

Performance and Safety of Femoral Central Venous Catheters in Pediatric Autologous Peripheral Blood Stem Cell Collection

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ABSTRACT

Introduction: Autologous peripheral blood hematopoietic progenitor cell collection (A-HPCC) in children typically requires placement of a central venous catheter (CVC) for venous access. There is scant published data regarding the performance and safety of femoral CVCs in pediatric A-HPCC.

Methods: Seven-year, retrospective study of A-HPCC in pediatric patients collected between 2009 and January 2017. Inclusion criteria were an age < 21 years, A-HPCC using a femoral CVC for venous access. Femoral CVC performance was examined by CD34 collection rate, inlet rate, collection efficiency (MNC-FE, CD34-FE), bleeding, flow-related adverse events (AE), CVC removal, and product sterility testing. Statistical analysis and graphing were performed with commercial software.

Results: 75/119 (63%) pediatric patients (median age 3 years) met study criteria. Only 16% of children required a CVC for ≥ 3 days. The CD34 collect rate and CD34-FE was stable over time whereas MNC-FE decreased after day 4 in 80% of patients. CD34-FE and MNC-FE showed inter- and intra-patient variability over time and appeared sensitive to plerixafor administration. Femoral CVC showed fewer flow-related AE compared to thoracic CVC, especially in pediatric patients (6.7% vs 37%, $P=0.0005$; OR=0.12 (95%CI: 0.03-0.45). CVC removal was uneventful in 73/75 (97%) patients with hemostasis achieved after 20-30 minutes of pressure. In a 10-year period, there were no instances of product contamination associated with femoral CVC colonization.

Conclusion: Femoral CVC are safe and effective for A-HPCC in young pediatric patients. Femoral CVC performance was maintained over several days with few flow-related alarms when compared to thoracic CVCs.

INTRODUCTION

Adequate venous access can be challenging in pediatric patients undergoing autologous peripheral blood human progenitor cell collection (A-HPCC). Most pediatric patients require a central venous catheter (CVC) to establish and maintain adequate blood flow for cell separation [1,2]. In older children and adults requiring CVC access, the preferred catheter is a double-lumen, polyurethane CVC placed in the subclavian vein or internal jugular [3]. In very small children, however, the rigidity and size of polyurethane CVC relative to patient anatomy increases the difficulty and potential risks associated with thoracic CVC [1]. To avoid polyurethane CVCs, some centers have used soft, silicone-type CVC for pediatric A-HPCC. Unfortunately, silicone-based catheters are prone to collapse, with an increasing risk of mechanical occlusion at small sizes [1]. In addition, A-HPCC using some tunneled silicone-type catheters still requires a peripheral intravenous catheter (PIV) for return to avoid recirculation due to the close proximity of the draw and return lumens [4]. Finally, long-term catheters have an increasing risk of infection, catheter dysfunction, and thrombosis in 10 to 74% of patients [5-8].

Our institution has routinely used short-term femoral CVC in young pediatric patients undergoing A-HPCC. Patients undergo femoral line placement the morning of their first scheduled A-HPCC, followed by line removal 6-24 hours after their last procedure. In critically ill children, femoral CVCs have a low rate of insertion-related complications, but are reported to have a higher rate of mechanical obstruction and thrombosis [9,10]. Likewise, at least one institution has anecdotally reported a high rate of catheter occlusion during A-HPCC in children younger than 3 years of age [11]. Femoral CVCs are also associated with a higher incidence of infection [12, 13]. As a

quality assurance project, we performed a 7 year review of femoral CVC performance on CD34 collection, product sterility, and procedure-related adverse events (AE) in pediatric patients undergoing A-HPCC.

MATERIALS AND METHODS

Patients and Study Design:

The study was a 7-year retrospective review of A-HPCC in pediatric patients at the University of Michigan between 1/1/2009 and 1/31/2017: Earlier collections were excluded due to the lack of consistent peripheral CD34 counts after day 1 and incomplete documentation of catheter-related issues during leukapheresis. Inclusion criteria included: 1) age \leq 21 years at the time of A-HPCC; 2) a double-lumen, femoral CVC for venous access; and 3) leukapheresis using either the COBE Spectra® or SPECTRA Optia and CMNC program (TerumoBCT, Lakewood, CO). Patients collected on the SPECTRA Optia using the MNC program were excluded because of internal data showing decreased collection efficiencies in children requiring a blood prime [14]. Among 119 pediatric patients who underwent A-HPCC, 75 met inclusion criteria. Forty-four patients were excluded due to alternative CVCs (n=19: 10 subclavian and 9 internal jugular), peripheral IV access (n=18), and collection using the SPECTRA Optia and MNC program (n=7).

Primary data elements included: patient demographics (age, weight, diagnosis); mobilization (chemotherapy, growth factors [Granulocyte colony-stimulating factor, G-CSF; Granulocyte-macrophage colony-stimulating factor, GM-CSF], plerixafor); laboratory studies (peripheral blood WBC, platelet count, MNC and CD34 counts) number of leukapheresis procedures, fractional collection efficiencies (FE), inlet rate

(mL/min, mL/min/kg) and product characteristics (cell yields, sterility testing). Catheter-specific information included a review of the operative procedure note for CVC size, manufacturer and adverse events (AE). Catheter-related issues impacting A-HPCC were identified from the procedure record and product master file. As previously published [15], CVC-related AEs during A-HPCC were defined as bleeding; catheter dysfunction requiring repeated flushing, line reversal, instillation of anti-thrombolytics, or use of alternate venous access; slow inlet rate (< 0.7 ml/min/kg); difficulty in establishing or maintaining an interface, circuit clotting and early termination of procedures. Femoral CVC performance was compared to a small cohort of pediatric (n=19) and adult myeloma patients (n=19) who underwent A-HPCC with thoracic CVC.

Femoral CVC

Patients underwent femoral CVC placement under general anesthesia the morning of their first scheduled leukapheresis collection. Catheter care was per institutional guidelines [16]. Following each apheresis session, catheter lines were flushed with 5 mL saline, followed by heparin (1:1000 units/mL, 0.9-1.3 mL fill volume) and then capped. Femoral CVCs were removed within 6 - 24 hours of the last A-HPCC. Criteria for removal included a platelet count of $\geq 50\text{K}/\mu\text{L}$ and correction of coagulation studies to assure the absence of residual citrate effect. Patients with a post-procedure platelet $< 50\text{K}/\mu\text{L}$ were transfused with platelets prior to line removal. Lines were removed at the patient bedside by Blood and Marrow Transplant (BMT) staff or in the operating room in coordination with other procedures. Following removal, patients were observed for a

minimum of 1 hour with activity restrictions for at least 6 hours. Patients were advised to avoid bathing or showering for up to 24 hours after CVC removal.

HPC Collection and Processing

All patients underwent large volume leukapheresis (LVL, 3 blood volumes) using either the COBE Spectra and WBC collection set or SPECTRA Optia and CMNC software as previously described [15,17]. Cell counts were performed on the Sysmex XE 5000 (Sysmex, Kobe, Japan). The WBC differential was determined manually. Peripheral CD34 counts and product yields were determined by flow cytometry, as recommended by the International Society of Hematology and Graft Engineering with modification [18,19]. Cells were volume adjusted and frozen in 10% dimethyl sulfoxide as previously described [17,18]. All cell processing was performed in biosafety hoods, located within a certified clean room.

