Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 11/25/2022
Approved on: 11/27/2023

ORIGINAL ARTICLE

Venous thromboembolism in childhood: a glance of 20 years in a Paediatric Intensive Care Unit

Margarida Almendra[1], Catarina Santiago Gonçalves[1,2], Anaxore Casimito[1], João Falcão Estrada[1]

Keywords:
Venous thromboembolism, Upper extremity deep vein thrombosis, Pulmonary embolism, Pediatrics.

Abstract

Objective: Clinical characterization and approach of patients with thromboembolism (VTE). **Metodology:** Retrospective, descriptive study of patients aged <18 years with VTE in a pediatric intensive care unit in a tertiary care hospital over 20 years [2002-2021]. **Results:** Identified 51 patients: deep vein thrombosis (DVT) (n=30), cerebral vein thrombosis (CVT) (n=21), pulmonary thromboembolism (PTE) (n=4), portal vein thrombosis (PVT) (n=2) and renal vein thrombosis (RVT) (n=1). In 5 patients CVT and DVT coexisted (n=1); PTE and DVT (n=3); and RVT and DVT (n=1). Mean 2.6 cases/year. 52.3% male, median 6 years [1M;17Y]. The presence of a central venous catheter was the main risk factor (72%) in DVT associated with edema in the region; Doppler ultrasound was the exam of choice. All with PTE were adolescents; 75% had chest complaints confirmed by angio-CT; identified =2 risk factors in each patient. The case of RVT was a 2-year-old child with renal neoplasm. The cases of PVT were adolescents with symptoms of portal hypertension. The main symptom in CVT was headache (63.6); 52.4% secondary to upper respiratory infection; thrombophilia study positive in 42.9%. Analytically, all had elevated D-dimers. Most started anticoagulation with enoxaparin (86.3%), which they maintained for 3 to 6 months after discharge. Mean hospital stay was 17.6 days. There was 1 episode of recurrence and 1 death unrelated to VTE. **Discussion:** The presentation of thromboembolic phenomena is nonspecific and approach guidelines are scarce in Pediatrics. However, early detection is crucial to prevent complications.

[1] Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, EPE, Unidade de Cuidados Intensivos Pediátricos, Departamento da Criança e do Adolescente - Lisboa - Lisboa - Portugal.
[2] Hospital do Espírito Santo de Évora, EPE, Serviço de Pediatria, Departamento da Saúde da Mulher e da Criança - Évora - Évora - Portugal.

Correspondence to:
Margarida Almendra.
Hospital Dona Estefânia.Rua Jacinta Marto, 1169-045 Lisboa, Portugal. E-mail: margaridaalmendra@hotmail.com

Resid Pediatr. 2024;14(1). DOI: 10.25060/residpediatr-2024.v14n1-995

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION:

Venous thromboembolism (VTE) encompasses Deep Vein Thrombosis (DVT), Pulmonary Thromboembolism (PTE), Renal Venous Thrombosis (RVT), Portal Vein Thrombosis (PVT) and Cerebral Venous Thrombosis (CVT).

In pediatric age, VTE is considered a rare entity[1] with an estimated annual incidence of 0.14-0.21/10,000 children, which increases to 20-60/10,000 in hospitalized children[2]. In a retrospective study in the Netherlands, 85% of VTE episodes occurred in hospitalized patients, when virtually all the patients (98%) had at least one underlying risk factor[3].

There has been an increasing incidence[1,4] of this phenomenon due to the increase in the age of pediatric care, improved health care, greater survival of children with chronic pathology, greater use of interventions with risk of VTE and greater awareness of this type of events.

It typically presents a bimodal age distribution[2,4-6], mainly affecting infants under two years of age and adolescents.

