Experiencia italiana en trombosis neonatal y pediátrica

Italian experience in neonatal and pediatric thrombosis

Thrombosis in children and neonates: data from the RITI registry
(Registro Italiano Trombosi Infantili)

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Background
The thrombotic disease of the newborn and the child is relatively rare compared to that of an adult. However, it is most frequently diagnosed today than in the past, especially in patients with acute illness also for greater awareness of the thrombotic complications that can occur(1). All forms of thromboembolism (TE) in both venous and arterial or intracardiac or atypical sites appear to be increasing for several reasons including i) the greater intensity of care and disposables put in place to support severe cases; ii) the widespread use of devices for vascular access; iii) typical risk factors which are more frequent in adulthood, today also present in childhood (the earliest use of oral contraceptives, obesity, sedentary lifestyle, etc).

The diagnosis of TE in neonatal and pediatric patients is often particularly difficult because vascular diagnostic techniques have been almost exclusively validated in adults and diagnostic criteria extrapolated outright to child. Appropriate specific clinical trials for the diagnosis of TE in children are needed to validate these protocols.

The natural history of the TE in the child is not completely elucidated yet. This fact has a significant practical implication in choosing whether and how to treat the thrombotic event. The event type (sometimes asymptomatic), the presentation (idiopathic or secondary), the evaluation of the risk factors predisposing to TE recurrence, the risk/benefit ratio of antithrombotic therapy, intensity and duration, the risk of bleeding related to treatment even if it is generally perceived as less relevant than in adults.

The use of antithrombotic drugs in pediatric patients is different than in adults for many reasons, including the epidemiology of the TE, the fact that the hemostatic system in the child varies with age,
the pharmacokinetics and pharmacodynamics of anticoagulants that also depends on age, the difficulty of the route of administration that can condition the choice of the drug, the absence of specific formulations for the pediatric age of most antithrombotic drugs, the diet that can strongly influence the absorption of drugs especially in the newborn, the compliance to therapy that may be suboptimal for several reasons related to the lack of understanding of the need for the therapy or emotional aspects in children.

Epidemiology of thromboembolism in children

There are many epidemiological studies on the incidence of TE in children. Some national and international registries have collected data on venous TE (VTE) and other thrombotic events in newborns and children. Some population studies in the Netherlands and Canada have estimated an annual incidence of VTE in the pediatric age below 18 years amounting to 0.7-1.4 per 100,000(2-6). In contrast to this finding, in US children’s hospitals for tertiary care, the incidence of VTE was 34 per 10,000 admissions in 2001 to 58 per 10,000 hospitalizations in 2007, which suggests an increase in the incidence of venous thromboembolism in the last years(1). The distribution of VTE in children by age shows a higher proportion of events in those aged less than 1 year, while there is a second peak of incidence during adolescence. There are few epidemiological data on pulmonary embolism in children. Retrospective autopsy studies report an incidence of PE equal to 0.05-4%(7).

The incidence of arterial thrombosis in children is reported only in a few studies. These are often iatrogenic thrombosis related to vascular access, in vasculitis (such as Kawasaki disease) or in connection with solid organ transplants. In a study conducted between 1999 and 2002, the incidence of arterial thrombosis was equal to 8.5 per 10,000 admissions to pediatric hospitals for tertiary care(8), which would make the arterial thrombosis rate comparable to that of the venous district.

The intracardiac thrombosis is more easily diagnosed in children who have central venous access with the tip of catheter reaching the right atrium. Other causes of intracardiac thrombosis may be cardiac surgery in patients with congenital heart disease(0-12).

Risk factor for thromboembolism

There are some basic concepts that differentiate the child from the adult as regards the risk factors. First, the idiopathic thrombosis is relatively rare in children and occurs in less than 10% of pediatric cases of thrombosis(13). Children tend to have at least one but generally more risk factors for concomitant thrombosis. Central venous catheters are the single most frequent risk factor being associated with about 90% of neonatal thrombosis and to 60% of pediatric thrombosis(2). Generally, the catheters are present in premature and in children with acute or chronic diseases, they are used for parenteral nutrition, or the administration of chemotherapeutic drugs and other therapies. There are many other acquired risk factors that may be associated with pediatric thrombosis including infections, malignancies, immobility, dehydration, obesity, oral contraceptive therapy, nephrotic syndrome, treatment with L-asparaginase, antiphospholipid antibody syndrome. Finally, there are anatomical abnormalities such as atresia of the inferior vena cava which can cause venous thrombosis in the limbs or lower output from thoracic outlet syndrome (Paget-Schroetter syndrome) that may be associated with subclavian-axillary axis venous thrombosis(14). Finally, compression by the right iliac artery on the left iliac vein can account for episodes of left ilio-femoral thrombosis apparently spontaneous(15).

