

## Review Article

# Venous Thromboembolism in the Pediatric Population: A Study in a Tertiary Hospital

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### Abstract

**Background:** Venous thromboembolism (VTE) which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) has been increasingly recognized in the pediatric population. The estimated incidence is 0.14 to 0.21 per 10.000 children per year. Most cases are associated with more than two risk factors.

**Objective:** To characterize the pediatric population with the diagnosis of DVT in a tertiary hospital, regarding its clinical presentation, associated risk factors, treatment and outcome.

**Methods:** Retrospective analysis of pediatric population (minimum 2 months, maximum 17 years) with the diagnosis of VTE in our hospital for a period of 6 years (2018-2023).

**Results:** Eleven patients were identified; six were females; median age was 9 years. The main symptoms were local pain, color alterations and edema. Lower limb was affected in nine patients. PE occurred in only one case involving a female adolescent who was using oral contraception, in whom a protein S deficiency was detected during the etiological investigation.

No family history was found. All patients had at least two identifiable risk factors. Initial treatment with enoxaparin was administered in all cases.

**Conclusion:** Although uncommon, VTE is an emerging reality in pediatric age, particularly during a hospitalization. Appropriated pre-

vention strategies and treatment are required as most orientations are extrapolated from adults.

### Introduction

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) is a rare yet increasingly recognized, potentially life-threatening event in pediatric population.

The exact incidence of VTE is unknown, but data from multiple studies suggest that diagnosis in hospitalized children has increased between 3 and 8 times, over a period of 15 years, ranging from 0.2 to 1.5 percent of the total admissions. [1] In general pediatric population, the incidence is around 0.14 to 0.21 per 10.000 children per year, whereas it is significantly higher, ranging from 2.5% to 5% in the general adult population. PE accounts for approximately 15% of VTE episodes [2].

A bimodal age distribution is observed in the pediatric population, with higher incidence among children less than 1 year of age and adolescents. Although most studies found no difference in incidence between genders, unless the higher incidence is in females due to combined oral contraceptive pill (OCP) use [3].

In the pediatric population, VTE often presents unique challenges due to anatomical and physiological differences when compared to adults. Risk factors are characterized by either a protein-losing state, inflammatory state, or vascular disruption and are summarized by Virchow's triad, which includes endothelial injury, stasis, and hypercoagulability.

More than 90% of cases exhibit two or more predisposing factors, a contrast to the adult population where 40% of cases are idiopathic. [4] In pediatric age, DVT is predominantly associated to access with central venous line (CVL) and tends to manifest in the upper limbs. Complications may either be absent or include recurring loss of CVL patency, sepsis-related CVL complications, limb swelling, limb discoloration, and prominent collateral circulation in the skin. Cases unrelated to CVL typically manifest in the lower limbs, although any venous territory can be affected (Table 1).

Death is a rare complication of VTE, around 2.2%. Medium and long-term complications include recurrence of the event (in rare cases during the course of treatment) and post-thrombotic syndrome (PTS), characterized by chronic venous insufficiency of the affected limb.

Our goal was to characterize the pediatric population, with the diagnosis of DVT of lower limbs in a tertiary hospital, regarding its clinical presentation, associated risk factors, treatment and outcome.

### Methods

We performed a retrospective and descriptive analysis of patients under 18 years old (minimum 2 months, maximum 17 years) diagnosed with DVT in a tertiary hospital's pediatric department and intensive pediatric care unit, during a period of 6 years (from January

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Temporary/Reversible	Persistent
Acquired risk factors	
Central venous line	
Cancer, chemotherapy and bone marrow transplant	
Total parental nutrition	
Immobilization	
Surgery <3 months	
Chronic kidney disease	
Recent Trauma	Cancer, chemotherapy and bone marrow transplant
Previous VTE	Congenital heart disease, prosthetic heart valves
Active infection	Systemic lupus erythematosus, antiphospholipid syndrome
Pregnancy and postpartum	Chronic kidney disease
Oral contraceptive pill	Previous venous thromboembolism
Obesity	
Nephrotic syndrome	
Congenital risk factors	
Factor V Leiden mutation	
Prothrombin G20210A mutation	
Antithrombin III deficiency	
Protein C deficiency	
Protein S deficiency	

**Table 1:** Risk factors for venous thromboembolism.

2018 to December 2023). Patients were identified in our database, using the International Classification of Diseases, 10th revision (ICD-10). Data was collected from clinical files, regarding clinical features, diagnostic procedures, treatment and outcome.

## Results

Eleven patients were identified, which corresponds to prevalence of 0.07 cases per 10,000 children admitted to the hospital at pediatric department and intensive pediatric care unit, in a period of 5 years (2.2 cases per year). Six patients were females. The median age was 9 years (minimum 2 months, maximum 17 years).

Three patients were diagnosed with DVT at admission and the other cases were found during hospitalization in the studied period.

The majority of cases presented symptoms (90%) mostly edema (73%), followed by color alterations (27%) and pain (18%).

