# Port-A-Cath–Related Thrombosis and Postthrombotic Syndrome in Pediatric Oncology Patients

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**Objective** To investigate Port-A-Cath (PAC)-related thrombosis and postthrombotic syndrome (PTS) in children with cancer.

**Study design** The study population was a consecutive cohort of children diagnosed with cancer and a PAC implanted at diagnosis. Children were evaluated for the presence of PAC-related thrombosis by magnetic resonance venography and the presence of congenital prothrombotic risk factors and PTS.

**Results** A total of 114 children (median age, 6.04 years) were included. Of these children, 48 (42%) were treated for solid tumors and 66 (58%) were treated for hematopoietic tumors, including 38 for acute lymphoblastic leukemia. At the time of magnetic resonance venography, 42 children (37%) had the PAC still in place, and 72 (63%) had the PAC removed. Overall, PACs were in place for a total of 324.92 PAC-years. PAC-related thrombosis was detected in 45 children (39.5%) with a current or previous PAC. Of these, 21 (47%) had a solid tumor, 14 (31%) had acute lymphoblastic leukemia, and 10 (22%) had another hematopoietic tumor. Younger age at diagnosis, female sex, duration of PAC use, and left-side PAC placement were independently associated with an increased risk of thrombosis, whereas asparaginase therapy and the presence of inherited prothrombotic risk factors were not. Mild PTS (ie, presence of prominent collateral vessels in the skin) was present in 5.6% of the children.

**Conclusion** PAC-related thrombosis is common in pediatric oncology patients. In some children, thrombotic complications can lead to the development of PTS. *(J Pediatr 2013;163:1340-6)*.

Port-A-Cath (PAC) devices are indwelling central venous catheters (CVCs) inserted percutaneously through the jugular or subclavian vein (SV).[1] These devices play an important role in the long-term management of pediatric patients with a variety of severe diseases, the most important of which is cancer.[2] In pediatric oncology patients, PAC devices allow easy delivery of treatments such as chemotherapy and antibiotics, and provide a better quality of life during cancer treatment.[2] However, PAC devices also are associated with important complications, including infections and deep vein thrombosis (DVT).[3,4]

CVCs are the most important risk factor for DVT in children, and account for approximately 60% of all cases of childhood DVT.[5] CVC-related DVT can manifest with typical symptoms but more commonly goes unrecognized or produces only indirect signs, such as repeated loss of patency and CVC-related sepsis. Although previous studies have estimated the incidence of asymptomatic CVC-related DVT as 66% in all children with a CVC and up to 40% in pediatric oncology patients, little information is available on long-term radiologic features and clinical relevance, or on predictors of PAC-related DVT, in these children.[6-10]

Postthrombotic syndrome (PTS) is a chronic, potentially disabling complication of DVT characterized by symptoms varying from mild edema to chronic pain and ulceration of the affected limb.[11] In adults, the incidence of PTS is correlate with the time interval after a DVT, with reported rates of approximately 17% at 1 year and 60% within 2 years.[12,13] Initial follow-up data from the Canadian Registry suggest an incidence of clinically detected lower extremity PTS of approximately 10%-12% in children.[14] No accurate information is available on the incidence, clinical features, and risk factors of upper body PTS after DVT in children.

The present study aimed to investigate the incidence, risk factors, and radiologic features, as well as long-term outcomes and complications, of PAC-related DVT in a large heterogeneous pediatric oncology population.

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| ALL | Acute lymphoblastic leukemia |
| AT | Antithrombin |
| CVC | Central venous catheter |
| DVT | Deep vein thrombosis |
| MRV | Magnetic resonance venography |
| PAC | Port-A-Cath |
| PC | Protein C |
| PS | Protein S |
| PTS | Postthrombotic syndrome |
| SV | Subclavian vein |
| SVC | Superior vena cava |

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## Methods

The study population comprised a consecutive cohort of pediatric patients with both a diagnosis of cancer and a PAC device implanted between January 1997 and June 2005, attending regular follow-up at the oncology outpatient clinic at the University Children's Hospital of Zurich. The study was designed to include children with a PAC currently in place as well as children with a removed PAC for comparison. Children were excluded from the study who had any of the following conditions: known allergy to gadolinium-containing contrast agents; implanted pacemaker, intracerebral ferromagnetic clip, or newly implanted metallic prosthesis; inability to undergo magnetic resonance venography (MRV); or lack of informed consent.

At the time of the first MRV, patients were evaluated for PTS symptoms using a previously published pediatric scoring system including both subjective and objective criteria with a score of 0 if not present and either 1 or 2 if present. The severity of PTS was classified as mild (score 1-3), moderate (score 4-8), and severe (score >8).[15] Demographic data and information on the underlying disease and the PAC for each child were obtained through chart review. This study was approved by the Ethics Board of the University Children's Hospital of Zurich, and all patients and/or their parents provided written informed consent.