The inherited thrombophilia

The main hereditary thrombophilia conditions are reported in Table 1. In recent years, however, the usefulness of the screening for hereditary thrombophilia study both in adults and children has been questioned(16,17). Most of the available data deal with thrombophilia associated with the presence of the factor V Leiden and the prothrombin G20210A variant (mostly the heterozygosity). Other hereditary conditions studied are the physiological coagulation inhibitors such as antithrombin, protein C and protein S. The attention has been paid to the high levels of factor VIII, lipoprotein (a) and homocysteine that were associated with an increased thrombotic risk, however, taking into account the fact that these changes are not necessarily attributable to specific genetic mutations.

The prevalence of hereditary thrombophilia in children with TE strongly depends on the selection of
case studies and the criteria used for the definition of thrombophilia(18). A meta-analysis has documented a significant association between all the major causes of hereditary thrombophilia and the first episode of venous thromboembolism in children (especially of more than one year old)(19). Another meta-analysis showed an association between pediatric stroke due to acute arterial ischemia or thrombosis of the cerebral venous sinuses and some of the common hereditary thrombophilia(20). Inherited thrombophilia is more present in adolescents with spontaneous thrombosis or caused by contraception or trauma and surgery, while in children where thrombosis is catheter related the role of thrombophilia is doubtful(21-23).

### Table 1. Main causes of inherited thrombophilia in children

| 1. | Defects or functional antithrombin |
| 2. | Defects or functional protein C |
| 3. | Defects or functional protein S |
| 4. | Factor V Leiden (homozygous or pseudo-homozygous) |
| 5. | Prothrombin variant G20210A (homozygous or homozygous) |
| 6. | Mild hyperhomocysteinemia |
| 7. | Dysfibrinogenemias |
| 8. | Increase of lipoprotein (a) |
| 9. | Increased levels of factor VIII and IX |
| 10. | Hyperfunctioning factor IX (Factor IX Padua) |
| 11. | Mutations of (pro) thrombin resistant to inactivation by antithrombin (prothrombin Yukuhashi, prothrombin Padua 2, prothrombin Belgrade) |

The information resulting from the thrombophilia screening today is considered of little use to handle the event of thrombosis and for decisions on the duration/intensity of anticoagulation or thromboprophylaxis of risk situations. Although some defects are associated with an increased incidence of thrombotic events, the current guidelines on the treatment of TE does not take into account the presence or absence of thrombophilia. This attitude, however, has limitations: 1) most information on the risk related to thrombophilia is derived from data that mainly concern the two most common genetic polymorphisms (factor V Leiden and the prothrombin variant G20210A) or even the mild hyperhomocysteinemia. These conditions present with low thrombotic risk even though they are frequent in the general population. In addition, only a few studies have evaluated the real role of thrombophilia in the risk of TE recurrence; 2) new causes of inherited thrombophilia have been identified that were unknown in the past and can cause thrombosis in children(24-26); 3) lack of prospective studies on the real risk of thrombosis in healthy children or those with diseases who are major carriers of hereditary thrombophilia. Thrombophilia screening is undoubtedly justified in infants presenting with purpura fulminans and that may have a homozygous defect of protein C or protein S. The incidence of such defects is extremely low, for homozygous defects in protein C being between 1: 250000 and 1: 500000(27). The concentrated protein C has proven extremely useful in the treatment of this serious clinical manifestation. The need for coagulation screening in asymptomatic children belonging to thrombophilic families where a hereditary defect has been identified is still a matter of debate. The absolute risk of a thrombotic event spontaneous or in the presence of predisposing conditions for healthy children belonging to thrombophilic families is extremely low(28). Therefore this information can have little impact on the decision for the clinical management of children. Since the risk increases with age, the presence of thrombophilia (especially the more severe thrombophilic conditions) can affect the decisions on the use of oral contraceptives during adolescence or drive a possible thromboprophylaxis during casts or surgery or immobilization. Doctors should be careful to manage properly the information coming from coagulation screening and the possible identification of a hereditary thrombophilia defect. The child or adolescent and his family should be informed of the exact meaning of this result avoiding to cause excessive anxiety as well as to transmit false reassurances.