Sterility Testing and Positive Cultures

Sterility testing of each product was performed before and after processing using the USP culture method per 21 CFR 610.12 [20]. All positive cultures were investigated and findings documented in the product record and master excel file. Recorded data included: culture results from the patient and product (pre- and post-processing); identification of the microorganism, date of positive culture; and presence/absence of infusion reactions.

Data Analysis

Quantitative data were reported as the mean \pm standard deviation (SD) unless noted otherwise. Variables with wide inter-patient values were reported as mean, median and range. CD34 and MNC fractional efficiencies (CD34-FE, MNC-FE) were calculated as described, where $FE = \text{total cell yield} / (\text{pre-procedure peripheral cell count}) \times (\text{total blood volume processed})$ [21]. Categorical data were analyzed by chi-square and odds ratio using EpiInfo (Center for Disease Control, Atlanta, GA). Linear regression, t-test (paired, unpaired), and graphics were performed with commercial software (Kaliedograph®, Synergy Software, Reading, PA). A *P* value < 0.05 was considered statistically significant.

RESULTS

Patient Demographics

A total of 119 pediatric patients underwent A-HPCC between 2009 and January 2017. Eighty-two patients (69%) underwent leukapheresis using a femoral CVC. Seven patients were excluded due to A-HPCC collection on the SPECTRA Optia and MNC program. In total, 75 patients (63%) and 119 procedures were eligible for further study. The median patient age was 3 years (range, 10 months to 17 years), with 25% and 69% of children < 3 and ≤ 5 years of age, respectively (Table I). Most children (74/75) were collected following mobilizing chemotherapy. The majority of patients (84%) required only 1-2 procedures.

Twelve patients required 3- 6 procedures to collect sufficient cells for transplant (Table II). Patients requiring 3 or more procedures were generally older (median age, 9.5

years), with delayed marrow recovery ($\text{WBC} > 5\text{K}/\mu\text{L}$) following cancer-specific chemotherapy (18.1 ± 1.5 days versus 13 days, cyclophosphamide, $P=0.06$). Several patients required an increase in G-CSF dosing (7/12, 58%), often supplemented with GM-CSF (2/12, 17%) and/or plerixafor (11/12, 92%).

Laboratory Studies

The mean peripheral WBC on Day 1 was 23 ± 17 K/ μL (median, 15.3K/ μL ; range, 4.6-84.4 K/ μL), which continued to slowly increase over time (Table III; Fig 1S, supplemental data). The mean absolute MNC count on Day 1 was 3.6 ± 2.3 K/ μL (range, 0.5 – 10.6 K/ μL) with the highest counts on Day 3. The mean peripheral CD34 counts were highest on Day 1 ($333 \pm 49/\mu\text{L}$ SEM; median, 199; range, 1-1740 / μL ; $P<0.0001$) due to a large cohort of well-mobilized young children. As a result, 71% of patients collected in a single procedure. Patients who required two or more procedures had significantly lower peripheral CD34 counts on subsequent days (Table III). The mean pre-procedure platelet count was also highest on Day 1 (95K/ μL , range, 35-253 K/ μL ; $P=0.003$) but fell 24-29% due to procedure-related platelet losses (Table III, FigS1). Six patients required a total of 10 additional platelet transfusions during the course of A-HPCC (Days 3-5) for procedure-related platelet losses (Table III).

Femoral Line Characteristics

All patients had a femoral line placed under anesthesia without complication. Fifty-three percent of patients required a platelet transfusion prior to CVC placement (Table I). Most children had CVC placed in the right femoral vein (95%): Four children had left-sided

femoral CVC due to anatomic issues and tumor involvement. Details regarding the CVC size and manufacturer were available in 67 (89%) of patients (Table I).

The median CVC size for all patients was 10 French (range, 7 – 14). In young children (<5 years), the median catheter size was 10 French (range, 7 – 12) including 50% of children under 3 years of age (Figure 2A). In children older than 5 years, the vast majority required a 12 French CVC or larger. When examined by patient weight (Figure 2B), the median CVC size was as follows: <10 kg (8 French; range, 7-8), 10-20 kg (10 French; range, 7 -12) and > 20 kg (12 French, range, 7 – 14).

Femoral Line Performance

Femoral CVC performance over the course of A-HPCC was also examined. CVC performance was analyzed relative to average inlet rates, cell collection rates, cell collection efficiency and access-related AE.

Inlet Rate

The average inlet rate was 27.7 ± 18.3 mL/min. When corrected for body weight, the mean inlet rate per procedure was 1.1 ± 0.43 mL/min/kg. Only 20% of procedures were performed at an inlet rate less than 0.9 mL/min/kg (Fig 3B; range, 0.7-0.89). The highest mean inlet rate was Day 3 (1.3 ± 0.79 mL/min/kg, $P=0.37$), but then progressively decreased over the next 3 days (Figure 3A). There was no correlation between inlet rates and either the peripheral WBC count or platelet counts (data not shown).

CD34 Collection and Cell Yields

CD34/kg yields were greatest on Day 1 due to a large cohort of well-mobilized young children (mean, $35.6 \pm 40 \times 10^6/\text{kg}$; $P < 0.0001$; Fig. 1F). As expected, there was a linear correlation between the peripheral CD34 count and the CD34/kg yield (Fig. 3C, insert; $R = 0.90$). We also examined the CD34 collection rate on Day 1 to subsequent procedures (Days 2-6). As shown in Fig 3C, there was no fall-off in CD34 collection with subsequent days.

A CD34-FE was available in 111/119 (93%) procedures. The mean CD34-FE for all collections was 0.59 ± 0.30 and was relatively stable over the course of A-HPCC (Fig 3F; range, 0.54-0.59; $P=0.42-0.90$). There was also no difference in CD34-FE in patients with left-sided femoral CVC (0.50 ± 0.19 versus 0.59 ± 0.32 , right; $P=0.37$). There was no significant correlation between CD34-FE and peripheral WBC count or platelet count.

MNC Collection and Cell Yields

The mean MNC was $3.3 \pm 2.2 \times 10^8/\text{kg}$ with the highest yield on Day 3 (4.5 ± 1.9 , $P=0.07$; Fig 1D). There was a weak linear correlation between MNC/kg and peripheral MNC count ($y = 1.3 + 0.56x$, $R = 0.58$). There was no difference in the slope or rate of MNC collection rate between Day 1 and subsequent days (Fig. 3E).

The mean MNC-FE for all collections was 0.55 ± 0.44 (range, 0.11-1.8) and inversely related to absolute MNC count ($y = 0.86 - 0.66\log x$, $R = -0.47$; data not shown) [22]. Although the median MNC-FE was relatively stable over time (Fig. 3F), there was a trend toward improved MNC-FE on day 2 (0.72 ± 0.16 , $p=0.12$), with 50% of all patients showing an increase in MNC-FE (Fig S2, *Supplemental Data*). By day 4,

MNC-FE (0.40 ± 0.24 , $p=0.37$) fell by 10-73% in 80% of patients (Fig S2) and mirrored the drop in inlet rate.