The pathophysiology of VTE is explained by Virchow's Triad, which includes blood stasis, endothelial injury and hypercoagulability. In most cases, the etiology is multifactorial, with at least one underlying risk factor[1,5]; only 5%-10% of cases are idiopathic; unlike the adult population, when it reaches 60%[7]. The main risk factor identified is having a central venous catheter (CVC)[1,2,4-6], responsible for up to 2/3 of the cases[1,2,5]. In the neonatal period, the overwhelming majority of episodes (>90%) of VTE are caused by CVC[6,8]. In adolescence, the use of oral contraceptives (OC), especially combined contraceptives (COC), increases the risk of VTE by two to five times, particularly in the first year of use[6].

The main acquired and hereditary risk factors associated with the formation of VTE are listed[1,2,4-6] (Table 1). There are some risk factors that temporarily increase the risk of developing VTE, which can be considered both acquired and hereditary.

Clinical manifestations vary according to the location and extent of the thrombus and age[3,5] (Table 2). Most present in a non-specific and subtle way, requiring a high index of clinical suspicion[2].

Complementary diagnostic tests are used according to the location of suspected VTE. In DVT, Doppler ultrasound (echo-Doppler) is the most used method[2,4-6]. Computed tomography (CT) pulmonary angiography [angio-CT] is the exam of choice for diagnosing PTE[2,4,9]. As with DVT, TVR and PVT, Doppler ultrasound is the exam of choice for the diagnosis[5,10]. Angiography magnetic resonance imaging [angio-MRI] is the test of choice for diagnosing and monitoring CVT in newborns and children[4,5,11].

In relation to the analytical study, D-dimers, a marker of fibrinolysis, have a low specificity in pediatric age and may be elevated for other reasons[5].

The cornerstone of the thromboembolic treatment is anticoagulation. However, recommendations on dosage, monitoring and duration of treatment are extrapolated from adults due to the lack of pediatric studies, and there are no established guidelines for pediatric patients[1,5,9].

Among the different types of anticoagulants, the drug of choice is low molecular weight heparin (LMWH), the most used being enoxaparin due to its better bioavailability, longer half-life, dose-dependent clearance and no need for dose adjustment in liver failure; it is also associated with fewer and less severe bleeding complications, compared to unfractionated heparin (UFH). Under a prophylaxis regime, monitoring is not required[1,4-6,9,12].

Vitamin K antagonists (e.g. warfarin) are increasingly out of use due to their need for frequent adjustments and multiple drug and food interactions; as is UFH, due to its variable clinical response and frequent and serious adverse effects[1,4-6,9,12].

A recent class of anticoagulants – new oral anticoagulants (NOACs) – has been used in promising clinical trials in pediatrics[6,9]. This class is administered orally, one to two doses/day, requires no monitoring, its metabolism is not influenced by diet and has fewer drug interactions[1,6,9]. Dabigratan (direct thrombin inhibitor) and rivaroxaban (direct factor Xa inhibitor) were approved by the European Medicines Agency for the treatment and prevention of VTE in pediatric patients based on age and weight[13,14].

Regarding evolution, there is recurrence of VTE in 4-21% of cases, and up to 70% develop post-thrombotic syndrome, characterized by chronic venous insufficiency, edema, chronic pain and ulceration of the affected limb[2,5,6]. Mortality from VTE events varies between 8-20%[2], with PTE being the main cause with mortality rates reaching 24%[9].

Just like in therapy, VTE prophylaxis is not well established in pediatric patients[1,5,6].

METHODS:

Retrospective and descriptive observational study of patients under the age of 18 years, hospitalized with VTE in a pediatric intensive care unit (PICU) in a tertiary hospital, for 20 years [January 2002-December 2021]. The study was approved by the Ethics Committee of the Centro Hospitalar Universitário Lisboa Central, EPE. The statistical analyses were carried out using the Excel version 2013 software (Microsoft Corporation).

RESULTS:

51 patients were identified corresponding to: DVT (n=30), CVT (n=21), PTE (n=4), DVT (n=2) and RVT (n=1). In five patients, CVT and DVT coexisted (n=1); PTE and DVT (n=3); and RVT and DVT (n=1). There was an average of 2.6 cases/year with a peak in 2019 (n=7) (Graph 1). There was a slight male predominance (52.3%) with an average age of 7.7 years and a median age of 6 years [1 month - 17 years].