### Clinical manifestations

The signs or symptoms of venous or arterial throm-
bosis depend on the location where the event occurs. Deep vein thrombosis of the upper limbs. It is relatively common and affects the subclavian vein, brachiocephalic, internal jugular and superior vena cava. It is usually associated with the presence of central venous catheter. The signs or symptoms are represented not only by the frequent loss of patency of the catheter with swelling, pain, limb skin discoloration, swelling of the face and neck (mantle edema) when superior vena cava is involved. It may be complicated by pulmonary embolism with the classic respiratory symptoms, chest pain, cardiac manifestations up to shock.

Deep venous thrombosis of the lower limbs. It may occur in the popliteal vein, superficial femoral, common femoral, external iliac and inferior vena cava. These districts are less affected than in adults especially in childhood. Symptoms are characterized by swelling, pain, tenderness, skin discoloration, thermal alterations. In case of caval thrombosis and/or bilateral thrombosis there may be the concomitant involvement of both lower limbs or it can take place the inferior vena cava syndrome. It may be associated with symptomatic or asymptomatic pulmonary embolism.

Pulmonary embolism. Pulmonary embolism occurs mainly in children with critical and central venous catheters and diseases among adolescents with hereditary thrombophilia. It is often missed in younger children who are not able to accurately describe the symptoms and wherein the underlying disease (eg, cardiac) can mask the respiratory deterioration linked to the embolism. Dyspnea, chest pain and hypoxemia are the signs and symptoms most frequently encountered in the course of pulmonary embolism in children.

Thrombosis of renal veins. It is the most common cause of thrombosis especially in male infants. Symptoms are characterized by hematuria, palpable mass and frequently thrombocytopenia. Among the risk factors, dehydration, maternal diabetes, perinatal asphyxia and prematurity can be present. Almost in 30% of cases, thrombosis is bilaterally and in about half of the cases the thrombus may extend to the inferior vena cava.

Thrombosis of the cerebral venous sinuses. Thrombosis of the cerebral venous sinuses are rare in children, but are now being diagnosed more frequently, and it is estimated that their incidence can be around the 0.67 per 100,000 children, with a preference for infants and young children. An unfavorable evolution of the disease or even death is found, respectively, in 38% of infants and in 4% of children; more than 5% develop recurrences. In infants the most common predisposing conditions are dehydration and septic events; in older children are coagulation disorders, heart disease, connective tissue disease, infections of the head and neck, otomastoiditis. MRI is the method of choice for the diagnosis of cerebral venous sinus thrombosis. The ultrasound Doppler investigation is another diagnostic method that can be used when magnetic resonance imaging is not available. MRI can be used also for the monitoring of the disease itself, having the ability to highlight bleeding complications or thrombus extensions.

Arterial thromboembolism. Arterial catheters are the leading cause of arterial thromboembolism in children, either catheters involving peripheral arterial access or umbilicals, or cardiac catheters. Arterial thrombosis unrelated to the catheter are rare in children. The etiology of these events can be familiar hyperlipidemia, hyperhomocysteinemia, Takayasu arteritis, Kawasaki disease, arterial structural congenital abnormalities and complications from a congenital heart disease.

Ischemic stroke. The ischemic stroke is rare in children with an incidence estimated that fluctuates from 12 per 100,000 per year in neonatal age to 0.5-6 per 100,000 in children older than 1 year. The most common predisposing conditions to cerebral ischemic events in children are congenital heart defects (atrial septal defects, patent foramen ovale), perinatal asphyxia, infections, arterial abnormalities, dissections. Other risk factors described in the literature may be homozygousity for sickle cell disease, the moy-a-moya disease, dehydration and iron deficiency anemia. The diagnosis of neonatal cerebral ischemia, because of the non-specificity of its clinical presentation can escape in the acute phase and can be done later when the young patient begins to show neurological disorders (presumed perinatal ischemic stroke). For the diagnosis of this disease in the acute phase the computed tomography or magnetic resonance imaging are indicated. Angiography via resonance imaging or traditional angiography should be considered for the display of small and medium brain arteries in the case that one cannot rule out a dissection, or in the case of unexplained
recurrent ischemic events\(^{37-39}\). About 35% of children who developed ischemic stroke remain normal from a neurological point of view, and 42% present with cerebral ischemic event outcome, neurological defects from medium-to-severe\(^{38}\). Newborns have the highest percentage of total recovery after an ischemic event, presenting a normal neurological picture at a distance from the event about 50% of those affected by the disease. The risk of recurrent cerebral ischemic events was assessed to be around 20%, with a mortality rate that is calculated around 6-14\%\(^{35,41-43}\).

