Paediatric venous thromboembolism: a report from the Italian Registry of Thrombosis in Children (RITI)

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Background. The Italian Registry of Thrombosis in Children (RITI) was established by a multidisciplinary team with the aims of improving knowledge about neonatal and paediatric thrombotic events in Italy and providing a preliminary source of data for the future development of specific clinical trials and diagnostic-therapeutic protocols.

Materials and methods. We analysed the subset of RITI data concerning paediatric systemic venous thromboembolic events that occurred between January 2007 and June 2013.

Results. Eighty-five deep venous thromboses and seven pulmonary emboli were registered in the RITI. A prevalence peak was observed in children aged 10 to 18 years and, unexpectedly, in children aged 1 to 5 years. A central venous line was the main risk factor (55% of venous thromboembolic events); surgery (not cardiac) (25%), concomitant infections (23%) and malignancy (22%) were the clinical conditions most often associated with the onset of venous thromboembolism. There was a diagnostic delay of more than 24 hours in 37% of the venous thromboembolic events. Doppler ultrasound was the most widely used test for the objective diagnosis of deep venous thrombosis (87%). Antithrombotic therapy was administered in 96% of venous thromboembolic events, mainly low molecular weight heparin (60%). In 2% of cases recurrences occurred, while post-thrombotic syndrome developed in 8.5% of cases.

Discussion. Although the data from the RITI are largely in agreement with published data, peaks of prevalence of thrombosis, risk factors and objective tests used for the diagnosis showed some peculiarities which may deserve attention.

Keywords: venous thrombosis, children, registry, Italy.

Introduction

Venous thromboembolic events (VTE) include deep venous thromboses (DVT) and pulmonary emboli (PE). Although VTE are rare in children, their recognition and diagnosis has increased in the last decades due to the greater availability of imaging techniques, the higher level of suspicion of VTE in particular clinical contexts, the longer survival of children with previously fatal or chronic diseases that can predispose to thrombosis, and to the more frequent use of central venous line (CVL)[1-8]. Indeed, the incidence of VTE in hospitalised children has increased 3- to 10-fold over the past 15 years[9-12]. In a single centre in Alabama, the reported incidence of VTE was 21.9 cases per 10,000 admissions between 2006 and 2008[13]. Drawing on information in an inpatient database (KID), Setty *et al*. reported a rate of 18.8 VTE per 10,000 discharges[14]. These data are supported by studies that specifically reported varying rates of VTE over time, i.e., 34 to 54 cases per 10,000 admissions in tertiary care hospitals in the United States between

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2001 and 2007[12] and 0.3 to 28.8 per 10,000 admissions between 1992 and 2005[15]. Other studies have also found increasing trends[16].

In recent years, awareness of the impact of VTE on mortality and chronic morbidity in children has also increased[6,7,17]. The true frequency of adverse outcomes such as VTE-related mortality, recurrent VTE, and the development of post-thrombotic syndrome does, however, remain unclear.

The epidemiology, risk factors, prevention, diagnosis and therapeutic management of VTE in paediatrics are poorly defined and still under discussion. Despite significant advances in the last two decades, randomised controlled trials are unavailable and most current treatment recommendations are still extrapolated from adult studies. National and international registries have been created in various countries (Canada, the Netherlands, Germany, and Denmark) to better define the epidemiology of VTE in children[2,18-20].

Limited data on thromboembolism in the Italian paediatric population have been published so far.

In 2007, a multicentre research network of Italian investigators, supported by the main national Paediatric Scientific Associations, set up a national prospective online registry of thrombosis in children (http://www.trombosi.org/it/progetti/riti.html) through a secure web database. The Italian Association against Thrombosis and Cardiovascular Diseases (*Associazione per la Lotta alla Trombosi e alle malattie cardiovascolari*, ALT) also funded the Registry. The Italian Registry of Thrombosis in Children (*Registro Italiano Trombosi Infantili*, RITI) was established in order to obtain more information about the pathogenesis, diagnosis, risk factors and management of thromboembolism in neonatal and paediatric age in Italy. It is organised in four parallel branches according to the age group affected (neonatal or paediatric) and to the site of thrombosis (systemic or cerebral). Results obtained for paediatric cerebral thromboembolic events and neonatal systemic thromboembolic events have already been reported21,22. In the present study we present risk factors, clinical and laboratory findings, instrumental diagnostic investigations, treatment and outcome of systemic VTE (DVT and PE) which occurred in children (29 days-18 years) and were recorded in the RITI up to June 2013.