Line-Associated Adverse Events during A-HPCC

Ten bleeding and/or flow-related AE were documented in 8 patients for an overall rate of 8% per procedure and 11% per patient (Table IV). Two patients had mild oozing on Day 1 that was easily controlled by a pressure dressing. In a third patient, there was significant oozing on Day 3 that was unresponsive to pressure and required application of a topical clotting agent and platelet transfusion (pre-procedure platelet count = $44\text{K}/\mu\text{L}$). It was subsequently determined that the line had dislodged a short distance.

Five patients had alarms and flow-related issues over the course of A-HPCC. Three patients required either repeated line flushing ($n=2$) or line reversal ($n=2$) on Day 2. While both patients who required line reversal experienced a decrease in CD34-FE (22%, 60%) relative to Day 1, there was no clinical evidence of recirculation per nursing notes. One patient developed new and significant difficulties in establishing an interface on Day 4 that prolonged the procedure by 30-40 minutes. Another patient experienced a 30% decrease in flow rate ($0.7 \text{ ml}/\text{min}/\text{kg}$) on Day 6.

Comparison of Femoral and Thoracic CVC in Pediatric A-HPCC

We also compared the performance of femoral CVC to a small cohort of 19 pediatric patients who underwent A-HPCC using thoracic CVC ($n=9$ internal jugular, $n=10$ subclavian; 33 procedures) during the same time interval. Patients with thoracic CVC were significantly older (13 ± 6.6 years, range, 1-21 years; $P < 0.0001$) and heavier ($58 \pm$

32 kg; range, 10-122 kg; $P=0.0002$) than patients with femoral CVC. The most common diagnosis in these patients was lymphoma (47%), followed by brain cancer (21%), neuroblastoma (16%), testicular carcinoma (11%), and Ewing's sarcoma (5%). Because some patients had CVC placed at outside facilities, the catheter size was only available in 81% of patients. The median thoracic CVC size was 12 French (range, 6-14). In children under 20 kg, a 6 to 7 French CVC was placed ($n=3$).

In terms of catheter performance, the total mean inlet rate with thoracic CVC was 44 ± 20 ml/min. When corrected for body weight, however, thoracic CVC had a slower inlet rate than femoral CVC (0.92 ± 0.31 ml/min, $P=0.02$; Figure 3B). The mean CD34-FE (0.51 ± 0.20 versus 0.59 femoral, $P=0.18$) and MNC-FE (0.48 ± 0.28 versus 0.55 femoral) was 13-15% lower than femoral CVC, although the difference was not statistically significant ($P=0.18-0.41$). Among 7/19 patients who underwent multiple A-HPCC with thoracic CVC, there was a drop in both CD34-FE (0.38 vs 0.55 Day 1; $P=0.18$, paired t-test) and MNC-FE (0.43 vs 0.52 Day 1, $P=0.37$) by the second or third procedure.

A comparison of access-related AE by CVC type indicate a substantially lower incidence (6.7% vs 26%, $P=0.0005$) and risk for flow-related AE with femoral CVC (OR=0.12; 95% CI, 0.03 – 0.45) (Table IV). We also compared the incidence of CVC-AE in pediatric patients to an equivalent cohort of adult multiple myeloma patients (19/81 patients) [15], who also underwent A-HPCC using thoracic CVC (Table IV). As shown in Table IV, pediatric patients with thoracic CVC also had higher flow-related AE rates than their adult counterparts (37% vs 16%, $P=0.14$). In both pediatric and adult patients, flow related AE associated with thoracic CVC tended to be more severe than

femoral CVC, including placement/use of alternate IV access, recirculation, circuit clotting, and aborted procedures.

Catheter Performance in Individual Patients over Time

Although the mean CD34-FE was stable over time, there was significant inter- and intra-patient variability between collections (Figure 2S, *Supplemental Data*). Because there was a trend toward decreasing inlet rate and MNC-FE after Day 3, we performed a detailed analysis of cell collection in 12 patients who required 3 or more procedures.

Nine patients had complete data for all A-HPCC: In 3 patients, a pre-procedure peripheral CD34 count was not performed on one or more days. As shown in Fig. 3, CD34-FE

varied over the course of collection and was unique for each patient. All patients successfully collected sufficient cells for transplant (Table II).

Interestingly, there was an apparent drop in CD34-FE in several patients within 12 to 24 hours after receiving the first dose of plerixafor (patients 7, 17, 21, 32, 45, 48, 49, and 55). Even though all patients showed a progressive increase in WBC over the course of A-HPCC, particularly after receiving plerixafor, there was no clear relationship between WBC and CD34-FE. In fact, the highest WBC was $\leq 30\text{K}/\mu\text{L}$ in 6/9 evaluable patients. There was also no correlation between CD34-FE and either the pre-procedure platelet count or recent platelet transfusion (data not shown).

Finally, we compared the course of CD34-FE with MNC-FE in 10 patients (Fig. 4A). In general, the MNC-FE declined over the course of A-HPCC. Surprisingly, the CD34-FE and MNC-FE showed a similar pattern in patients (Fig. 4A). The mean MNC-FE (0.59 ± 0.4) and CD34-FE (0.56 ± 0.24 , $p=0.55$) in these patients were nearly

identical (Fig. 4B). Likewise, there was a linear correlation between the MNC-FE and CD34-FE (Fig. 4C, $R=0.68$). There was no correlation between CD34-FE, MNC-FE and MNC content (%MNC) of the product. Three patients showed an alternating pattern between CD34-FE and MNC-FE (Figure 3S, *Supplemental Data*), suggesting possible technical issues with cell separation and interface stability.

Femoral Line Removal

Femoral lines were removed 6-24 hours after the last A-HPCC at the bedside or in the operating room in conjunction with another procedure. Approximately 37% (28/75) of patients required a platelet transfusion before CVC removal due to procedure-related platelet losses. An additional 6 patients had received pre-procedure platelet transfusion on the day of line removal. The mean platelet count prior to CVC removal was 89 ± 29 K/ μ L, with higher counts observed in transfused patients (104 ± 35 vs 81 ± 22 K/ μ L; $P=0.02$).

In 72/74 (97%) patients, there were no complications associated with femoral CVC removal. Hemostasis was achieved after 5- 40 minutes (median time, 20 minutes) of direct pressure. There was also no clear correlation between the platelet count and time to hemostasis (Fig 4S, *Supplemental Data*). Patients who clotted within 20 minutes had platelet counts ranging between 50 and 138 K/ μ L, whereas platelet counts > 100 K/ μ L were documented in 4 patients who required pressure for 30 minutes or longer. Platelet transfusion did not shorten the time to hemostasis (median time, 20 minutes in transfused and non-transfused). Two patients experienced bleeding following femoral CVC removal. In both patients, there was no evidence of an underlying coagulopathy. The

patients had normal liver function and PT values. There was no history of an inheritable clotting disorder. Neither patient was receiving systemic heparin or other anticoagulants.

One patient (41 kg, 6 year old female) underwent a single A-HPCC collection with a post-procedure platelet count of 44K/ μ L. She received a platelet transfusion prior to line removal. Following removal, the CVC site was noted to have prolonged oozing.

The patient's hospital stay was extended an additional night for observation. She was discharged the following morning with no evidence of bleeding or hematoma.