DVT was identified in 30 patients, five of which were associated with another type of VTE: three with PTE, one with CVT and one with RVT. In the remainder, the presence of CVC

Table 1. Risk factors.

Acquired	
Central venous catheter (CVC)	Neoplasia / myeloproliferative diseases
Infection	Falciform cells anemia
Surgery (+ orthopedic, neurosurgery)	Nephrotic syndrome
Trauma	Chronic total parenteral nutrition
Long immobilization	Pregnancy / Puerperium
Congenital cardiac disease / Valvular prosthesis	Obesity
Chronic inflammatory disease (e.g.: SLE, RA, BD, IBD, KD)	Drugs [(e.g.: OC, chemotherapy (asparaginase), steroids]
Hereditary	
Hereditary thrombophilia	Leiden Factor V
	Mutation in the prothrombin gene G2021OA
	Antithrombin deficit
	C protein deficit
	S protein deficit
	Combine deficits
	Lipoprotein A elevation
Anatomical / vascular malformations (May-Thurner syndrome)	
Hereditary and/or acquired	
Hereditary or acquired thrombophilia	Factor VIII levels rise
	Hyperhomocysteinemia
	Antiphospholipid antibodies

Legend: CVC = Central venous catheter; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; BD = Behçet's disease, IBD = inflammatory bowel disease; KD = Kawasaki disease; CO = oral contraceptives.

Table 2. VTE Clinical Manifestations.

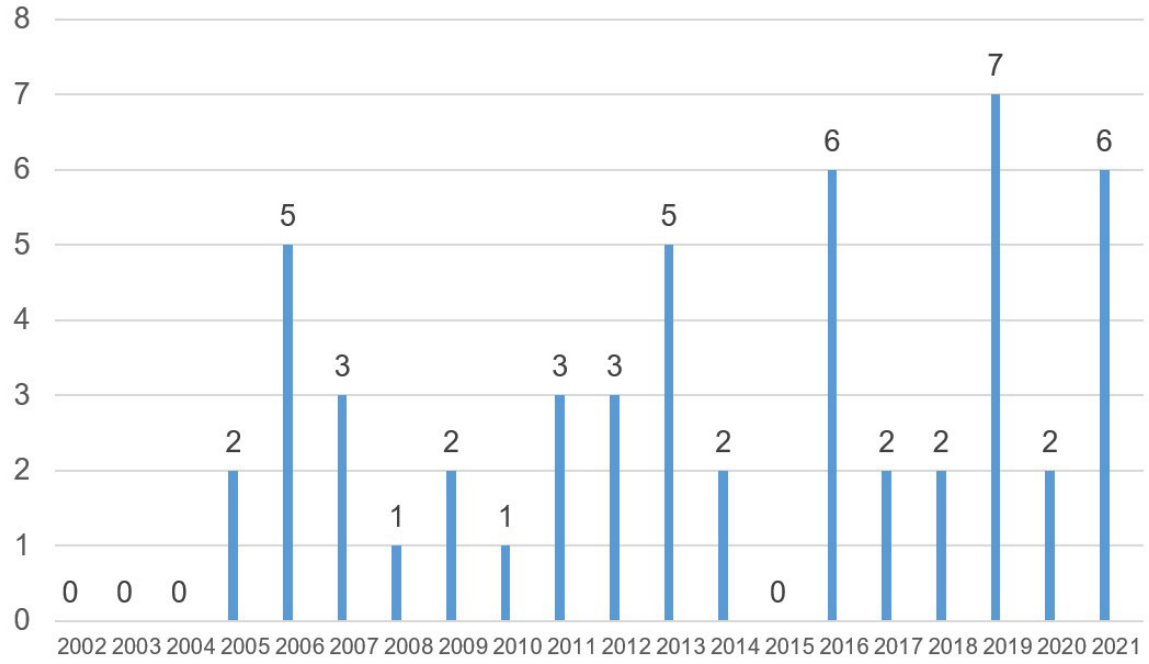
DVT	More common in the lower limbs; inflammatory signs in the limb[2,4]
PTE	Non-specific symptoms of asymptomatic, 50%: chest/pleuritic pain, sudden dyspnea; hemoptysis; tachypnea; tachycardia and hypoxemia[2,8,10]
RVT	Hematuria, anuria, vomit, proteinuria, thrombocytopenia, palpable mass in the side; may be insidious and without kidney symptoms[4]
PVT	Acute abdomen or later with portal hypertension (splenomegaly and high digestive hemorrhage secondary to esophageal varices)[2]
CVT	Diffuse neurological signs and symptoms (headache, vomit, change in conscience status) or focal (convulsion, hemiparesis, cranial nerves paresis; dysarthria, visual changes; aphasia, ataxy); in the newborn: seizures, lethargy, hypotony, apnea[4,9]

