demonstrated a significant decrease in CLABSI without an increase in bleeding complications utilizing low-dose unfractionated heparin infusion (LDUFHI) at 100 unit/kg/day [64]. Furthermore, nosocomial blood stream infections result in significantly higher healthcare costs [65, 66].

Overall, PICUs have higher reported rates of nosocomial blood stream infections when compared to other units and those with longer durations of stay are at increasing risk [67, 68].

Current incidence rate estimates of PICU acquired blood stream infections are 8.4% (15.17 per 1000 bed days) and longer durations of stay increase probability of infection [67]. More specifically, CVC associated CLABSI incidence rates in PICU settings vary between 6.5% and 2.31-14.4 per 1000 catheter days [63, 68-72]. Furthermore, critically ill patients with CVCs placed at external institutions have increased risk for CLABSI (HR = 2.65) [63]. Although study populations differ, PICC associated CLABSI incidence rates range 2.6-5.7% and 1.77-1.8 per 1000 catheter days [21, 61, 73, 74]. These rates are similar to reported tunneled line CLABSI rates (1.7-5 per 1000 catheter days) and totally implantable venous access devices (1.45-3.5 per 1000 catheter days) [75-77].

Besides the possible benefit of prevention of catheter-related thrombosis, other advantages of using anticoagulants for CVC maintenance include increased duration of catheter use and a decrease in CLASBIs and catheter dysfunction.

Multiple studies have assessed the efficacy of low dose heparin infusion and the majority do not demonstrate benefit [9, 31, 78]. Thus, we attempt to determine if the usage of LDUFHI at 10 units/kg/hr in critically ill children to maintain catheter patency results in a lower incidence of VTE, CLABSI and catheter dysfunction without increasing bleeding complications in comparison to historically reported data.

Specific Aims/Objectives

a) To determine if the continuous low-dose unfractionated heparin infusion through central venous catheters decreases the incidence of central venous catheter-related venous thromboembolic events in pediatric critical care patients.
b) To study complications associated with continuous infusion of low-dose heparin.
c) To measure the incidence of catheter dysfunction and central line-associated blood stream infections with continuous infusion of low dose heparin prophylaxis.

Relevance to Hematology

CVCs are the single greatest risk factor for VTE in the pediatric population. With advancements in pediatric care, the utilization of a CVC has become the standard of care in critically ill children. If a continuous low-dose heparin infusion demonstrates a reduction in CVC-related VTE, catheter dysfunction, and CLASBIs, without an increase in the risk of bleeding or other complications, it could greatly impact the care of many pediatric patients who are reliant on CVCs for their critical, life-threatening conditions. This study could improve the quality of care provided and change current guidelines for catheter maintenance and thromboprophylaxis.

Methods

The Penn State Health Children's Hospital Pediatric Intensive Care Unit (PICU) is an 18 bed, level I trauma center in a tertiary medical center. It provides care for pediatric patients with critical illnesses, post-operative care including cardiothoracic and neurosurgery, and pediatric trauma. A retrospective chart review involving all admissions to the PICU from 1/1/2015 to

12/31/2015 was performed. Complications associated with CVCs and anticoagulation therapy such as thrombus, central line infections, symptomatic bleeding, heparin-induced thrombocytopenia, and catheter dysfunction was assessed. Study was approved by the Penn State Health Institutional Review Board (STUDY00005505).

a. Patient Demographics

The study included all patients ages 0-17.99 years that had a CVC during admission to the PICU during the 2015 calendar year. Patient demographic information included age, BMI, sex, personal and family history of VTE, admitting diagnosis, duration of PICU and hospital admission, and reason for line insertion.

b. Exclusion Criteria

i. Age $\geq$ to 18 years at time of PICU admission
ii. Conditions which required anticoagulation (Extracorporeal membrane oxygenation, mechanical heart valves, etc.)
iii. Other form of anticoagulation for DVT prophylaxis
iv. Presence of any VTE (DVT, PE or stroke) at admission to PICU

c. Line Characteristics

Central catheters were defined all non-tunneled central venous catheters (NT-CVC), PICCs, totally implantable venous access devices (e.g. Mediport ™), and tunneled CVCs (e.g. Broviac ™). Details about each CVC placed was obtained and included the location of placement, number of attempts, French size, days of total use, days until complication (VTE, CLABSI, catheter dysfunction), the reason for insertion, if an ultrasound was utilized during insertion, the level of training of medical staff member placing the line, and number of lumens. All anticoagulation therapy was reviewed.

All unused central line lumens receive 30 unit heparin flushes every 8 hours and have central line caps and tubing replaced every 96 hours.

d. Low-dose Unfractionated Heparin Prophylaxis (LDUFHI)

LDUFHI was defined as an infusion rate between 5-15 unit/kg/hr through a central line. Duration of usage and rate were recorded.

e. Catheter-related venous thromboembolic event (VTE)

A catheter-related thrombus was defined as an acute thrombosis on venous ultrasonography with Doppler that occurred in the same anatomic location as the CVC. This definition has been used in the published literature [79].

f. Central Line Associated Blood Stream Infection (CLABSI)

Catheter line infections were defined as per the Center for Disease Control and Prevention National Healthcare Safety Network (NHSN) [80]:

i. Central line that has been in place for more than two consecutive calendar days following the first access of the central line, in an inpatient location, during the current admission. Line is considered eligible for CLABSI events until the day after removal from the body or patient discharge, whichever comes first.