### Diagnosis of PAC-Related DVT

PAC-related DVT was diagnosed using MRV. All MRV studies were performed on a 1.5-T scanner (Signa MR/i Twinspeed; GE Medical Systems, Milwaukee, Wisconsin) with the smallest coil allowing coverage of the neck and the chest (ie, quadrature head coil, different-sized multichannel phased-array surface coils). Contrast-enhanced MRV was performed using a 3D fast spoiled gradient echo sequence with linear *k*-space filling, flip angle of 30°, bandwith of ±62 kHz, repetition time of 3.2-3.4 ms, and echo time of 0.9-1.1 ms. The field of view (260-480 mm), slice thickness (2-3.2 mm), and number of partitions (26-48) were adjusted to the child's size. A matrix of 256 × 160 and zerofilling interpolation in all 3 axes (512, 4) provided a spatial resolution ranging from 0.5 × 0.5 × 0.8 $mm^3$ to 0.8 × 0.9 × 1.5 $mm^3$. A double dose (0.2 mmol/kg body weight; maximum dose, 20 mL) of gadolinium-based contrast medium (dimeglumine gadopentate [Magnevist; Bayer, Zurich, Switzerland] or gadodiamide [Omniscan, GE Healthcare, Wädenswil, Switzerland]) was injected intravenously as a bolus over 10 seconds with a power injector (Medrad Spectris, Pittsburgh, Pennsylvania), and then flushed with the same volume of saline solution and the same injection rate. Image acquisition was timed to the first pass of the contrast medium through the aorta by a test bolus of 1 mL contrast material. For assessment of the systemic veins, the 3D data acquisition was repeated 3 times. Children under sedation with propofol (32 MRV studies) and those not able to hold their breath (6 MRV studies) were imaged during quiet breathing, and the other children (82 MRV studies) were imaged during 4 consecutive breath holds of 20-seconds duration.

MRV images were reviewed on an off-line workstation (Advantage Workstation; GE Healthcare) with standard reformatting software (Volume Viewer 2, VoxTool 6.11.2, GE Healthcare). From the acquired sets of images, the set with the highest signal in the systemic veins was selected for analysis. The SVs, internal jugular veins, brachiocephalic veins, and superior vena cava (SVC) were each assessed on coronal source images, multiplanar reformatted images, and subvolume maximum intensity projection images for thrombosis-related vessel abnormalities using the following criteria: (1) complete occlusion: vein completely filled with nonenhancing low-signal thrombotic material or not visualized at all; (2) partial occlusion: hypointense filling defects adherent to the vessel wall or catheter; and (3) stenosis: localized narrowing of the vein with a diameter reduction of >50% (**Figure**). Radiologically diagnosed asymptomatic PAC-related DVT was not considered an indication for anticoagulation.

### Evaluation for Prothrombotic Conditions

Blood samples for laboratory evaluation of inherited prothrombotic disorders were collected into tubes containing 0.105 M buffered trisodium citrate (3 mL final volume) for the determination of antithrombin (AT), protein C (PC), protein S (PS), and activated protein C resistance; 1.6 mg EDTA/mL blood (2.7 mL final volume) for the determination of prothrombin G20210A and factor V Leiden mutations; and 35 IU heparin/mL blood (1.2 mL final volume) for measurement of lipoprotein (a).

AT activity, PC activity, and activated protein C resistance were measured by chromogenic assay (Berichrom Antithrombin III and Berichrom Protein C Kits [Dade Behring, Schwalbach, Germany] and Coatest [Chromogenix, Milan, Italy]). PS activity was measured by a clotting assay (StaClot Protein S; Diagnostica Stago, Asnières sur Seine, France), free and total PS were measured by enzyme-linked immunosorbent assay (Zymutest Total Protein S and Zymutest Free Protein S; Hyphen BioMed, Neuville sur Oise, France). Prothrombin G20210A and factor V Leiden mutations were detected by polymerase chain reaction amplification (FV-PTH StripAssay; ViennaLab Labordiagnostika, Vienna, Austria). Lipoprotein (a) was measured by an immunoturbidimetric assay performed with a Cobas Integra analyzer (Roche, Basel, Switzerland). AT, PC, and PS results were interpreted using appropriate age-reference ranges.[16]

### Statistical Analyses

Descriptive statistics are presented as frequency, mean, or median with range as appropriate. Significant differences between groups were assessed by ANOVA or the $\chi^2$ test. To determine predictors of PAC-related DVT and PTS, univariate logistic regression analyses were performed, with data presented as ORs with 95% CIs. Analyzed variables included age at diagnosis, sex, duration of chemotherapy, doses of asparaginase, duration of PAC placement, PAC location, positive blood cultures, PAC dysfunction (ie, difficulties with