Caption: VTE = venous thromboembolism; DVT = Deep Vein Thrombosis; PTE = Pulmonary Thromboembolism; TVR = Renal Venous Thrombosis; PVT = portal vein thrombosis; TVC = Cerebral Venous Thrombosis.

was the main risk factor identified (72%, n=18). Other risk factors identified: neoplasm (n=8), recent surgery (n=9), infection (n=7), congenital heart disease/valvular prosthesis (n=5) and hereditary thrombophilia (n=4) (Table 3) . The main symptom was edema (n=18) in the CVC region and Doppler ultrasound was the test of choice. All cases of DVT associated with the presence of CVC occurred in patients hospitalized for another reason.

Caption: VTE = venous thromboembolism; DVT = Deep Vein Thrombosis; PTE = Pulmonary Thromboembolism; RVT = Renal Venous Thrombosis; PVT = portal vein thrombosis; CVT = Cerebral Venous Thrombosis; CVC = central venous catheter

The patients with bilateral PTE (n=4) were all teenagers. Three patients concomitantly presented with DVT; 75% had chest complaints and 50% pain and edema of the lower limb; 75% had increased cardiac markers and an EKG compatible with sinus tachycardia. Angio-CT confirmed the diagnosis of bilateral PTE in 3 cases; the last by chest CT; the latter case, due to clinical worsening, subsequently underwent CT angiography which confirmed bilateral PTE as well as evidence of pulmonary infarction. At least two risk factors were identified in each patient. Thrombophilia was positive in 75% of patients: primary antiphospholipid syndrome (n=1), heterozygous mutation in prothrombin gene G20210A concomitant with protein-S deficiency (n=1) and elevated factor VIII (n=1) (Table 3). Three patients showed signs of right ventricular dilation and were transferred to the Pediatric Cardiology Unit of the Hospital. Due to maintained hemodynamic stability with progressive improvement in myocardial injury markers and in the absence of cardiac dysfunction, it was decided not to perform systemic fibrinolysis. Three patients repeated their angio-CT 3 to 6 months after the event; half did not reveal the presence of thrombi; one patient showed signs of chronic PTE.



Graph 1: Annual distribution of VTE cases

The case of RVT was in a 2-year-old child with renal neoplasia; an insidious clinical presentation over months and without associated kidney symptoms.

PVT (n=2) was identified in two adolescents with symptoms of portal hypertension. A protein S and protein C deficiency was identified in one of the patients.