Materials and methods

The Italian Registry of Thrombosis in Children

The RITI is available online through the website http://www.trombosi.org/it/progetti/riti.html. Subscription to the Registry is open to all medical doctors in Italy, after identity verification. The recruitment of thrombotic cases is event-based. The general features and the structure of the RITI have been described previously[21].

Thrombotic events occurring between 1st January, 2007 and 30th June, 2013 were registered by 153 Italian physicians from 55 centres of care in 15 Italian regions between 1st May, 2010 and 30th June, 2013. Overall, 465 thromboembolic events (cerebral and systemic) occurred in 432 patients (neonates and children) and were included in the RITI. One hundred and eighty-three of the 465 events (39%), occurred in neonates (age 0-28 days) whereas 282 (61%) occurred in paediatric patients (29 days-18 years).

Our study

The focus of the present study was an evaluation of the branch of the Registry concerning paediatric systemic VTE, including all paediatric DVT and PE recorded in the Registry.

The study was conducted according to the Helsinki declaration; patients' data were anonymised and informed consent to inclusion in the Registry had to signed by the children's parents or legal guardians.

Inclusion criteria were asymptomatic incidentally recognised VTE or acute symptomatic VTE, provided the event was confirmed by objective tests (ultrasound, magnetic resonance imaging, magnetic resonance angiography, computed tomography, computed tomography angiography, angiography, ventilation-perfusion scan) or was an intra-operative or post-mortem finding.

DVT was defined as a partial or complete thrombotic obstruction of one or more veins of a lower limb (and/or pelvis), upper limb or splanchnic district; PE was defined as the presence of thrombus (or fragments of it) in the pulmonary arterial circulation or interruption of the flow within the pulmonary circulation. DVT and PE were classified as paediatric if they occurred between the 29th day of postnatal life and the 18th year of age.

Exclusion criteria were inconsistency of data and impossibility of contacting the referring physician.

For each VTE, we analysed the following variables:

- age and sex distribution;
- number of prothrombotic risk factors (one, two or more) and type:
  - clinical conditions associated with increased thrombotic risk (heart disease, vascular disease, infections, cancer, metabolic disease, blood disease, kidney disease, headache, neurological disease, inflammatory bowel disease, autoimmune disease, trauma, surgery, immobility, dehydration);
  - thrombophilic conditions (factor V Leiden [FVL], prothrombin mutation G20210A [PT G20210A], MTHFR C677T polymorphism with or without hyperhomocysteinaemia), inherited deficiencies of physiological

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anticoagulants such as protein C, protein S, or antithrombin (deficiency confirmed in at least two determinations at an interval of at least 3 months and confirmed in one of the parents), increased levels of procoagulant factors VIII, IX and XI, persistence (in two or more determinations at intervals of at least 3 months) of anti-phospholipids antibodies (lupus anticoagulant, anti-cardiolipin immunoglobulin IgG or IgM, anti-β2 glycoprotein IgG or IgM);
- presence of a CVL;
- clinical presentation (incidental finding, malfunctioning CVL, signs/symptoms of venous thrombosis);
- site of thrombosis: upper district DVT, lower district DVT (proximal/distal), splanchnic venous thrombosis;
- time interval between onset of symptoms and instrumental diagnosis (diagnostic delay) : <3 hours, 3-6 hours, 6-24 hours, >24 hours;
- admission to the Paediatric Intensive Care Unit;
- antithrombotic therapy (thrombolytic therapy, anticoagulation [type of drug], antiplatelet therapy, others);
- complications of antithrombotic therapy (bleeding, heparin-induced thrombocytopenia, others);
- outcome at discharge;
- outcome at last follow up (recurrences, death, post-thrombotic syndrome, neurological symptoms, others).

Results

During the study period, 282 events were recorded in the section of paediatric VTE of the registry. Of these 282 paediatric thromboembolic events, 170 (60.5%) were cerebral thromboembolic events (79 cerebral arterial thromboses and 91 cerebral venous thromboses), 12 (4%) were intracardiac thromboses and 8 (3%) were arterial systemic thromboses.