The second case involved a 12 kg, 3-year old who underwent one A-HPCC, followed by line removal later that evening. The patient initially achieved hemostasis after 15 minutes of pressure, but subsequently developed increased bleeding that did not respond to pressure (80 minutes) and platelet transfusion. Hemostasis was finally achieved after application of a topical adhesive by Pediatric Surgery. A small hematoma was noted the following morning. Post-procedure (4 hours) laboratory studies showed an adequate platelet count (84K/ μ L), but a prolonged aPTT (119 seconds (s); normal range, 22-32 s). A repeat aPTT was improved, but still elevated (38.2 s). Of note, this patient had a long-term, tunneled CVC for infusions and blood draws with multiple prolonged aPTT, consistent with heparin-contamination [23].

There were no reports of infection, thrombosis, limb swelling, extravascular effusions, or arteriovenous fistulas associated with femoral CVC in any patient in this series [9,10,13].

Product Sterility

There were no positive cultures in any product collected (0/118). In a 10-year retrospective review of all pediatric A-HPCC, only 4/338 (1.1%) products from 3/197 patients (1.5%) were culture positive. Two products were collected via femoral CVC for an estimated culture-positive rate of 0.7% per product and 1.2% per patient. In both cases, only the post-processing sample was positive with a non-viable organism after 11-14 days of culture, consistent with a lab contaminant.

Two products from the same patient were culture positive with coagulase-negative *Staphylococcus* within 5-7 days. The patient, catheter tip, and products (pre- and post-processing) were positive with coagulase-negative *Staphylococcus*. This was considered a true positive attributed to a colonized subclavian CVC (PowerLine®) placed approximately one month earlier [7].

DISCUSSION

In this study, we describe our single-institution experience using femoral CVC for stem cell collection in children, including children as young as 10 months. Children typically undergo femoral line placement in the morning of their first scheduled A-HPCC. The vast majority (84%) of the children in this series collected in 1 or 2 procedures with only 16% patients requiring a line for 3 or more days. CVC were subsequently removed by BMT staff within 6-24 hours after the last A-HPCC. Hemostasis was achieved after 10-30 minutes of pressure without complication in 97% patients. Only two patients experienced prolonged bleeding, with one patient developing a small hematoma. There were no patients who experienced serious long-term sequelae following femoral CVC placement.

Clinically, there were few issues with femoral CVC for A-HPCC. A total of ten AE were documented in 10.8% patients and 8.5% procedures. AE were limited to mild bleeding and flow-related AE, which were amendable to correction by routine maneuvers. This was significantly better than the AE rate in 19 pediatric patients with thoracic CVC (42%, $P=0.001$). Pediatric patients with thoracic CVCs had a significantly higher rate of flow-related AE and were more likely to have prolonged procedures due to a slow inlet rate (< 0.7 ml/min/kg), require alternate venous access, and in two patients, early termination of the procedure (Table III) [15]. Finally, there were no confirmed cases of bacterial contamination using femoral CVC in the last 10-years whereas a tunneled thoracic CVC was linked to line-associated bacterial contamination of two products.

These results are equivalent or better than those reported in adults (Table V) [1,4,24-41]. Shariatmadar and Noto reported bleeding in 1/63 (1.6%) of autologous adult patients, with no episodes of occlusion or flow-related AE, even after 6 days [24]. In contrast, Moreiras-Plaza et al encountered catheter-related flow issues in 12% (29/232) of procedures that were resolved by patient repositioning or reversing lines: other AE included minor bleeding after insertion (2%) and hematoma (15.8%) [25]. A larger study of 147 adults and 488 HPCC reported catheter-related AE rate in 5% of procedures and 16.8% of patients. Documented AE included bleeding and large hematomas requiring platelet transfusion or red cell transfusion (6.8%); catheter malplacement, occlusion and thrombosis (8.1%); arteriovenous fistulas (1.3%); and infection (0.6%) [26]. Breast cancer patients were particularly susceptible to thrombosis, with femoral vein thrombosis and pulmonary embolism in 4.7% and 5.9% of patients, respectively [27]. More recently,

Donmez observed a 1.8% occlusion rate and 10.7% overall AE rate in 268 adults undergoing A-HPCC, with bleeding and hematoma accounting for most recorded AE (57%) [28]. In healthy donors, femoral CVC had a 8.7% AE rate due to catheter malfunction/malposition (3.5%) and hematomas (5.2%) [29]. Product contamination rates using femoral CVC in adults are approximately 1% [28].

Although femoral CVC access is used by many centers for pediatric HPCC [30,31,42,43], there is limited published data regarding catheter performance. Yocco et al anecdotally reported a high incidence of alarms, obstructions and kinked lines using femoral CVC in children < 3years of age, prompting them to use a soft leg splint to immobilize patients [11]. Sevilla et al noted hematoma (8%) and bleeding (25%) in 12 children under < 10 kg [31]. Kanold et al reported overall good performance in 14 children < 15 kg, although one patient developed an abscess [43]. Bolan et al used femoral CVC in 80% (31/38) of pediatric patients, with serious bleeding and hematoma formation in one patient who underwent LVL (5 BV) with heparin anticoagulation [30]. In pediatric ICU patients, similar rates of bleeding (5-9%) and hematoma (3%) have been reported, although the incidence of catheter obstruction and thrombosis were higher (11-28%) [9,10].

We also examined femoral CVC performance over time for the entire population, as well as individual patients. In general, the mean FE was stable over the course of A-HPCC, despite significant day-day variability in individual patients. Two patients required reversal of arterial and venous lines, which has been reported to increase recirculation approximately 3-fold during dialysis [44,45] and decrease CD34-FE in A-HPCC [30]. This was a major concern since femoral CVC have a higher base-rate of

recirculation relative to thoracic CVC [46,47]. Although both patients experienced a decrease in CD34-FE (22%, 60%), it is difficult to attribute the decrease to recirculation given the normal intra-patient variation observed in our patient cohort.

One interesting observation was the apparent drop in CD34-FE 12-24 hours after receiving plerixafor in many patients. The findings were unexpected and are difficult to explain. Plerixafor is not considered prothrombotic or proinflammatory [48]. In animal models, plerixafor can moderate inflammatory immune disorders, decrease fibrosis and promote revascularization [49]. However, plerixafor is associated with an increase in peripheral WBC counts that is independent and synergistic with G-CSF [48,49]. The latter could theoretically impact CD34-FE due to the inverse exponential relationship between peripheral WBC and CD34-FE [18,50,51]. In adult myeloma patients, peripheral WBC greater than 20-35K/ μ L have been reported to depress CD34-FE [18,50], with some centers dictating a slower inlet rate at high peripheral WBC [51]. In our limited pediatric series, most (7/9, Fig. 3) patients had relatively modest peripheral WBC counts after plerixafor (range, 10-22K/ μ L). There was no consistent correlation between CD34-FE, peripheral WBC, or platelet count in these patients.

Our study shows the safety and good performance characteristics of femoral double-lumen polyurethane dialysis CVC in pediatric HPCC, especially in small and very young children. Access options used in this population include double and single lumen CVCs (silicon, polyurethane), radial artery catheters, and PIVs [1,4,33,52,53]. Long-term, silicone CVCs are soft and would appear to be an attractive option in young children; however, they are prone to collapse under the negative pressure encountered during automated apheresis [1]. Moreover, the risk of mechanical occlusion increases

with decreasing lumen size, leading one investigator to recommend a 10 French or larger when using silicone CVCs [1]. Fishmeister et al compared long-term, tunneled, silicone CVCs (7-12 French) in 51 children and young adults undergoing A-HPCC [4]. Low inlet rates, reversal of draw and return lines, and line occlusion occurred in 28% of patients and 20% of procedures. Furthermore, patients still required PIV for return to avoid recirculation due to the close proximity of the draw and return lumens. Likewise, Orbach observed a 23% occlusion rate during HPCC using pre-existing thoracic CVC [33]. Finally, long-term, CVCs have an increasing risk of thrombosis, dysfunction and infection over time [5-8]. As noted earlier, the only case of true bacterial infection and product contamination in our pediatric population was associated with a tunneled, subclavian CVC.