ii. Laboratory confirmed bloodstream infection where an eligible bloodstream infection organism is identified and an eligible central line is present

iii. A primary blood stream infection in a patient that had a central line within the 48- hour period before the development of the blood stream infection from an organism not included on the NHSN common commensal list and is not related to an infection at another site.

iv. Patient of any age has at least one of the following signs or symptoms: Fever >38^{0}C, chills, or hypotension AND organism is not related to an infection at another site AND same HSN commensal organism from two or more blood specimens collected on separate occasions

g. CVC Dysfunction

Dysfunction of the CVC was defined as the inability of the catheter to flush, aspirate blood, or deliver medications [7, 81, 82].

h. Bleeding complications

Bleeding complications were classified as major or non-major as previously defined by the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis [83]. Non-major bleeding was further divided into clinically relevant and non-relevant bleeding. Clinical relevance was defined if treatment was directed for the bleeding or a change in anticoagulation was necessary.

i. Heparin-induced thrombocytopenia

Heparin induced thrombocytopenia (HIT) was defined along with previously published definitions [64].

Statistical Analysis

The study samples the patient's main demographic and clinical characteristics will be summarized using descriptive statistics such as means or medians (standard deviations) for quantitative variables and proportions for categorical variables. The main outcome is the incidence of central line related VTE, which is a binary variable. The rate of CVC related thrombosis from the study sample will be reported with its 95% confidence interval, which will then be compared to a national average. Then the main outcome variable will be correlated to possible predictors (some factors such as patient's age, BMI, location of CVC,

personal and family history of VTE, and other medical factors of interest). Two-sample T-test or nonparametric Wilcoxon Rank-Sum test, or Chi-square test will be used when appropriate. The other outcome variables include the incidence of complications with heparin prophylaxis, and the incidence of catheter dysfunction with heparin prophylaxis, both of which will be analyzed in a similar statistical manner. All analysis will be done using statistical software SAS version 9.4 or higher (SAS Institute, Cary, NC, USA). The significance level to be used is 0.05 and all tests will be two-sided.

The number of admissions averages 650 per year at PSCH PICU and about 67% have a CVC president during an PICU admission. The estimated clot incidence rate is about 10-15%. If we set the clot incidence as 13%, and based on the sample size of n=800 (one-year data in HMC), then we can get a 95% confidence interval with a marginal of error equals to ±2.3%. To compare to a national average clot incidence rate of 18%, we have more than 97% statistical power in detecting the difference.

Study data were collected and managed using REDCap electronic data capture tools hosted at Penn State College of Medicine [84]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Results

A total of 412 subjects were identified of which a total of 49 were excluded for age (n = 18), duplicate records (n = 9), ECMO (n = 4), no line record (n = 10), no line in PICU (n = 1), mechanical heart valve (n = 1), thrombosis on arrival (n = 3) or received low molecular weight heparin (LMWH) for VTE prophylaxis (n = 2) or for treatment (n = 1) (Figure 1). Of the resultant 363 eligible patients, 234 (56.8%) were male and the median age was 1.8 years (range 0-17.99). Subjects with catheters receiving LDUFHI were younger at time of admission (1.15 vs 3.1 yrs, $p<0.001$). The subjects accounted for 406 PICU admissions with 43 subjects having multiple admissions (26 with two admissions, 14 with three admissions and 3 with four admissions).

Overall, the median PICU length of stay was 5 days (range 0-369) and a median hospital length of stay was 10 days (range 0-637). Subjects with LDUFHI had longer PICU courses and hospitalizations respectively (8 vs. 4 days, $p<0.001$ and 14 vs. 7 days, $p<0.001$) (Table 1). The majority of subjects (69.8%) required mechanical ventilation during their hospitalization with a larger majority of subjects with LDUFHI requiring mechanical ventilation in comparison to subjects without LDUFHI (78.6 vs. 58%, $p<0.001$) (Table 1). A cardiac diagnosis was the most common reason for PICU admission (40.2%) but LDUFHI and non-LDUFHI subjects significantly differed in their admission diagnoses ($p<0.001$) (Table 1). Only 8 subjects had a personal history of VTE prior to PICU admission.

A total of 483 central line events during PICU admissions were recorded for a mean of 1.33 central lines per subject. Non-tunneled CVCs were the most common (307, 63.6%) followed by tunneled CVCs (90, 18.6%), PICCs (40, 8.3%), totally implantable devices (30, 6.2%), Broviacs (13, 2.7%, and dialysis catheters (3, 0.6%) (Table 2). There were a total of 4245 catheter days of which 3226 days (76%) were with LDUFHI administration and 276 (57.1%) of central lines received LDUFHI.

Overall, the median central line duration was 4 days (mean 9.07 days, range 0-122). LDUFHI catheters had longer median durations compared to non-LDUFHI catheters (6 vs. 3 days, $p<0.001$) (Table 2). Non-LDUFHI catheters most commonly were placed under ultrasound guidance (59.9% vs. 46.4%, $p=0.003$). The overall median catheter size was 4 Fr as well in the LDUFHI and non-LDUFHI groups. There was no statistical difference in number of attempts between LDUFHI and non-LDUFHI groups ($p=0.22$).