Of the CVT cases (n=21), four patients were under two years of age and 10 were teenagers. The main presenting symptom was headache (63.6%, n=14), followed by vomiting in 59.1% (n=13), fever in 45.5% (n=10), visual symptoms in 36.4 % (n=8), seizures in 9.5% (n=2) and dysarthria in 9.5% (n=2) of the patients; 52.4% (n=11) of the cases were secondary to infection of the sinuses, ear and/or the mastoid. Three teenagers were undergoing chemotherapy. Other acquired risk factors identified: presence of CVC in the jugular region (n=3), use of OC (n=3) and recent orthopedic surgery/ neurosurgery (n=3). The presence of hereditary thrombophilia was identified in nine patients, four of which had at least two concomitant changes (Table 3). Except for patients with CVT associated with the presence of CVC in the neck, all underwent CT-CE as the first imaging test and the majority (76.2%, n=16) completed the study with MRI/angio-MRI. The diagnosis was made by CT in 52.4% (n=11) and the remainder by MRI/angio-MRI. Of note, five patients showed signs of intracranial hypertension with evidence of papilledema and the need for therapy with acetazolamide; 38.1% underwent surgery (ENT surgery n=5, neurosurgery n=3) and four patients required anti-epileptic medication during hospitalization. CVT was the reason for hospitalization in most patients, only four patients were previously hospitalized for another reason. In the 6-month follow-up, 52.4% (n=11) had a repeat MRI-CE; and partial repermeabilization was found in the majority (63.6%, n=7), and total repermeabilization in 36.4% (n=4) . 42.9% (n=9) did not present neurological sequelae, while the remainder required some type of rehabilitation support and/or medication.

Analytically, all had elevated D-Dimers at the time of diagnosis with a mean of 2037.1 ug/L [247 – 24704 ug/L] and a median of 4765 ug/L (reference value: <230 ng/mL).

The majority started anticoagulation with LMWH (enoxaparin) (86.3%, n=44), of which four were initially treated with UFH. A patient with CVT discontinued enoxaparin due to a cerebral hemorrhagic complication with subsequent neurosurgical drainage. Anticoagulation was maintained 3 to 6 months post-discharge; At the time of discharge, NOACs were prescribed to 4 adolescents (in two cases of PTE, one of CVT and one of PVT) which they maintained for between 6 months and permanently.

The average length of stay was 17.6 days [1 day – 7 months] and the median was 11 days.

An episode of recurrence was recorded in one of the patients with PVT who was re-admitted to the PICU due to a liver abscess, with consequent DVT associated with the presence of a CVC.

One death was recorded due to multiorgan failure in the context of progression of an inoperable neoplastic disease; After discharge from the PICU, there were eight deaths, three of which were due to known neoplasia.

Table 3. Risk factors found in patients with VTE.

	DVT	PTE	RVT	PVT	CVT	n= Total
Acquired						
CVC	18				3	21
Infection	7	1			11	19
Recent orthopedic/neuro surgery	9	1			3	13
Neoplasia	8		1		3	12
Congenital heart disease / Valvular prosthesis	5					5
Oral contraceptive		2			3	5
Chemotherapy					3	3
Obesity		3				3
Immobilization		1				1
Hereditary						
Factor VIII rise	2	1			4	7
S protein deficit	1	1		1	1	4
Antithrombin deficit					3	3
Positive Lupus anticoagulant (DRVVT)					2	2
Hyperhomocysteinemia	1				1	2
History of VTE		1			1	2
Heterozygotic mutation in the prothrombin gene G20210A		1			1	2
May Thurner syndrome		2				2
C-protein deficit				1		1
VTE family history		1				1
Heterozygotic Factor V Leiden mutation					1	1
PAI-13 gene heterozygotic mutation	1					1
MTHFR gene mutation – Heterozygotic pair 677C>T and 1298A>C					1	1
Primary antiphospholipid syndrome		1				1
Falciform trace					1	1

Caption: VTE = venous thromboembolism; DVT = Deep Vein Thrombosis; PTE = Pulmonary Thromboembolism; RVT = Renal Venous Thrombosis; PVT = portal vein thrombosis; CVT = Cerebral Venous Thrombosis; CVC = central venous catheter.

DISCUSSION:

Despite being a rare entity in pediatric patients, more than half of these patients were previously hospitalized, which is in line with the higher incidence of thromboembolic phenomena observed in hospitalized children[2].