Femoral CVCs may have other advantages in young children relative to subclavian and internal jugular CVC. Subclavian lines have a lower success rate for insertion (87% versus 94% femoral CVC), with 26% to 40% of children experiencing an AE [9,10]. Furthermore, bleeding complications arising during cannulation and insertion of subclavian and internal jugular lines can be difficult to manage, leading to hemothorax, cardiac tamponade and even death [8]. Other complications of thoracic CVC are pneumothorax, cutaneous emphysema, air embolism, brachial plexus injury, and cardiac arrhythmias (Table V) [1,3,8,32-39,54]. As noted by Gorlin [1], very young children may be particularly susceptible to cardiac arrhythmias due to their small anatomy relative to catheter length, leading to a significant risk of the tip extending deep into the right atrium with mechanical irritation of the sinoatrial node [1,3]. Finally,

thoracic CVC are associated with greater intra-procedure decreases in blood pressure during apheresis procedures [55].

Subclavian CVCs also have approximately 15% incidence of catheter malposition and dysfunction [9,10,56], with flow-related issues in 3%-64% of patients (Table V).

This is particularly true of left subclavian CVCs, which have a 16%-50% AE rate during A-HPCC and account for 19% of severe procedure-related AE at our institution [15,38,57-60]. The increased length associated with left subclavian lines inherently increases resistance to flow and the potential for anatomic obstruction [57]. The distal tip can either adhere along the lateral superior vena cava with intermittent occlusion, or reflect back into the left brachial cephalic vein with intravascular knotting [4,57].

In summary, we report our experience using short-term femoral CVC for A-HPCC in young children. Femoral CVC provided adequate venous access with few flow-related alarms or complications when compared to thoracic CVC in our pediatric population. Our experience with femoral CVC for A-HPCC is equivalent or better than that reported in adults [24-29]. Potential disadvantages of femoral CVC are mobility restrictions due to risk of catheter kinking, breaking or disconnection; vessel injury, thrombosis, and infection [11, 61]. Studies in adults, however, have shown that patients with femoral lines can undergo limited physical activities (sitting, standing, limited walking) without CVC-related AE [61]. In addition, femoral and thoracic CVC placement in young children typically require anesthesia [42,62], which has a reported 2-3% complication rate in this population [62] although none of our patients experienced anesthetic complications associated with femoral CVC insertion. Inherent limitations of our findings is the single institution, retrospective study design. Nonetheless, to our

knowledge, this is the first study to report an in-depth analysis of femoral CVC performance and outcomes in pediatric A-HPCC in a moderately large cohort of young children.

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Abbreviations:

AE, adverse event; A-HPCC, autologous peripheral blood hematopoietic cell collection; BV, blood volume; CVC, central venous catheter; FE, fractional collection efficiency; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage-colony stimulating factor; PIV, peripheral intravenous catheter; s, second.

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TABLE I. Patient Demographics

Variable	No. Patients (%)
No. Patients	75
Sex (M/F)	37/38
Age, years ^a	4.8 ± 4.0
(median, range)	(3, 0.8 – 17)
≤ 2 years (%)	19 (26%)
≤ 5 years (%)	52 (70%)
> 5 years (%)	22 (30%)
Weight, kg ^a	21.8 ± 15.8
(median, range)	(16.4, 8 – 97)
≤ 10 kg (%)	8 (11%)
≤ 20 kg (%)	51 (69%)
>20 kg (%)	23 (31%)
Primary Diagnosis (%)	
Neuroblastoma	45 (60%)
CNS malignancy	17 (23%)
Lymphoma	5 (7%)
Hepatoblastoma	2 (2.7%)
Ovarian carcinoma	2 (2.7%)
Ewing's sarcoma	2 (2.7%)
Germ cell tumor	1 (1%)
Nephroblastoma	1 (1%)
Mobilization (%)	
Chemotherapy	74 (99%)
Cytokine-only	1 (1%)
Plerixafor	12 (16%)
GM-CSF	2 (3%)
CD34 Target Yields (%)	
10-15 x 10 ⁶ /kg	62 (83%)
3 x 10 ⁶ /kg	13 (17%)
Femoral CVC Placement (%)	
Right	70 (95%)
Left	4 (5%)
Platelet Transfusion ^b	40 (54%)
CVC Brand ^c (%)	
medCOMP	26 (35%)
Mahurkur	26 (35%)
Arrow International	15 (20%)
Unknown	8 (10%)
No. HPCC Procedures/patient (%)	
1	53 (71%)
2	10 (13%)
3 or more	12 (16%)

- a. mean \pm SD
- b. No. patients requiring a platelet transfusion before femoral CVC placement.
- c. Mahurkar, Covidein, Mansfield, MA; medCOMP, Haleysville, PA; Arrow International, Reading, PA.

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TABLE II. Patients who Required Three or More A-HPCC Procedures

Pt. No.	Age/ Sex	Diagnosis ^a	Mobilization Regimen			CD34/kg Yields per Procedure Day					
			Mobilizing Chemotherapy ^a	G-CSF ($\mu\text{g}/\text{kg}/\text{day}$) ^b	Plerixafor (Day) ^c	1	2	3	4	5	6
7	5/F	Hepatoblastoma	ICE	10 -> 17	1-2	0.3	1.4	1.5	-	-	-
17	13/M	Pineal Germ Cell Tumor	Cisplatin Cyclophosphamide	10 -> 20	1-3 ^c	0.7	0.9	3.8	4.9	-	-
19	12/M	Medulloblastoma	Cyclophosphamide	10 -> 14	1-3	0.2	1.8	1.2	1.2	-	-
21	3/M	Lymphoma (NHL)	Cyclophosphamide	10	3	0.5	0.4	0.8	1.4	-	-
25	5/M	Neuroblastoma	ICE	10 -> 18	1-2	0.5	0.5	0.9	-	-	-
32	15/F	Lymphoma (NHL)	R-ICE	10	4-6 ^d	0.2	-	-	0.8	0.9	0.9
43	9/F	Ovarian Cancer	ABVE Cisplatin Cyclophosphamide	10 -> 20	none	0.9	1.1	2.6	-	-	-
45	4/F	PNET	ACNS 033	10 -> 16, + GM-CSF	2-5	0.2	0.2	0.5	1.3	4.1	3.7
48	2/F	Neuroblastoma	IE	10 -> 20	1-2	0.6	2.5	4	-	-	-
49	11/M	Medulloblastoma	Cisplatin Lomustine Vincristine	10	1-2	1.7	2.2	3.8	-	-	-
50	10/F	Ovarian Mixed Germ Cell Tumor	Cyclophosphamide	10	2-4 ^c	0.3	0.7	0.4	1.7	1.3	-
55	13/M	Lymphoma (HD)	ICE	10, + GM-CSF	2-4 ^c	0.2	0.5	1.7	1.9	-	-