All nine VTE events were DVTs for an overall incidence rate of 1.86% and 2.12 per 1000 catheter days (Table 3). Overall, the median length of time until VTE was 5 days (mean 8.11 days, range 1-35). Seven of the nine (77.7%) VTEs involved catheters receiving LDUFHI. There was no statistical difference in VTE incidence per 1000 catheter days between catheters with or without LDUFHI exposure (2.17 vs. 1.96, $p=0.9$) (Table 3). Neither of the two subjects who did not receive LDUFHI required mechanical ventilation whereas 6/7 (85.7%) receiving LDUFHI required mechanical ventilation. Only a single subject experienced a VTE prior to their first PICU admission.

A total of 10 CLABSI events occurred in 8 subjects (three CLABSIs occurred in a single subject) for an overall incidence rate of 2.1% and 2.35 per 1000 catheter days (Table 3). The majority of CLABSI events (8/10) occurred in catheters receiving LDUFHI. There was no statistical difference in CLABSI incidence per 1000 catheter days between catheters with or without LDUFHI exposure (2.48 vs. 1.96, $p=0.77$). The median length of time until the CLABSI event was 27.5 days (mean 27.8 days, range 1-61) (Table 3). The majority of CLABSIs (6/8) occurred in subjects younger than one year of age. Non-tunneled CVCs were the most common catheter (50%) with femoral insertion (40%) and right sided placement (90%) being the most common.

Catheter dysfunction occurred in a total of 67 catheters and mean length of time until administration was 8.11 days (median 5 days, range 1-35). There was no statistical difference in catheter dysfunction incidence per 1000 catheter days between catheters with or without LDUFHI exposure (15.5 vs. 16.78, $p=0.79$) (Table 3).

A subset analysis, excluding subjects with a primary admission diagnosis of a cardiothoracic etiology, was performed. Of the 363 initial eligible subjects, 125 were excluded for a primary diagnosis of cardiothoracic surgery (Figure 1). The resultant 238 subjects accounted for 334 CVCs for a mean of 1.4 CVCs per subject. The majority of CVCs received LDUFHI (69%). The overall median age was 3.75 years with the subjects receiving LDUFHI were significantly younger at admission (2.5 vs. 5.3 years, $p=0.002$). Subjects receiving LDUFHI had longer median PICU durations and hospitalizations in comparison to subjects who did not receive LDUFHI (6 vs. 3 days, $p<0.001$ and 13 vs. 8 days, $p=0.009$) (Table 4). The

reason for admission was significantly different between LDUFHI and non-LDUFHI groups with respiratory and other causes being the most common respectively (Table 4). Seventy-three percent of subjects required mechanical ventilation with a larger frequency within the LDUFHI subjects (75.8% vs 66%, p=0.06) (Table 4).

Non-tunneled CVCs remained the most commonly placed catheter (51.2%) followed by tunneled CVCs (25.7%), PICCs (10.8%), totally implantable devices (7.8%), Broviacs (3.6%), and dialysis catheters (0.9%) (Table 5). Femoral insertion was the most frequent overall (56.2%) and the location of placement did significantly differ between the two groups (p=0.001) (Table 5). Right sided placement was more commonly performed. Ultrasound guidance was utilized in 36.8% of placements which was decreased from the 52.2% in the initial analysis. The included catheters resulted in 2567 days of use of which 2100 days (81.8%) were included in the LDUFHI group.

Median line duration was 4 days with longer durations in the LDUFHI group (5 vs. 3 days, p<0.001) (Table 6). Non-tunneled CVCs, tunneled CVCs, and totally implantable devices receiving LDUFHI had longer durations of use versus non-LDUFHI lines (6 vs. 3 days, p<0.001; 3 vs. 2 days, p=0.03; 6 vs. 2 days, p=0.04) (Table 6).

There were 7 VTEs events for an incidence rate of 2.1% and 2.73 per 1000 catheter days. While the LDUFHI group experienced more VTEs (5 vs 2), there was a lower incidence rate (2.73 vs. 4.28 per 1000 catheter days, p=0.48). The overall median time to a VTE event was 4 days and was later in the LDUFHI group (5 vs. 1 days, p=0.13) (Table 8). This trend was seen in the LDUFHI NT-CVC and PICC groups but did not reach statistical significance (Table 8). LDUFHI NT-CVCs and PICCs did demonstrate lower incidence rates in comparison to non-LDUFHI lines but did not reach statistical significance (2.21 vs. 4.88 per 1000 catheter days, p=0.92 and 1.46 vs. 12.82 per 1000 catheter days, p=0.39) (Table 9). The femoral vein was the most common insertion location and there was a nearly even distribution between line types (Table 11).

There were 5 CLABSI events for an incidence rate of 1.5% and 1.9 per 1000 catheter days. Only three events occurred in the LDUFHI group which resulted in a lower incidence rate in comparison to non-LDUFHI catheters (1.43 vs. 4.28 per 1000 catheters days, p=0.23) (Table 7). The overall median time to a CLABSI event was 6 days with a longer time to event in the LDUFHI group (18 vs. 4 days, p=0.59) (Table 8). Further subset line analysis was not possible as events did not involve both LDUFHI and non-LDUFHI within the same line type (Table 8). Non-LDUFHI NT-CVCs and PICCs had lower incidence rates in comparison to LDUFHI lines but did not reach statistical significance (0 vs. 2.21 per 1000 catheter days, p=0.66 and 0 vs. 1.46 per 1000 catheter days, p=0.9) (Table 9). Both non-LDUFHI CLABSI events occurred in Broviac lines with the LDUFHI events occurring in non-tunneled CVCs (n=2) and a PICC (n=1) (Table 12).