Our study presents two major age groups affected: adolescents, especially in PTE and PVT; and young school-age children in CVT and DVT, the majority associated with respiratory infections and the presence of CVC, respectively.

In the five adolescents who had been under OC for less than 6 monthws, the thrombophilia study was positive, which was unknown until now. However, the majority had other risk factors such as obesity or recent orthopedic surgery. It is known that OCs, especially COCs, increase the risk of VTE, particularly in the first year of use[6], so the first prescription of OCs in adolescents must be carefully considered.

DVT can occur in any venous segment, being more common in the lower limbs; however, when related to the presence of CVC, it tends to affect the upper limbs. The presence of CVC was, by far, the main risk factor identified, which is in line with the literature[1,2,4-6]. Given that all cases of DVT associated with the presence of CVC occurred in hospitalized patients, assessment of CVC function and limb edema should happen daily[5].

The main risk factor in PTE was obesity, which curiously was not identified in any other VTE group. Three of the four patients were obese, two of them grade III. Considering that obesity is a risk factor for the formation of VTE and that there has been an increase in obesity worldwide, especially associated with periods of confinement and consequent immobilization imposed by the COVID-19[15] pandemic, this may have contributed for the formation of thrombotic events in pediatric patients, given that 2021 was the second year with the most cases of VTE in our study.

PTE represents 15% of VTE episodes[16], which in our study corresponded to 7.7%. Right ventricular dysfunction plays a preponderant role in the outcome of PTE, in which acute right ventricular failure with low systemic output is the main cause of death in high-risk PTE[17]. However, not only was there a low number of PTE in our unit, but there were no deaths. Patients transferred to the Pediatric Cardiology Unit of the Hospital were stratified as intermediate-low risk PTE, which is why there was no indication for fibrinolysis. Our low incidence compared to current literature[18] in tertiary pediatric centers may reflect underdiagnosis due to low suspicion of PTE, as well as our study being carried out, specifically, in a PICU. Follow-up of PTE in pediatric patients is highly variable and recommendations are scarce[18]. Despite evidence of chronic PTE in one of the patients, there was no recurrence in any of them.

RVT is an entity mainly of the neonatal period, corresponding to 15-20% of VTE cases in newborns[10]. In older children, RVT may be associated with nephrotic syndrome and kidney transplantation[10]. Our only case of RVT was a 2-year-old child with an insidious clinical course and no associated nephrological symptoms, with a hard mass palpable only on the day of diagnosis, similar to that described in the literature[2]. Because we have a neonatal intensive care unit in our hospital, our unit does not receive newborns, which contributes to the low incidence of RVT in our study.

DVT also frequently occurs in the neonatal period. However, this age group is usually asymptomatic and is only identified in those who develop symptomatic portal hypertension years after the initial thrombotic event[10]. The diagnosis of our patients was made in adolescence, the first after surgical removal of an abdominal ganglioneuroma, and the second in the context of cholangitis. In the presence of cavernous transformation, anticoagulation is contraindicated due to the risk of variceal hemorrhage[10]. In both adolescents, anticoagulation was suspended due to symptomatic portal hypertension.

CVT, although rare, is a potentially fatal complication of acute otitis media, one of the most common pediatric infectious diseases. It should be noted that CVT cases corresponded to almost half of the total number of VTE cases, a warning on the likely underdiagnosis of this entity. Due to its subtle presentation, a high degree of suspicion is necessary for a timely diagnosis and appropriate treatment, in order to avoid serious sequelae. However, the appropriate treatment is not defined[19]. Recent guidelines recommend LMWH[20,21]; however, the duration and type of anticoagulation is not a consensus[19]. The patients in our study had a repeat MRI-CE approximately 6 months to 1 year after the initial event, meaning they only suspended anticoagulation after this time window, and, if so, in the presence of repermeabilization of the venous sinuses.