Ninty-two out of the 282 thromboembolic events (32.5%), were systemic VTE, comprising 85 DVT (92%) and seven PE (8%). Two of the cases of PE occurred as a result of DVT.

The 92 systemic VTE occurred in 88 patients (median age: 5 years; range: 1 month - 18 years), with a slight prevalence of male sex (47/88, 54%); 86% (76/88) developed in Caucasians.

The age distribution of systemic paediatric VTE is shown in Figure 1.

Risk factors

A previous history of VTE was reported in 10/92 (11%) events. Two of these cases were PE following DVT. Fifty-five percent (51/92) of VTE were related to a CVL.

A single clinical condition associated with an increased risk of thrombosis was reported in one-third (33%) of events, while more than one clinical condition of increased thrombotic risk was reported in about half of the cases (56%). The clinical prothrombotic conditions associated with systemic VTE are summarised in Table I.

One thrombophilic abnormality was reported in 15 patients; two or more thrombophilic abnormalities were reported in eight patients. Thrombophilic abnormalities commonly reported in the Registry are summarised in Table II.

Clinical presentation

The diagnosis of DVT was made after the onset of signs and symptoms in 72/85 (85%) cases, whereas the DVT were asymptomatic in the remaining 13/85 (15%) cases and the diagnosis was therefore

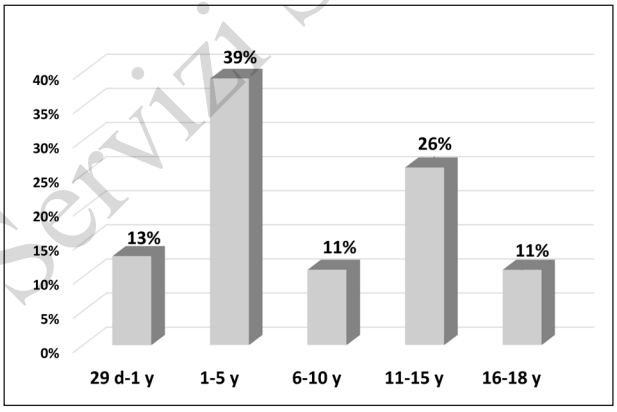


Figure 1 - Age distribution of systemic VTE in children reported in the RITI.
VTE: venous thromboembolic event; RITI: Italian Registry of Thrombosis in Children; d: day; y: year.

Table I - Clinical conditions associated with prothrombotic risk in cases of VTE.

Prothrombotic condition	N	%
Surgery	23	25
Infection	21	23
Malignancy	20	22
Kidney disease	12	13
Heart disease	10	10
Haematological disease	9	10
Immobility	8	9
Metabolic disease	6	6
Trauma	5	5.5
Dehydration	5	5.5
Vasculopathy	4	4
Autoimmune disease	3	3

VTE: venous thromboembolic event.

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Table II - Thrombophilic conditions associated with VTE reported in the Registry.

Thrombophilic alteration	N. for whom data available	Results	Notes
Lupus anticoagulant	26/88	3 (11.5%)	
FVL G1691A	37/88	5 (13.5%)	Heterozygous in 3 cases; Homozygous in 2 cases
PT G20210A	35/88	4 (11.4%)	Heterozygous in 3 cases; Homozygous in 1 case
Inherited defect of protein S	N/A	5	Homozygous in 3 cases; Heterozygous in 2 cases
Inherited protein C deficiency	N/A	1	Heterozygous

VTE: venous thromboembolic event; N/A: not available.

incidental; in 7/13 (54%) of these latter cases, the DVT were CVL-related. Of the total 85 DVT, 49 (58%) were CVL-related; of these 49 CVL-related DVT, 7 (14%) were asymptomatic and 15 (31%) had CVL malfunction as a first sign. Table III summarises the clinical presentation of the symptomatic DVT.

Differently from DVT, PE was always diagnosed in the presence of clinical signs and symptoms. In 2/7 (28.5%) cases of PE, an association with DVT was reported. Table IV summarises the clinical presentation of PE.

Site of thrombosis

DVT affected the lower deep venous system in 55/85 (65%) cases, the upper deep venous system in 29/85 (34%) cases and the splanchnic venous system in 1/85 (1%) cases (thrombosis of renal vein after kidney transplantation).