Forty-four episodes of catheter dysfunction occurred with 35 of the episodes occurring in the LDUFHI group. The overall incidence of dysfunction was 13.1% and 17.14 per 1000 catheter days (Table 7). There was a lower incidence rate of dysfunction in the LDUFHI versus the non-LDUFHI group (16.67 vs. 19.27 per 1000 catheter days, p=0.7). The overall median

time to catheter dysfunction was 7 days with episodes occurring later in non-LDUFHI groups (5 vs. 9 days, p=0.69) (Table 8). This trend was evident only in the NT-CVC group and did reach statistical significance (p=0.04) (Table 8). Other line types (T-CVC, PICC, totally implantable devices) demonstrated a trend of greater time to dysfunction in the LDUFHI group (Table 8).

There were no episodes of major bleeding and three LDUFHI subjects experienced non-clinically significant bleeding. There were zero episodes of HIT.

Discussion

The majority of the non-LDUFHI subjects were admitted to the PICU in a planned fashion for perioperative care for cardiothoracic procedures. It is our institution's practice to place an ultrasound guided, non-tunneled CVC in the right internal jugular vein at the time of surgery. These catheters do not routinely receive LDUFHI and are commonly removed after 3 days. This is in contrast to many of the non-cardiothoracic surgery PICU admissions which are unexpected and rely on catheter placement in less ideal conditions. These subjects often have extended and more complicated PICU courses requiring longer catheter durations and are at increased risk for complications (VTE, CLABSI, and catheter dysfunction). Therefore, a subset analysis, excluding cardiothoracic subjects, was performed to determine if LDUFHI was beneficial to acutely ill children.

When focusing on the subset of subjects that excludes cardiothoracic subjects, incidence rates of VTE, CLABSIs and catheter dysfunction are lower with LDUFHI. This trend was evident in the most commonly utilized CVCs (NT-CVCs and PICCs) although did not reach statistical significance. LDUFHI CVCs were more commonly placed in femoral locations and subjects receiving LDUFHI had significantly longer PICU length of stays and hospitalizations. It is unknown if those subjects receiving LDUFHI were more critically ill but a larger percentage required mechanical ventilation during their hospitalization. Longer hospitalizations, femoral placement and the need for mechanical ventilation have been shown to be risk factors for CVC-related VTEs and CLABSIs [12, 15, 28, 38, 45, 67, 68]. This could attribute for the overall higher number of complications in the LDUFHI cohort. However, LDUFHI had lower rates of complications overall despite multiple risk factors.

CVCs receiving LDUFHI has significantly longer durations of use. The practice of LDUFHI could be beneficial in prolonging CVC duration especially in patients with extended PICU admissions, more critical illnesses or poor vascular access. By reducing the need for CVC replacement, CVC-associated complications could be minimized also. This measure could make dramatic differences in the morbidity, mortality, length of stay and cost of hospitalizations.

Major bleeding events in children receiving anticoagulation are rare [85]. Within our study, there were only three episodes of non-clinically significant minor bleeding. This demonstrates that this practice is safe even in critically ill children.

Our study does encompass a larger number of subjects and CVCs than some previously published reports [29, 30, 45]. Furthermore, it reports complication incidence rates in a more accurate way by using measuring per catheter days.

Within this study population, there were a lower number of some CVC complications (VTE and CLABSI) and similar rates compared to published reports [43, 46, 61, 67]. This could be attributed to the PICU's high quality clinical care, daily assessment on CVC necessity and nursing driven protocols. As this was a single institution study, all CVCs received the same comprehensive standard of care for central line maintenance. This minimizes any variables between the care of LDUFHI and non-LDUFHI CVCs.

As LDUFHI is the standard of care in our PICU, it limits the number of non-LDUFHI catheters to serve as a comparison group. We are actively working on collaborations with other institutions that do not practice LDUFHI to increase our comparative sample.

As the study is a retrospective chart review, our data are limited to the accuracy of the medical record and some complications could not have been recorded. However, the three main complications of CVC use (VTE, CLABSI, catheter dysfunction) should be accurately captured as each relies on specific testing or medication administration if suspected or proven and must be recorded in the electronic medical record.

The retrospective nature of this study does not allow for the capture of asymptomatic VTEs. In a previous study utilizing systematic VTE screening, Faustino *et al*. demonstrated that 16% of children with a CVC had an asymptomatic VTE [33]. This rate is much higher than other studies and highlights the limitation of studies with only symptomatic screening. It is likely that some of our subjects had asymptomatic and undiagnosed VTEs but its exact incidence is unknown.

Overall, LDUFHI is a safe practice and does show some benefit in decreasing the incidence of catheter related VTE and CLABSIs. This practice should be further investigated in a multicenter, randomized clinical trial with systematic screening to fully determine if the practice is beneficial to all critically ill pediatric patients or if any specific groups may receive benefit.