- a. Abbreviations: -, not performed. ABVE, adriamycin, bleomycin, vincristine, etoposide; ACNS 033; cisplatin, etoposide, cyclophosphamide, vincristine, methotrexate; IE/ICE/R-ICE, ifosfamide, carboplatinum, etoposide \pm rituximab (R); NHL, non-Hodgkin's lymphoma; PNET, primitive neuroectodermal tumor;
- b. Daily G-CSF dose at time of first A-HPCC. Several patients had an increase in dose (->) during course of A-HPCC.
- c. Day plerixafor administered for A-HPCC the next day. In general, plerixafor was administered in the early evening (~8 pm), approximately 12 hours prior to scheduled leukapheresis as recommended in the package insert. In two patients (17 and 50), the first dose of plerixafor administration was inadvertently administered after midnight. In patient 55, plerixafor was actually given the morning of Day2, an hour prior to leukapheresis. The first effective dose, therefore, is Day 3.
- d. Patient 32 did not undergo A-HPCC on days 2 and 3 due to low CD34+ counts and evidence of persistent delayed marrow recovery.

TABLE III: A-HPC Collection by Day

	All Procedures	Procedure Day			
		Day 1	Day 2	Day 3	Days 4 - 6
A-HPCC					
No. procedures	119	75	22	12	10
No. patients	75	75	22	12	7
Median age, years	3	3	6	8.5	12
Median weight, kg	16.4	16.4	20.8	29.5	42
Total blood volume, mL ^a (median, range)	1793 ± 1062 (1286,530-4984)	1566 ± 1025 (1611)	1909 ± 966 (1909)	2372 ± 1029 (2738)	1793 ± 1062 (2545)
Liters processed ^a (median, range)	4.3 ± 3.5 (3.8, 1.2-22.5)	4.6 ± 3.4 (3.5)	5.6 ± 2.9 (4.1)	7.2 ± 3.8 (7.2)	7.7 ± 3.9 (8.7)
Median BV processed	3	3	3	3	3
Total inlet rate, mL/min ^a	27.7 ± 18.3	23 ± 14.7	32 ± 19.8	41.1 ± 26.6	35.6 ± 16.2
Adjusted inlet rate ^a (mL/kg/min)	1.1 ± 0.43	1.09 ± 0.37	1.14 ± 0.42	1.3 ± 0.79	0.98 ± 0.14
Pre-Peripheral Blood Counts					
WBC (10 ⁹ /L) ^a	24.7 ± 16.8	22.7 ± 17.3	24 ± 14.3	33.1 ± 17.6	31.3 ± 13.2
%MNC ^a	7.5 ± 10.6	18.9 ± 11.6	16 ± 8.2	15.8 ± 8.9	12.9 ± 7.7

MNC ($10^9/L$) ^a	3.6 ± 2.3	3.3 ± 2.7	3.5 ± 2.7	4.5 ± 2.7	3.4 ± 1.6
CD34 (per μL) ^b	224.3 ± 34.4	333.1 ± 48.9 ^c	32.1 ± 8.5	13.1 ± 7.1	23.5 ± 7.2
Platelet ($10^{11}/L$) ^a		96.9 ± 44.3 ^d	73 ± 32.3	75.3 ± 35.4	69.1 ± 30.6
Cell Yields					
CD34/kg ($\times 10^6$) ^a	23.5 ± 35.8	35.6 ± 40.5 ^c	4 ± 4.5	1.8 ± 1.3	2.2 ± 1.4
MNC/kg ($\times 10^8$) ^a	3.3 ± 2.2	3.1 ± 2.3	3.3 ± 2.3	4.5 ± 2.3	3.5 ± 1.9
Platelet transfusions					
Pre-procedure	78	52	10	7	9
CVC removal	50 ^e	40 ^e	4	3	3
	28	12	6	4	6

a. Results are mean ± SD.

b. Results are mean ± SEM.

c. Peripheral CD34/ μL and CD34/kg significantly higher on Day 1 ($P < 0.0001$).

d. Peripheral platelet count significantly higher on Day 1 ($P = 0.003$).

e. Forty patients received a platelet transfusion prior to femoral CVC insertion (see Table 1).

TABLE IV: Incidence of CVC-associated AE during A-HPCC

	Femoral CVC (n = 75)	Thoracic CVC ^a					
		Total ^a (n = 38)	<i>P</i> ^b	Pediatric ^c (n = 19)	<i>P</i> ^b	Adults ^d (n = 19)	<i>P</i> ^b
No. Patients Access AE (%)	8 (10.7%)	12 (31.6%)	0.006	8 (42%)	0.0011	4 (21%)	0.23
Bleeding	3 (4%)	2 (5.3%)	0.76	1 (5.3%)	0.80	1 (2.6%)	0.80
Flow-related AE ^e	5 (6.7%)	10 (26.3%)	0.004	7 (37%)	0.0005	3 (15.8%)	0.20
Repeated flushing	2 (2.7%)	3 (7.9%)		2 (10.5%)		1 (5.3%)	
Line reversal	2 (2.7%)	1 (2.6%)		0		1 (5.3%)	
Slow inlet rate	2 (2.7%)	9 (23%)		6 (31.6%)		3 (15.8%)	
Interface issues	1 (1.3%)	1 (2.6%)		1 (5.3%)		0	
Alternate IV access	0	4 (10.5%)		2 (10.5%)		2 (10.5%)	
Recirculation	0	1 (2.6%)		0		1 (2.6%)	
Aborted procedure	0	3 (7.9%)		2 (10.5%)		1 (2.6%)	

a. Adult and pediatric patients with thoracic CVC.

b. Significance relative to pediatric femoral CVC patients by chi-square.

c. Pediatric other CVC: 10 subclavian, 9 internal jugular.

d. Adult myeloma patients collected with thoracic (subclavian) CVC between 2010 and 2013.

e. More than one flow-related AE in some patients over the course of A-HPCC.

Table V. Literature review of CVC performance in pediatric and adult HPC collection

Reference	CVC location	Patient type	No. Patient	No. HPCC ^a	CVC-related AE (% patients [% procedures]) ^b		
					Flow ^b	Bleeding ^b	Other AE ^b
This study	femoral	pediatric	75	1 (1-6)	6.7% (5.9%)	4% [2.5%]	1.3% hematoma 2.6% bleeding post-removal
Sevilla ³⁰	femoral	pediatric	12	1 (1-2)	0	0	8.3% hematoma 25% minor bleeding post-removal
Bolan ³¹	femoral	pediatric	31	1	na	3.2%	3.2% hematoma
Shariamatmadar ²⁴	femoral	adult	63	1 (1-4)	0	1.6% [1.1%]	none
Sohn ²⁹	femoral	adult	57	1 (1-3)	3.5% [1.8%]	0	5.2% hematoma
Adorno ²⁶	femoral	adult	147	3(1-8)	3.4% [1%]	na	6.8% hematoma 4.7% thrombosis 0.6% infection 1.3% arteriovenous fistula
Moreiras-Plaza ²⁵	femoral	adult	95	2 (1-4)	30.5% [12%]	2% [0.9%]	15.8% hematoma
Donmez ²⁸	femoral	adult	268	3 (1-8)	1.8%	0.7% (0.2%)	4.7% hematoma 0.7% bleeding post-removal 1.8% thrombosis 1% product contamination
Saif ²⁷	femoral	adult	85	2 (1-4)	0	na	10.6% thrombosis post-removal