DVT involved multiple sites in 41/85 (48%) cases; half of these cases (21/41) were CVL-related. Data about the site of CVL-related DVT were available in 46/49 cases. CVL-related DVT affected the lower deep venous system in 28/46 (61%) cases and the upper deep venous system in 18/46 (39%) cases.

As regards PE, thrombosis involved the right pulmonary artery in 3/7 cases, the left pulmonary artery in 2/7 cases, and minor pulmonary branches in 4/7 cases.

Time to diagnosis

Data about time to diagnosis were available for 87/92 (94.5%) of the systemic VTE. The lag time between the onset of symptoms or signs (clinical suspicion) and the objectively documented diagnosis was less than 24 hours in 55/87 (63%) cases and more than 24 hours in 32/87 (37%) cases.

Objectively documented diagnosis of deep vein thrombosis

Data on diagnostic procedures used to objectively document DVT were available for 77/85 (90.5%) events. Compression ultrasonography and/or echo-colour Doppler were performed in 67/77 (87%) cases and were consistent with a diagnosis of DVT in all. Compression ultrasonography and/or echo-colour Doppler were followed by computed tomography scanning in nine cases, computed tomography angiography in seven and magnetic resonance angiography in one.

Echocardiography was performed in 32/77 (41%) cases; it was abnormal in 14 cases, although it showed thrombosis directly in only four cases (2/4 CVL-related cases).

Angiography was the only diagnostic examination in three cases and was abnormal in all: two patients had DVT of a limb and one patient had an inferior vena cava thrombosis.

Table III - Clinical presentation of symptomatic cases of DVT.

Signs and symptoms	N	%
Oedema	47	65
Pain	31	43
Discoloration (cyanosis, pallor) of the involved limb or extremity (signs of stasis)	29	40
Superficial collateral circulation	6	8
Superior vena cava syndrome (mantle oedema)	5	7
Chylothorax	3	4
Renal failure	1	1

DVT: deep venous thrombosis.

Table IV - Clinical presentation of PE.

Signs and symptoms	N	%
Dyspnoea	4	57
Chest and abdominal pain	2	28.5
Tachycardia	2	28.5
Cough	1	14
Respiratory failure	1	14

PE: pulmunary embolism.

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Objectively documented diagnosis of pulmonary embolism

Data were available for 4/7 cases. Computed tomography scanning of the chest was performed in two cases and was abnormal in both. Chest computed tomography angiography was performed in the other two cases and was abnormal in both. Echocardiography was performed in two cases and was abnormal in both. No patient underwent ventilation/perfusion scintigraphy.

Therapy

Admission to the Paediatric Intensive Care Unit was necessary in 25/92 (27%) systemic VTE.

Antithrombotic therapy was administered in 88/92 (96%) events. Intravenous therapy with unfractionated heparin was administered in 15/88 (17%) cases, and therapeutic doses of low molecular weight heparin were used in 63/88 (71.5%). Oral anticoagulants were given in 19/88 (21.5%) cases (warfarin in 17 cases; acenocoumarol in 2 cases). Thrombolytic therapy was administered in 8/88 (9%) cases (recombinant tissue plasminogen activator in 6 cases; urokinase in 2 cases). Antiplatelet therapy with acetylsalicylic acid was administered in 4/88 (4.5%) cases.

The CVL was electively removed in 10/51 events. Thrombectomy was performed in a patient with a massive thrombosis of the inferior vena cava.

Out of 74 events undergoing pharmacological treatment, 30 (4%) required more than one drug (Table V).

Complications of anticoagulant therapy occurred in 5/88 (5.5%) patients; two patients were reported to have developed heparin-induced thrombocytopenia (one patient during treatment with unfractionated heparin and the other during treatment with low molecular weight heparin) while three patients receiving thrombolytic therapy (2 with recombinant tissue plasminogen activator; 1 with urokinase) had major bleeding.

Outcome

Outcome at discharge

Data were available for 92 VTE (85 DVT and 7 PE), which occurred in 88 patients.

No thromboembolism-related deaths were reported. Two patients (2%) died from their underlying disease.

VTE recurrence was reported in two cases (2%); two patients (2%) had PE complicating DVT. Thirty-seven children (40%) had complete resolution of VTE, 22 children (24%) showed partial recanalisation and 10 (11%) had persistent occlusion at the site of the DVT. Extension of thrombosis at discharge was observed in one case.