Grant Support

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APPENDIX

Figure 1. Eligible Subjects

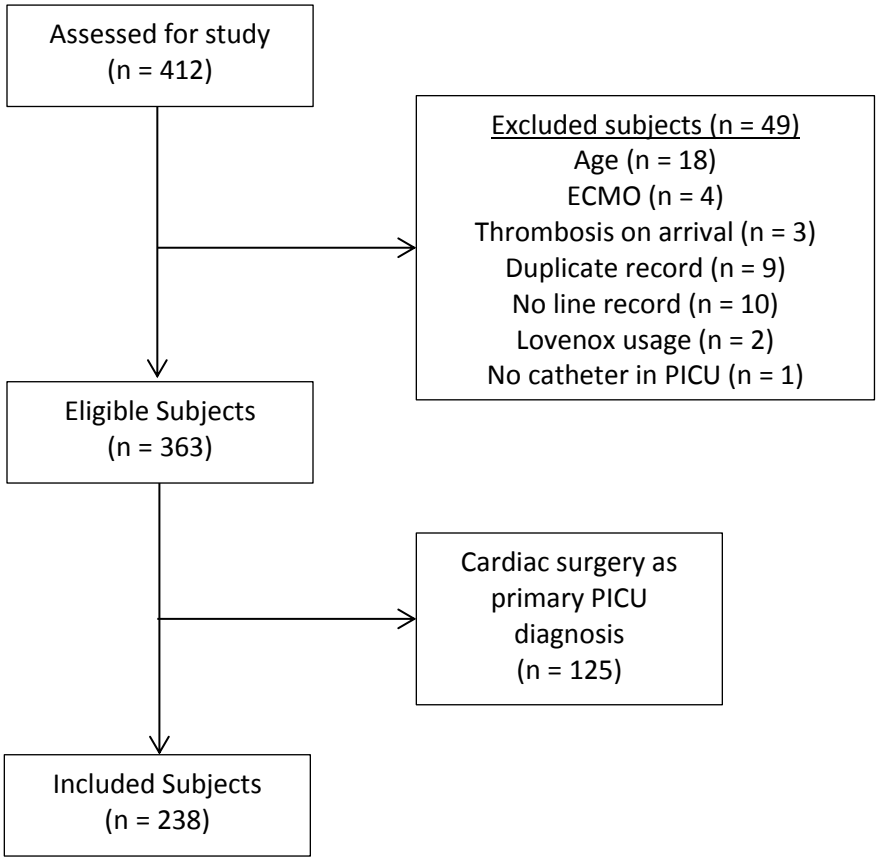

Table 1. Subject Demographics

	Overall (n = 483)	**LDUFHI (n = 276)**	**No LDUFHI (n = 207)**	**p-value**
Age (yrs)	1.80 (0.30, 8.80)	1.15 (0.20, 7.10)	3.10 (0.50, 10.40)	<0.001
BMI	16.25 (13.90, 19.15)	15.80 (13.50, 19.00)	16.90 (15.20, 19.50)	0.003
Duration of PICU admission (days)	5.00 (3.00, 13.00)	8.00 (3.00, 21.50)	4.00 (2.00, 6.00)	<0.001
Duration of hospital admission (days)	10.00 (5.00, 25.00)	14.00 (7.00, 35.50)	7.00 (3.00, 14.00)	<0.001
Mechanical Ventilation				
Yes	337 (69.8%)	217 (78.6%)	120 (58.0%)	<0.001
No	146 (30.2%)	59 (21.4%)	87 (42.0%)	
Reason for PICU admission				
Infection	24 (5.0%)	14 (5.1%)	10 (4.8%)	<0.001
Respiratory	125 (25.9%)	97 (35.1%)	28 (13.5%)	
Cardiac	194 (40.2%)	91 (33.0%)	103 (49.8%)	
Autoimmune	2 (0.4%)	1 (0.4%)	1 (0.5%)	
Trauma	25 (5.2%)	7 (2.5%)	18 (8.7%)	
Cancer	5 (1.0%)	4 (1.5%)	1 (0.5%)	
Neurological	53 (11.0%)	37 (13.4%)	16 (7.7%)	
Other	55 (11.4%)	25 (9.1%)	30 (14.5%)	
Personal History of VTE	8 (2.2%)			

Table 2. Line Characteristics

	Overall (n = 483)	LDUFHI (n = 276)	No LDUFHI (n = 207)	p-value
Line type				
Non-tunneled CVC	307 (63.6%)	172 (62.3%)	135 (65.2%)	<0.001
Tunneled CVC	90 (18.6%)	69 (25.0%)	21 (10.1%)	
PICC	40 (8.3%)	27 (9.8%)	13 (6.3%)	
Totally implantable device	30 (6.2%)	6 (2.2%)	24 (11.6%)	
Broviac	13 (2.7%)	1 (0.4%)	12 (5.8%)	
Other	3 (0.6%)	1 (0.4%)	2 (1.0%)	
Duration of line (days)	4.00 (2.00, 10.00)	6.00 (3.00, 12.00)	3.00 (2.00, 6.00)	<0.001
Location of placement				
Femoral	200 (41.8%)	156 (56.5%)	44 (21.8%)	<0.001
Jugular	193 (40.4%)	67 (24.3%)	126 (62.4%)	
Basilic	51 (10.7%)	32 (11.6%)	19 (9.4%)	
Subclavian	2 (0.4%)	1 (0.4%)	1 (0.5%)	
Brachial	26 (5.4%)	17 (6.2%)	9 (4.5%)	
Other	6 (1.3%)	3 (1.1%)	3 (1.5%)	
Side				
Left	111 (23.7%)	68 (25.0%)	43 (21.8%)	0.64
Right	358 (76.3%)	204 (75.0%)	154 (78.2%)	
Catheter size (Fr)	4.00 (4.00, 5.50)	4.00 (4.00, 5.50)	4.00 (4.00, 5.50)	0.18
Ultrasound Guided				
Yes	252 (52.2%)	128 (46.4%)	124 (59.9%)	0.003
No/Unreported	231 (47.8%)	148 (53.6%)	83 (40.1%)	
Number of Attempts				
1	164 (66.4%)	130 (68.8%)	34 (58.6%)	0.15
>1	83 (33.6%)	59 (31.2%)	24 (41.4%)	
Lumens				
1	45 (9.3%)			
2	306 (63.3%)			