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Madero ³²	thoracic	pediatric	56	1 (1-3)	15%	na	7% insertion AE 2.3% pneumothorax
Fishmeister ⁴	thoracic	pediatric	46	3 (1-10)	28% [20%]	0	0.6% infection
Orbach ³³	thoracic	pediatric	24	2 (1-4)	16%	0	
Gorlin ¹	thoracic	pediatric	14	6 (3-8)	64% [16%]	0	7% pneumothorax
Diaz ³⁴	thoracic	pediatric	31	1 (1-3)	na	na	3.2% pneumothorax
Salazar-Riojas ³⁵	thoracic	pediatric	22	1 (1-2)	0	0	none
This study	thoracic	pediatric	19	2 (1-4)	37% [24%]	6% [5.3%]	5.2% hematoma
Goldberg ³⁶	thoracic	adult	75	1(1-6)	16%	na	1.3% pneumothorax 1.3% cardiac tamponade 50% thrombolytic therapy 2.3% procedure aborted
Alegre ³⁷	thoracic	adult	110	2 (1-13)	1.8%	na	1% pneumothorax 3.6% infection
Meisenberg ³⁸	thoracic	adult	156	na	10.2%	na	3.6% pneumo/hemothorax 5.7% thrombosis 7% infection
Hahn ³⁹	thoracic	adult	153	4 (2-12)	5.2% [1.1%]	na	5% thrombosis 3% infection

							2% hematoma
							0.6% pneumothorax
Papadimitriou ⁴⁰	thoracic	adult	72	1 (1-2)	6% (5.3%)	na	na
Reik ^{41,24d}	thoracic	adult	88	2 (1-5)	21% [13%] ^d	na	na

- a. The median (range) of HPCC procedures performed.
- b. The percent patients and [% HPCC procedures] with documented CVC-related AE. Flow-AE and bleeding AE refer to occlusion and bleeding during leukapheresis. Other AE include AE associated with catheter insertion, catheter removal, infection and thrombosis.
- c. na, not available.
- d. Reik et al documents a 13% occlusion rate among 88 patients. A subsequent publication from the same group states that all the documented flow-related AE were in patients with subclavian CVC [24].

FIGURE LEGENDS:

Figure 1: Distribution of femoral CVC size by patient age (A) and weight (B).

Figure 2: Femoral CVC performance. A) Distribution of inlet rate/min/kg by patient weight in pediatric patients with femoral CVC (black) and thoracic CVC (gray). B) Mean inlet rate by day. C) CD34 collection rate (CD34 yield per peripheral CD34 count) comparing Day 1 (—●—) versus subsequent days (Day 2-6, --o--). Insert, CD34 collection rate for all procedures. D) CD34-FE for all patients by procedure day. E) MNC collection rate comparing Day 1 (—●—) versus Days 2-6 (--o--). F) MNC-FE for all patients by procedure day. The number of procedures per day is listed in Table 1. Data in figures D and F are box plots, showing the median, 25th and 75th percentile, bracketed lines are the minimum and maximum values based on the interquartile range (IQR,). Values exceeding 3IQR are outliers and are denoted by open circles.

Figure 3: Correlation between CD34-FE, peripheral CD34 and WBC counts in 9 individual pediatric patients undergoing A-HPCC using a femoral CVC. CD34-FE are plotted along the left y-axis (—●—). Peripheral WBC (K/uL, --□--) and CD34 (CD34/uL, --o--) are plotted along the right y-axis. Also shown are changes in G-CSF dosing and the addition of GM-CSF and plerixafor. Please note that in patients 17 and 50, plerixafor had been inadvertently administered in the early morning hours, < 6 hours prior to A-HPCC. In patient 55, plerixafor had been administered by IV immediately prior to A-HPCC.

Figure 4: Correlation between CD34-FE and MNC-FE in individual patients. CD34-FE and MNC-FE values are plotted along the left (—●—) and right (--o--) y-axis, respectively. The

MNC content (%MNC) of the collected product is denoted along the X-axis. Line and flow related issues in three patients (19, 49, 45) are also shown. A) Data for 7 patients with similar profiles for CD34-FE and MNC-FE. B) Mean CD34-FE and MNC-FE for all 7 patients. C) linear correlation between MNC-FE and CD34-FE. D) Data for 3 patients with inverse changes in MNC-FE and CD34-FE. In two patients (21, 45), MNC-FE trended downward over the course of A-PBPCC, as shown by the hatched line bisecting the plot and negative slope ($-0.41x, -0.08x$).

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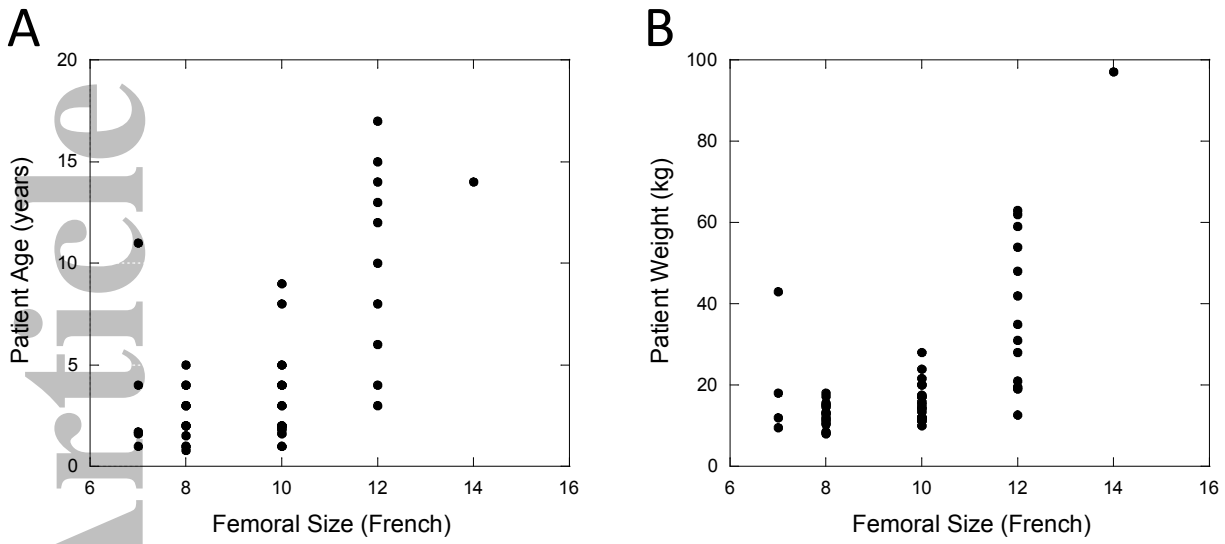