The cases involved: lower left limb affecting the femoral vein (two cases); lower left limb affecting the inferior vena cava and iliofemoral territory (one case); lower left limb affecting the popliteal and iliofemoral territories (two cases); lower right limb affecting the iliac territory (one case); lower left limb affecting the iliofemoral territory (two cases); upper left limb affecting the jugular territory (two cases); upper right limb affecting the jugular territory (one case). The lower limb was more affected. There were no cases of bilateral disease.

In all patients, DVT was confirmed by venous Doppler ultrasound. No deaths occurred. Considering the risk factors identified at admission plus the congenital risk factors identified later, we found that all patients exhibited concomitant risk factors, with the majority presenting at least four. The most common associated risk factors were immobilization (eight), active infection (nine) and presence of central

venous line (eight). Other identified risk factors were recent surgery (four), congenital heart disease (two), cancer (two), recent trauma (one), and obesity (one). In some cases, there was an underlying pathology such as Chylous ascites (one), Spinal muscular atrophy (two), and Crohn's disease (one) and three cases had a history of prematurity.

A teenage girl taking oral contraceptives developed complicated DVT with PE, confirmed by computed angiogram. Subsequently, an etiological study revealed a protein S deficiency as the underlying cause of thrombophilia.

There were no idiopathic cases. Family history of VTE was found in one patient. The treatment with enoxaparin, a low-molecular-weight heparin, was initiated in all confirmed cases of DVT, in addition to the recommended Postural drainage in a lying position with elevation of the respective limb. The treatment duration varied from 3 to 6 months. None of the patients needed other therapeutic approaches, such as fibrinolytic agents, IVC filters or surgical thrombectomy. The combined oral contraceptive pill was discontinued.

After discharged all patients had follow-up appointments in Pediatrics and Immunohemotherapy. No complications or recurrence cases were recorded during the follow-up.

## Discussion

Though is rare, VTE is an emerging reality in pediatric populations, especially in younger children and adolescents. This can be related to multiple situations: increase of survival of children with pathologies previously considered fatal (with VTE being a consequence of those pathologies or a consequence of its treatment) and also increasing recognition of this entity by physicians and better diagnose techniques.

The study covered a period corresponding to the COVID-19 pandemic, during which the number of hospital admissions significantly decreased, which may have contributed to a VTE case prevalence of 0.07 per 10,000 admissions, a value significantly lower than reported in the literature. From the obtained data and in accordance with the literature, all cases presented with more than two risk factors, more associated with hospitalization.

The majority of cases of DVT associated with CVL affected the lower limb, which may be justified by the more frequent placement in the femoral vein. Therefore, placing access in another location, such as the internal jugular or subclavian veins, might be advantageous. No relationship was found between non-CVL related DVT and the location in the upper limb.

Screening for thrombophilias should not be offered routinely to all adolescents with a family history of VTE and/or thrombophilia, before starting OCP, but selective testing of adolescents with a family history of high-risk thrombophilias (deficiency of protein C, protein S and antithrombin III) may inform the choice regarding less thrombotic contraceptive options, such as the progesterone-only pill. In the case of the adolescent who developed a TVP complicated with a PE while using OCP, a protein S deficiency was discovered during the etiological investigation. So, in this sample, PE accounted corresponding of 9% cases, which is lower than in other studies conducted previously.

Low-molecular-weight heparins are recommended for acute anticoagulant therapy and should be kept for at least 5 days. Ongoing therapy is usually made with oral vitamin K antagonists, which should be initiated at the same time or a day after the heparin. The choice of anticoagulant depends on a number of factors, such as age,

patient compliance and underlying pathology. For a first VTE, if it is idiopathic, it is recommended to keep anticoagulant therapy for 6-12 months, but if a reversible risk factor is present, therapy should be continued until that factor has resolved, and last a minimum of 3 months. If a reversible risk factor is present, the approach should be the same as if it was a first case of VTE. In the cases reviewed, the majority were treated for a duration of 6 months. Despite each patient having multiple risk factors, in the majority of cases, these were reversible and were related to acute illness and hospitalization, except in cases of previously known disease.

Anticoagulant prophylaxis should also be considered for children who are undergoing chemotherapy, long-term home total parenteral nutrition or prolonged immobilization.

Currently, several VTE risk assessment schemes for hospitalized children consider the number of present risk factors. Based on the assessed risk, mechanical prophylaxis (including early mobilization, elastic compression stockings, and/or sequential compression devices) or pharmacological prophylaxis may be considered, even outside the intensive care or oncologic context.

## Conclusion

Venous thromboembolism is a rare and potentially life-threatening event in pediatric population. In contrast with adults, in whom idiopathic cases are common; VTE in pediatric populations is usually multifactorial. Therefore, DVT should be considered in the differential diagnosis of limb pain, edema and color alterations.

The potential consequences of VTE in children can be significant, necessitating timely diagnosis and appropriate management, for those healthcare professionals must exercise a high degree of suspicion when assessing symptoms. In this context, understanding VTE is essential for healthcare practitioners to provide timely and effective care, minimizing the potential long-term complications and optimizing the child's overall well-being.

More studies are required in pediatric populations in order to define prevention strategies and optimize VTE treatment, as well as to evaluate the long-term consequences of this condition, as most orientations are extrapolated from studies in the adult population.

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