3	123 (25.4%)			
Unknown	9 (1.8%)			
Indication for insertion				
Hemodynamic monitoring				
Yes	165 (34.2%)	130 (47.1%)	35 (16.9%)	<0.001
No	318 (65.8%)	146 (52.9%)	172 (83.1%)	
Difficult venous access				
Yes	212 (43.9%)	167 (60.5%)	45 (21.7%)	<0.001
No	271 (56.1%)	109 (39.5%)	162 (78.3%)	
Sclerotic drug				
Yes	96 (19.9%)	72 (26.1%)	24 (11.6%)	<0.001
No	387 (80.1%)	204 (73.9%)	183 (88.4%)	
Nutrition				
Yes	28 (5.8%)	21 (7.6%)	7 (3.4%)	0.05
No	455 (94.2%)	255 (92.4%)	200 (96.6%)	
Chemotherapy				
Yes	12 (2.5%)	2 (0.7%)	10 (4.8%)	0.004
No	471 (97.5%)	274 (99.3%)	197 (95.2%)	

Table 3. Central venous catheter complications

	Overall (n = 483)	**LDUFHI (n = 276)**	**No LDUFHI (n = 207)**	**p-value**
Complication (per 1000 catheter days)				
VTE	2.12	2.17	1.96	0.9
CLABSI	2.36	2.48	1.96	0.77
Dysfunction	15.78	15.50	16.78	0.79

Table 4. Subject demographics (Cardiothoracic surgery excluded)

	Overall Median (Q1, Q3) or n (%)	**LDUFHI Median (Q1, Q3) or n (%)**	**No LDUFHI Median (Q1, Q3) or n (%)**	**P-value* (Heparin vs No Heparin)**
Age	3.75 (0.70, 11.30)	2.50 (0.50, 10.10)	5.30 (1.50, 13.80)	0.002
BMI	17.40 (15.30, 20.50)	17.00 (15.00, 20.10)	18.40 (16.00, 20.90)	0.01
Duration of PICU admission	5.00 (2.00, 13.00)	6.00 (3.00, 15.00)	3.00 (2.00, 7.00)	<0.001
Duration of hospital admission	10.50 (5.00, 24.00)	13.00 (6.00, 29.00)	8.00 (4.00, 18.00)	0.009
Mechanical ventilation				
Yes	243 (72.8%)	175 (75.8%)	68 (66.0%)	0.06
No	91 (27.2%)	56 (24.2%)	35 (34.0%)	
Reason for admission				
Infectious	24 (7.2%)	16 (6.9%)	8 (7.8%)	<0.001
Respiratory	125 (37.4%)	102 (44.2%)	23 (22.3%)	
Cardiac	45 (13.5%)	35 (15.2%)	10 (9.7%)	
Autoimmune	2 (0.6%)	1 (0.4%)	1 (1.0%)	
Trauma	25 (7.5%)	7 (3.0%)	18 (17.5%)	
Cancer	5 (1.5%)	4 (1.7%)	1 (1.0%)	
Neurological	53 (15.9%)	38 (16.5%)	15 (14.6%)	
Other	55 (16.5%)	28 (12.1%)	27 (26.2%)	

Table 5. Line Characteristics (Cardiothoracic surgery excluded)