Thrombophilia screening is not indicated in children with well-defined risk factors[5]. It should be performed if spontaneous VTE of severity disproportionate to the identified risk factor, recurrent VTE, family history of VTE and unusual location (intra-abdominal, cerebral venous sinuses), and should be performed outside the period of acute illness[4]. In our study, all patients with PTE and CVT underwent the study, except for four patients with CVT (two with the presence of CVC and two with a history of previous otomastoiditis/sinusitis). In patients with DVT, only those that occurred in association with septic shock/severe infection were studied.

Regarding prophylaxis, there is no consensus on its indication in pediatric patients[1,5]. In order to determine which patients benefit from prophylaxis, the risk of VTE must be assessed[6]. Jinks[22] developed an algorithm that assesses the risk of venous thromboembolic events in adolescents over 13 years of age with expected reduced mobility in the next 48 hours, considering prophylaxis according to risk stratification. General measures, such as hydration, early mobilization and CVC removal whenever possible, should apply to all patients[1,5,22]. In case of moderate and high risk, consider mechanical and pharmacological prophylaxis, respectively[1,22].

Due to the increase in the age of pediatric care up to 17 years, one of the challenges we have been seeing in Pediatrics is to include young people with similar or even greater weight than adults, as well as risk factors, sometimes forgotten in Pediatrics; such as OCs and pregnancy. Two of our patients weighed more than 140kg, and the adult dose was used. The 4 adolescents who were prescribed NOACs - dabigatran and rivaroxaban - (in two cases of PTE, one of CVT and one of PVT) had no complications or recurrences with good compliance to therapy, highlighting the need for clinical trials with this new therapeutic class in pediatric age.

Our study has important limitations. Our hospital is a national reference center with multiple pediatric specialties, so it would be interesting to know the reality of other hospitals. However, our findings probably cannot be extrapolated to all pediatric centers due to the complex biased population of a tertiary hospital. Our main limitation is that it is a retrospective study. It is possible that we are missing some information because our system transitioned from paper to digital during the study period, which contributes to the lack of registration in certain patients as well as the possible lack of registration of possible patients. The existence of a specific Pediatric Cardiology and Neonatal Intensive Care center in our Hospital Center also justifies the underrepresentation of patients with congenital heart disease and newborns, respectively.

CONCLUSION:

VTE is a rare event in Pediatrics. However, there is the possibility that Pediatrics will be faced with a new reality previously excluded from this age group, drawing attention to the particularities of the different forms of presentation.

Treatment and prophylaxis protocols are based on the adult population, so there are few evidence-based recommendations to identify pediatric patients at higher risk of thrombosis. More studies are needed, including the assessment

of risk factors, especially in hospitalized patients, in order to improve patient treatment and establish approach guidelines in Pediatrics. Although there is no consensus, its early detection is crucial, with a subsequent better prognosis.

REFERENCES:

1. Sanmartín MF, Quintela JT, Núnez A. Anticoagulación, antiagregación y trombolysis. In: Cid JL, Rey CC, Galán C, Núnez A. Manual de Cuidados Intensivos Pediátricos. 5ª ed. Publimed; 2019.
2. Brás M, Ferrão A, Morais A. Tromboembolismo venoso. In: Correia M, Levy A, Camilo C, Abecasis F, Vieira M, Quintas S. Protocolos de urgência em pediatria. 4ª ed. Departamento de Pediatria, Hospital de Santa Maria: ACSM Editora; 2019.
3. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: A prospective two-year registry in The Netherlands. J Pediatr. 2001;139(5):676-81.
4. Pollmar MIR, Banares MJB, Román MTA. Síndromes de hipercoagulabilidad. In: Guerrero RD, Sánchez C, Bonis B, Suso M. Manual de Diagnóstico e Terapéutica en Pediatría. 6ª ed. Libro Verde Hospital Infantil LA PAZ. Buenos Aires: Editorial Medica Panamericana; 2017.
5. Alcalá FJC, Aguilar CRT. El nino com patologia crónica o compleja. In: Guerrero RD, Sánchez C, Bonis B, Suso M. Manual de Diagnóstico e Terapéutica en Pediatría. 6ª ed. Libro Verde Hospital Infantil LA PAZ. Buenos Aires: Editorial Medica Panamericana; 2017.
6. Jaffray J, Young G. Deep vein thrombosis in pediatric patients. Pediatr Blood Cancer. 2018;65(3).
7. Andrade JA et al. Tromboembolismo Venoso em Idade Pediátrica: Estudo Retrospetivo de 15 anos. Acta Med Port. 2018 Sep;31(9):489-95.
8. Longo MCR, De Lucca PM, Goldsmit G, Fariña D, Lipsich J, Rodríguez S. Catheter-related deep vein thrombosis in newborn infants. Arch Argent Pediatr. 2021;119(1):32-8.
9. Navanandan N, Stein J, Mistry R. Pulmonary Embolism in Children. Pediatr Emerg Care. 2019;35(2):143-51.
10. Kumar R, Kerlin BA. Thrombosis of the Abdominal Veins in Childhood. *Front Pediatr.* 2017;5:188. DOI: https://doi.org/10.3389/fped.2017.00188
11. Brás M, Quintas S, Morais A. Trombose venosa cerebral. In: Correia M, Levy A, Camilo C, Abecasis F, Vieira M, Quintas S. Protocolos de urgência em pediatria. 4ª ed. Departamento de Pediatria, Hospital de Santa Maria: ACSM Editora; 2019.
12. Morais A, Camilo C, Correia M. Terapêutica antitrombótica. In: Correia M, Levy A, Camilo C, Abecasis F, Vieira M, Quintas S. Protocolos de urgência em pediatria. 4ª ed. Departamento de Pediatria, Hospital de Santa Maria: ACSM Editora; 2019.
13. European public Assessment report: Xarelto. European Medicines Agency; 2021.
14. European public Assessment report: Pradaxa. European Medicines Agency; 2020.
15. Lange SJ, Kompaniyets L, Freedman DS, Kraus EM, Porter R, DNP3, et al. Longitudinal Trends in Body Mass Index Before and During the COVID-19 Pandemic Among Persons Aged 2-19 Years – United States, 2018-2020. MMWR Morb Mortal Wkly Rep. 2021;70(37):1278-83. DOI: https://doi.org/10.15585/mmwr.mm7037a3.
16. Carpenter SL, Richardson T, Hall M. Increasing rate of pulmonary embolism diagnosed in hospitalized children in the United States from 2001 to 2014. Blood Adv. 2018 Jun;2(12):1403-8. DOI: https://doi.org/10.1182/bloodadvances.2017013292.
17. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjoça VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonar embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. DOI: https://doi.org/10.1093/eurheartj/ehz405.
18. de Bragança RL, Gorito V, Cibele DG, Gonçalves LR, Ribeiro A, Baptista MJ, et al. Pulmonary embolism in pediatric age: A retrospective study from a tertiary center. Pediatr Pulmonol. 2021;56(8):2751–60.
19. Castellazzi ML, di Pietro GM, Gaffuri M, Torretta S, Conte G, Folimo F, et al. Pediatric otogenic cerebral venous sinus thrombosis: a case report and a literature review. Ital J Pediatr. 2020;46(1):122. DOI: https://doi.org/10.1186/s13052-020-00882-9.
20. Chalmers E, Ganesen V, Liesner R, Maroo S, Nokes T, Saunders D, et al. Guideline on the investigation, management and prevention of venous thrombosis in children. Br J Haematol. 2011;154(2):196-207. DOI: https://doi.org/10.1111/j.1365-2141.2010.08543.x.
21. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e737S-801S. DOI: https://doi.org/10.1378/chest.11-2308.
22. Jinks S, Arana A. Venous thromboembolism in paediatrics. BJA Educ. 2019 Sep;19(9):305-12. DOI: https://doi.org/10.1016/j.bjae.2019.05.003.