VTE-related complications and sequelae were reported at discharge in 13/92 (14%) cases: loss of vascular access in six cases (requiring repositioning in 5 cases); sensory-motor deficit in the limb affected by DVT in four cases; renal failure in one patient with PE; loss of the transplanted kidney in one patient with renal vein thrombosis; and necrosis of the proximal phalanx of the big toe in 1 one patient.

Outcome at last follow up

The duration of follow up ranged from 3 months to 50 months. Data were available for 34 VTE (32 DVT and 2 PE), which occurred in 33 patients, representing only 37% of the VTE registered in the RITI.

Asymmetry in the growth of the limbs was reported in two cases of DVT and post-thrombotic syndrome occurred in eight cases (8.5%) of DVT.

Discussion

In this study, 92 paediatric VTE (85 DVT and 7 PE), registered in the RITI, were analysed. This is a considerable number of events in view of the relative rarity of this condition in childhood. Indeed, data in the literature show higher incidences of VTE in neonates and young adults than in children[1,2,11,12,18,19]. In our study, 36% of the VTE were reported in children aged 10 to 18 years old. Unexpectedly, 39% of VTE were found in children aged 1 to 5 years old, possibly reflecting the changing epidemiology of risk factors.

Table V - Treatment of systemic VTE.

Treatment	N
OA only	3
UH therapy	
UH only	2
UH and OA	4
UH and LMWH	4
UH and LMWH and OA	1
LMWH therapy	
LMWH only	38
LMWH and OA	10
Thrombolytic therapy (r-tPA or UK)	
Thrombolytic and UH	1
Thrombolytic and UH and LMWH	3
Thrombolytic and LMWH	4
Antiplatelet therapy	
Antiplatelet only	1
Antiplatelet and LMWH	2
Antiplatelet and LMWH and OA	1
Supportive care only	4
Antithrombotic therapy not known	14

VTE: venous thromboembolic event; OA: oral anticoagulant; UH: unfractionated heparin; LMWH: low molecular weight heparin; r-tPA: recombinant tissue plasminogen activator; UK: urokinase.

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As found in other Registries[3,23], the presence of a CVL was the main risk factor for VTE (55% of cases).

About half of the VTE were associated with clinical conditions at increased risk of thrombosis, such as surgery (not cardiac), concurrent infections or malignancy, confirming the role of these clinical conditions in favouring the onset of thrombosis[2,12,18,19,24,25].

Unfortunately, the data relative to thrombophilia in our study are incomplete because only a few cases underwent full investigation. FVL and the PT G20210A mutation, as well as the presence of antiphospholipid antibodies and/or lupus anticoagulant, were the thrombophilic factors most frequently investigated.

The diagnosis of DVT was incidental in 13/85 cases. The clinical importance of asymptomatic DVT is still a matter of debate[26,27].

Most cases of DVT, especially those related to upper limb CVL, were reported as asymptomatic and often clinically unrecognised[3,21,28,29]. In our study, 54% of asymptomatic DVT were related to a CVL. CVL-related asymptomatic DVT could be related to CVL infections and represent a frequent cause of PE[30]. Furthermore, recurrent occlusion of a CVL may result in loss of venous access[30].

Probably CVL-related cases of DVT are more severe in the present study since 51% of the DVT affected multiple sites, and the events had a wide extension. Similarly, an Australian study showed that patients with thrombosis in more than one site, often had a CVL[31].

The diagnosis was delayed, beyond 24 hours after the onset of the symptoms, in 37% of the cases of systemic VTE. Such a delay can be partly explained by the non-specificity and heterogeneity of the clinical presentation of VTE (and therefore also by a delay in medical examination and clinical investigations for non-hospitalised patients) or by a low index of suspicion on the part of physicians. A delayed diagnosis has also been previously reported in children with stroke[3] and in adult patients with VTE[32]. A late diagnosis can expose patients to acute complications due to a delay in starting antithrombotic therapy and can have a negative impact on the prognosis[8,32,33].