	Overall Median (Q1, Q3) or n (%)	LDUFHI Median (Q1, Q3) or n (%)	No LDUFHI Median (Q1, Q3) or n (%)	P-value* (Heparin vs No Heparin)
Line types				
Non-tunneled CVC	171 (51.2%)	123 (53.3%)	48 (46.6%)	<0.001
Tunneled CVC	86 (25.7%)	65 (28.1%)	21 (20.4%)	
PICC	36 (10.8%)	27 (11.7%)	9 (8.7%)	
Totally implantable device	26 (7.8%)	10 (4.3%)	16 (15.5%)	
Broviac	12 (3.6%)	3 (1.3%)	9 (8.7%)	
Other	3 (0.9%)	3 (1.3%)	0 (0.0%)	
Duration of line	4.00 (2.00, 10.00)	5.00 (3.00, 11.00)	3.00 (1.00, 6.00)	<0.001
Location				
Femoral	185 (56.2%)	146 (63.5%)	39 (39.4%)	0.001
Jugular	67 (20.4%)	34 (14.8%)	33 (33.3%)	
Subclavian	44 (13.4%)	26 (11.3%)	18 (18.2%)	
Brachial	1 (0.3%)	1 (0.4%)	0 (0.0%)	
Basilic	26 (7.9%)	19 (8.3%)	7 (7.0%)	
Other	6 (1.8%)	4 (1.7%)	2 (2.0%)	
Side				
Left	100 (31.0%)	63 (27.9%)	37 (38.1%)	0.07
Right	223 (69.0%)	163 (72.1%)	60 (61.9%)	
Indication for insertion				
Hemodynamic monitoring				
Yes	145 (43.4%)	113 (48.9%)	32 (31.1%)	0.002
No	189 (56.6%)	118 (51.1%)	71 (68.9%)	
Difficult venous access				
Yes	189 (56.6%)	147 (63.6%)	42 (40.8%)	<0.001
No	145 (43.4%)	84 (36.4%)	61 (59.2%)	
Sclerotic drug				
Yes	87 (26.0%)	67 (29.0%)	20 (19.4%)	0.07
No	247 (74.0%)	164 (71.0%)	83 (80.6%)	
Nutrition				
Yes	24 (7.2%)	19 (8.2%)	5 (4.9%)	0.27
No	310 (92.8%)	212 (91.2%)	98 (95.2%)	
Chemotherapy				
Yes	11 (3.3%)	2 (0.9%)	9 (8.7%)	<0.001
No	323 (96.7%)	229 (99.1%)	94 (91.3%)	
Ultrasound guided				
Yes	123 (36.8%)	86 (37.2%)	37 (35.9%)	0.82
No/unknown	211 (63.2%)	145 (62.8%)	66 (64.1%)	
French size	4.00 (4.00, 5.50)	4.00 (4.00, 5.50)	5.00 (4.00, 6.60)	0.05
Number of attempts				
1	148 (66.7%)	117 (67.6%)	31 (63.3%)	0.95
2	45 (20.3%)	33 (19.1%)	12 (24.5%)	
3	16 (7.2%)	13 (7.5%)	3 (6.1%)	
4	4 (1.8%)	3 (1.7%)	1 (2.0%)	
5	6 (2.7%)	5 (2.9%)	1 (2.0%)	
6	3 (1.4%)	2 (1.2%)	1 (2.0%)	
Number of attempts				
1	148 (66.7%)	117 (67.6%)	31 (63.3%)	0.57
>1	74 (33.3%)	56 (32.4%)	18 (36.7%)	

Table 6. Length of line duration (Cardiothoracic surgery excluded)

Catheter Type	Overall Median Days (Q1, Q3)	LDUFHI Median Days (Q1, Q3)	No LDUFHI Median Days (Q1, Q3)	P-value
All types	4.0 (2.0, 10.0) (n=334)	5.0 (3.0, 11.0) (n=231)	3.0 (1.0, 6.0) (n=103)	<0.001
Non-tunneled CVC	5.0 (3.0, 10.0) (n=171)	6.0 (3.0, 11.0) (n=123)	3.0 (1.0, 6.0) (n=48)	<0.001
Tunneled CVC	3.0 (2.0, 6.0) (n=86)	3.0 (2.0, 7.0) (n=65)	2.0 (1.0, 4.0) (n=21)	0.03
PICC	9.5 (3.0, 26.5) (n=36)	11.0 (3.0, 41.0) (n=27)	9.0 (2.0, 11.0) (n=9)	0.26
Totally Implantable device	3.0 (2.0, 10.0) (n=26)	6.0 (3.0, 15.0) (n=10)	2.0 (1.5, 6.5) (n=16)	0.04
Broviac	4.0 (1.5, 10.0) (n=12)	13.0 (4.0, 76.0) (n=3)	3.0 (1.0, 5.0) (n=9)	0.07
Other	2.0 (1.0, 11.0) (n=3)	2.0 (1.0, 11.0) (n=3)	---	---

Table 7. CVC complications per 1000 catheter days (Cardiothoracic surgery excluded)

	Overall	LDUFHI	No LDUFHI	Rate Ratio [95% CI]	p-value
VTE	2.73	2.38	4.28	0.56 [0.11, 2.87]	0.48
CLABSI	1.95	1.43	4.28	0.33 [0.06, 2]	0.23
Catheter dysfunction	17.14	16.67	19.27	0.86 [0.42, 1.8]	0.7