Figure 1

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Figure 2

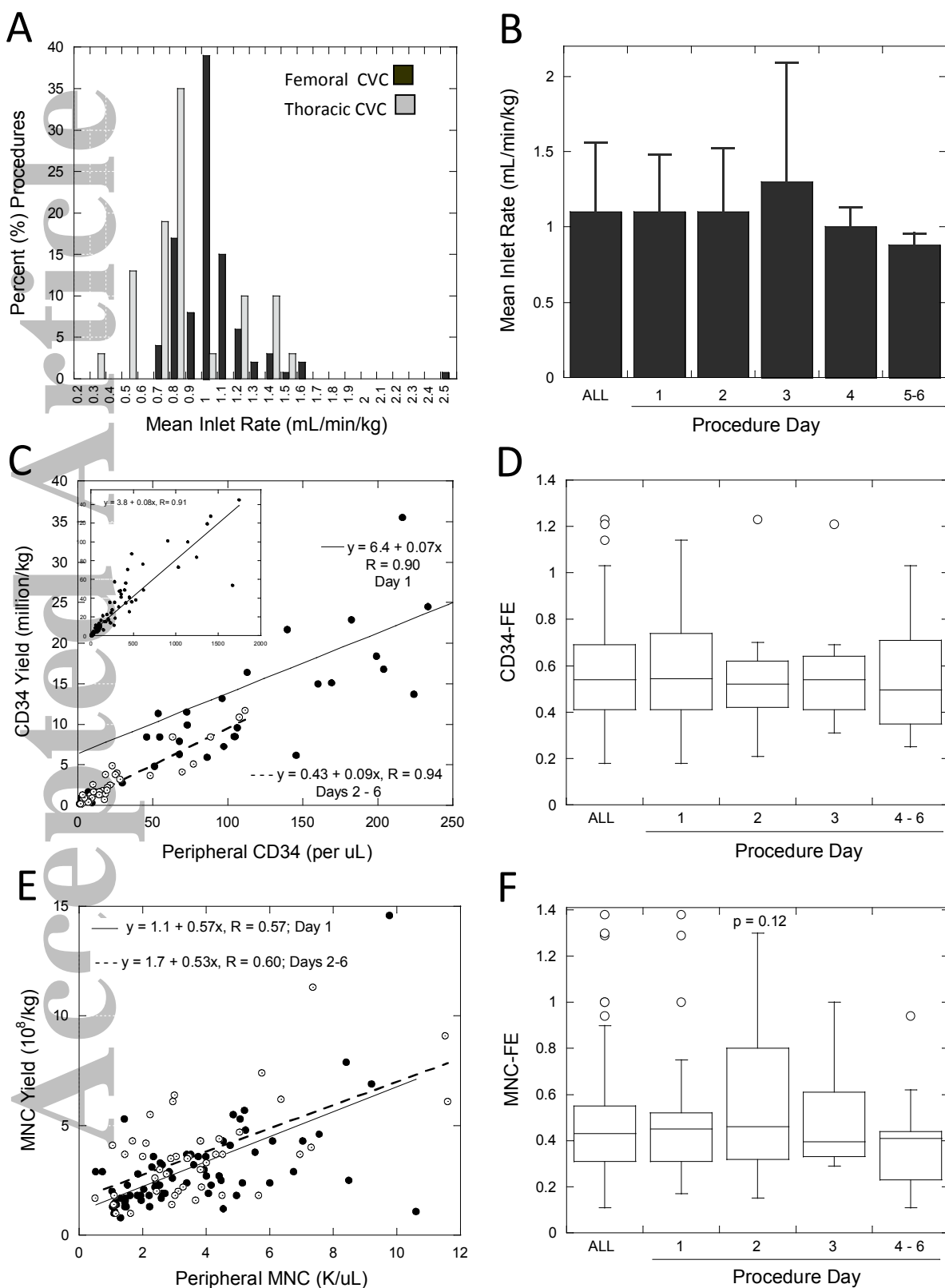


Figure 3

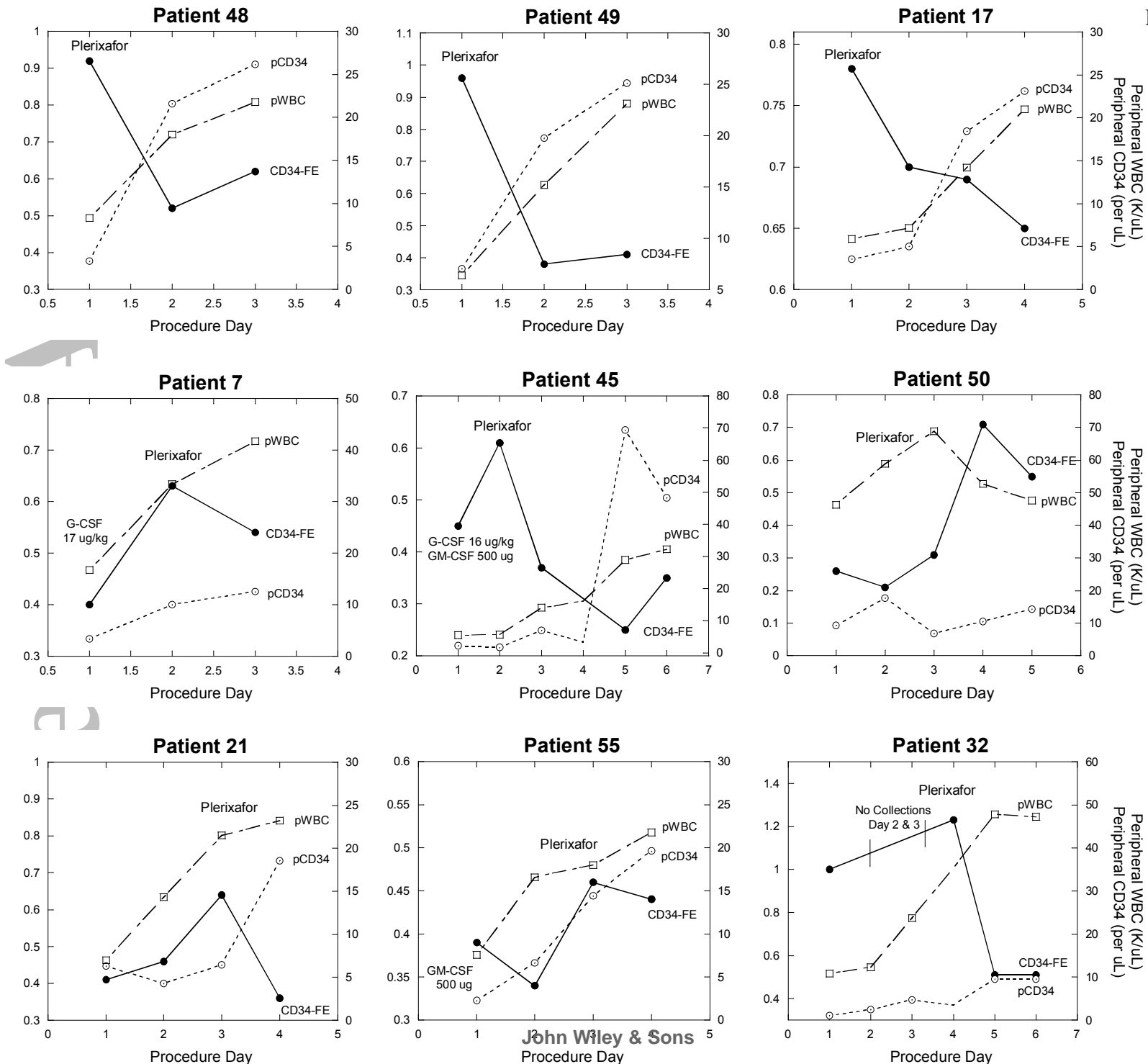


Figure 4