The diagnosis of VTE was made by objective tests in all our cases. In our study Doppler ultrasonography was the most widely used instrumental examination for the diagnosis of DVT and it allowed diagnosis in all cases. In the Canadian register of VTE, venography alone or associated with other instrumental methods was the most frequently used diagnostic technique[2]. Since 1990-1992, when the Canadian registry of VTE was released, the use of the Doppler ultrasound has increased thanks to the wide availability of the test, its cost and the non-invasiveness of the technique; this increased use has been shown by the British and Dutch registries of paediatric VTE, as well as by a single-centre Australian study[18,19,20,31].

Despite the high accuracy of Doppler ultrasound, our patients underwent computed tomography in 16 cases and magnetic resonance imaging in one case, to confirm the thrombosis or define it better.

Venography was performed in only three of our cases and in only one of them, a central DVT (inferior vena cava thrombosis) was detected. Angiographic study associated with computed tomography or magnetic resonance imaging was preferred to venography, even in cases of central DVT, despite the well-documented higher diagnostic sensitivity of venography for central intrathoracic thrombosis[23,34,35].

Data on the sensitivity and the specificity of imaging investigations for the diagnosis of PE in paediatric age are scarce. In contrast to the data reported in the Canadian and Dutch registries, ventilation-perfusion lung scanning was not performed in our cases for the diagnosis of PE[2,18].

Ninety-six percent of VTE were treated with antithrombotic therapy. In the Canadian and Dutch registries[2,18], the patients were mainly treated with unfractionated heparin, followed by oral anticoagulants, but more recent data indicate an increase in the use of low molecular weight heparin[11,12,19]. The majority of our cases of VTE were treated with low molecular weight heparin alone or followed by oral anticoagulation, in agreement with the recent guidelines[24,30].

Canadian and Dutch registries reported a VTE-related mortality rate of approximately 3% whereas the Canadian Childhood Thrombophilia Registry reported a death rate of 2.2%[2,18,36]. Two deaths were recorded in our Registry, both of which were unrelated to the VTE.

In our study, VTE improved in 64% of cases at discharge, with complete resolution in 40% of events. These results are in agreement with those previously reported in the literature[2,12].

The incidence of post-thrombotic syndrome in our study was similar to that reported by Monagle *et al*.[36] but lower than that found in the Canadian registry of paediatric VTE[2]. The incidence of post-thrombotic syndrome in our and other paediatric registries is, however, lower than that in adults[37]. Since data on the follow up of many of our cases are lacking, the frequency of post-thrombotic syndrome is likely to be underestimated.

Our study has several limitations. Firstly, since the RITI is a collection of VTE and not a study population, it is not possible to estimate the incidence of VTE in Italian children. Furthermore, available data were incomplete in several cases. Thirdly, information about a relationship of thrombophilia with outcome/follow up needs further investigation because only limited data were available. The financial crisis and consequent

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constraints on resources that the Italian health system has been subjected to in recent years could have contributed to inequality in registry compilation across the country, as data are classically entered by young physicians and grant recipients. Because of irregular distribution of facilities over the country, some paediatric hospitals may have entered only a few of their cases.

Conclusions

Despite the above-mentioned limitations, the RITI offers interesting data on paediatric VTE in Italy which are comparable with data from other paediatric registries and contribute to establishing a network for further studies on paediatric VTE. Stronger efforts should be made to render this resource more effective and representative of the Italian situation, moving from a voluntary organisation to an established national health system tool.

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Authorship contributions

PG, MG, PS, and PSi analysed and interpreted the data and drafted the manuscript; AS and SS drafted the manuscript; ACM, CG, DL, ML, MCP, and LLR revised the manuscript and contributed to the data collection; GI, FP and the members of the Paediatric Thrombosis Working Group of the RITI (see Authors in appendix) contributed to data collection.

The Authors declare no conflicts of interest.

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Appendix I

Other members of the Paediatric Thrombosis Working Group of the *Registro Italiano Trombosi Infantili* (RITI) who registered thrombotic events: Bianca Bassi, Elisa Bertoni, Anna Capretta, Anna Casani, Daniela Farinasso, Marcella Gaffuri, Elena Gallo, Giulia Ghirardo, Anna Guida, Francesca Maschio, Donata Panzeri, Margherita Nosadini, Andrea Pettenazzo, Giovanna Russo, Roberto Sangermani, Nicola Santoro, Domenico Sperlì, Daniela Tormene, and Antonella Tufano.

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