Table 8. Days until CVC Complications

Complication	Catheter Type	Overall Median (Q1, Q3)	LDUFHI Median (Q1, Q3)	No LDUFHI Median (Q1, Q3)	P-value*
VTE	*All Types*	4.0 (1.0, 7.0) (n=7)	5.0 (4.0, 7.0) (n=5)	1.0 (1.0, 1.0) (n=2)	0.13
	Non-tunneled CVC	3.0 (1.0, 7.0) (n=3)	5.0 (3.0, 7.0) (n=2)	1.0 (1.0, 1.0) (n=1)	---
	Tunneled CVC	4.5 (4.0, 5.0) (n=2)	4.5 (4.0, 5.0) (n=2)	---	---
	PICC	6.0 (1.0, 11.0) (n=2)	11.0 (11.0, 11.0) (n=1)	1.0 (1.0, 1.0) (n=1)	---
	Totally Implantable device	---	---	---	---
	Broviac	---	---	---	---
	Other	---	---	---	---
CLABSI	*All Types*	6.0 (1.0, 18.0) (n=5)	18.0 (2.0, 42.0) (n=3)	4.0 (2.0, 6.0) (n=2)	0.59
	Non-Tunneled CVC	10.0 (2.0, 18.0) (n=2)	10.0 (2.0, 18.0) (n=2)	---	---
	Tunneled CVC	---	---	---	---
	PICC	42.0 (42.0, 42.0) (n=1)	42.0 (42.0, 42.0) (n=1)	---	---
	Totally Implantable device	---	---	---	---
	Broviac	4.0 (2.0, 6.0) (n=2)	---	4.0 (2.0, 6.0) (n=2)	---
	Other	---	---	---	---
Catheter dysfunction	*All types*	7.0 (4.5, 10.0) (n=44)	5.0 (4.0, 11.0) (n=35)	9.0 (6.0, 10.0) (n=9)	0.69
	Non-tunneled CVC	7.0 (5.0, 9.0) (n=25)	5.0 (5.0, 8.0) (n=21)	10.0 (9.5, 10.0) (n=4)	0.04
	Tunneled CVC	5.0 (3.0, 5.0) (n=9)	5.0 (3.0, 5.0) (n=7)	3.5 (1.0, 6.0) (n=2)	0.88
	PICC	20.0 (11.5, 41.0) (n=8)	30.0 (16.0, 43.0) (n=6)	13.0 (7.0, 19.0) (n=2)	0.43
	Totally Implantable device	6.0 (1.0, 11.0) (n=2)	11.0 (11.0, 43.0) (n=1)	1.0 (1.0, 1.0) (n=1)	---
	Broviac	---	---	---	---
	Other	---	---	---	---

Table 9. VTE Incidence by line type (Cardiothoracic surgery excluded)

	Overall			**No LDUFHI**			**LDUFHI**			
Line Type	Total Number of Lines	Number of VTEs	VTEs per 1000 catheter days	Total Number of Lines	Number of VTEs	VTEs per 1000 catheter days	Total Number of Lines	Number of VTEs	VTEs per 1000 catheter days	LDUFHI vs. No LDUFHI P-value
Non-tunneled CVC	171	3	2.70	48	1	4.88	123	2	2.21	0.92
Tunneled CVC	86	2	5.14	21	0	0.00	65	2	6.23	0.69
PICC	36	2	2.63	9	1	12.82	27	1	1.46	0.39
Port	26	0	0.00	16	0	0.00	10	0	0.00	---
Broviac	12	0	0.00	9	0	0.00	3	0	0.00	---
Other	3	0	0.00	0	0	---	3	0	0.00	---

Table 10. CLABSI Incidence by line (Cardiothoracic surgery excluded)

	Overall			**No LDUFHI**			**LDUFHI**			
Line Type	Total Number of Lines	Number of CLABSIs	CLABSIs per 1000 catheter days	Total Number of Lines	Number of CLABSIs	CLABSIs per 1000 catheter days	Total Number of Lines	Number of CLABSIs	CLABSIs per 1000 catheter days	LDUFHI vs. No LDUFHI P-value
Non-tunneled CVC	171	2	1.80	48	0	0.00	123	2	2.21	0.66
Tunneled CVC	86	0	0.00	21	0	0.00	65	0	0.00	---
PICC	36	1	1.31	9	0	0.00	27	1	1.46	0.90
Port	26	0	0.00	16	0	0.00	10	0	0.00	---
Broviac	12	2	14.71	9	2	46.51	3	0	0.00	1.00
Other	3	0	0.00	0	0	---	3	0	0.00	---

Table 11. Characteristics of subjects with VTE (Cardiothoracic surgery excluded)

Subject #	Age at admission (yrs)	LDUFH administration	Line Type	Size (Fr)	Lumens	Side	Location	Attempts	Time to VTE (days)
199	0.8	No	Non tunneled CVC	4	2	Right	Femoral	Unknown*	1
222	0.6	No	PICC	3	3	Right	Saphenous	Unknown	1
6	4.9	Yes	Tunneled CVC	5.5	3	Right	Femoral	2	5
8	0.6	Yes	Non Tunneled CVC	4	2	Left	Femoral	Unknown	7
9	0.7	Yes	Non tunneled CVC	4	2	Right	Femoral	2	3
113	7.6	Yes	PICC	4	2	Right	Basilic	3	11
137	4.1	Yes	Tunneled CVC	5.5	3	Right	Femoral	1	4

***= Line wire knotted**

Table 12. Characteristics of subjects with CLABSI (Cardiothoracic surgery excluded)

Subject #	Age at admission (yrs)	LDUFH administration	Line Type	Size (Fr)	Lumens	Side	Location	Attempts	Time to CLABSI (days)	Organism(s)
24	0.6	No	Broviac	4.2	1	Right	Jugular	Unknown	2	*Candida albicans*
178	1.2	No	Broviac	Unknown	2	Right	Unknown	Unknown	6	*Enterobacter cloacae*
8	0.3	Yes	Non tunneled CVC	4	2	Right	Femoral	1	18	*MSSA; Enterococcus faecelis*
307	0.1	Yes	Non tunneled CVC	4	2	Right	Jugular	Unknown	2	*Haemophilus influenzae, non typeable*
346	17.9	Yes	PICC	5	2	Right	Basilic	1	42	*Micrococcus species*

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