**The Italian Registry of Thrombosis in Children**

Since 2008 it was established the Registro Italiano delle Trombosi Infantili (RITI) (Italian Registry of Thrombosis in Children) thanks to a network of physicians involved in the treatment of thrombosis in children. The aim of the Registry is to enroll the largest number of cases of systemic and cerebral thrombosis in infant and child and gather data on risk factors, treatment, outcomes in the short and long term. The Registry site is www.trombosinfantili.it. Some reports on the RITES data are already available in the literature\(^{44-45}\). Figure 1 shows the RITI’s Logo.

The first available report by Suppiej et al, deals with paediatric cerebral thrombotic events occurred in Italy between January 2007 and June 2012\(^{44}\). Similarly to data from other national and international registries, a prevalence of male gender both in AIS and CSVT was observed as well as a slightly higher mean age at diagnosis in the CSVT as compared to the AIS events. Clinical presentation was also in agreement with the literature and the anterior circulation was most frequently involved in the AIS events, followed by the posterior, and both anterior and posterior circulation. Isolated infarctions prevailed over multiple infarctions and differences between the side of hemispheric involvement were not found. In CSVT, the thrombotic process mostly involved the superficial venous system. Brain MRI and MRA were the neuroimaging studies most frequently performed at presentation both in the AIS and in the CSVT events, but other tools such as conventional catheter angiography were used in a lower proportion of cases. As regards etiologies, it was unknown in nearly a fourth of AIS events. This proportion is highly variable in the literature, ranging from lower percentages in the IPSS international registry and in the Swiss registry to nearly half of cases in the Argentinean registry. In CSVT, the proportion of events with unknown etiology was lower than that of AIS in the RITI. In the RITI, the AIS cases with known etiology were mostly due to underlying chronic diseases, vasculitis, cardiac disease and infections. In the RITI, in paediatric CSVT cases the most frequent risk factors were chronic disorders (especially tumors) and infections, similarly to the Canadian and the Argentinean registries. The major difference between the RITI and other registries was the considerably delayed time to diagnosis in our population, especially for CSVT. Diagnostic delay is a worldwide acknowledged problem in the paediatric population compared to adults. However, in Italy diagnostic delay appears greater compared to other countries. Indeed, diagnosis of paediatric stroke is more difficult than that of adult stroke, considering its relative rarity, the high frequency of stroke mimics and the difficulty recognizing symptoms in young children; all these factors possibly contribute to a delayed diagnosis. At this respect, in our Registry the thrombotic event was an incidental finding in 2.94 % of the AIS events and in 14.08 % of the CSVT events. The main goal of the Registry was to improve management of thrombosis in children, to highlight its clinical features and most adequate diagnostic investigations, in order to possibly improve time to diagnosis in the future and make early interventions more effective. Late stroke diagnosis delays timely treatment and represents a major obstacle to thrombolysis. In AIS, reperfusion therapy with alteplase is a recommended intervention in adults within 3 h of symptoms onset, and its
In our population, concomitant prothrombotic/thrombophilia were contributing associated factors. Maternal/placental disease as well as fetal inherited was clinically diagnosed on the first day of life, and in premature babies. Notably, in 25% the event was confirmed, particularly significant for renal vein thrombosis and also for spontaneous aortic arch thrombosis. In the RITI, male predominance (65%) was confirmed, particularly significant for renal vein thrombosis (100%) and for AT diagnosed at birth (90%). However, evaluation analysis of risk conditions found no difference in males compared with females. Systemic thrombosis occurred in almost 70% of cases in premature babies. Notably, in 25% the event was clinically diagnosed on the first day of life, and maternal/placental disease as well as fetal inherited thrombophilia were contributing associated factors.

In our population, concomitant prothrombotic/inflammatory conditions were present at time of diagnosis, as infections and CVL. Much work over the past has focused on the bidirectional activations of inflammation and thrombosis, as fibrin sheaths formed around catheter tips may serve as a nidus for bacterial adherence/growth, and inflammation generated by systemic infection may activate thrombin formation on indwelling catheters. Indeed, vascular catheters constitute one of the most significant acquired risks for development of thromboembolism in neonates (20%-65%). Increased length of catheter stay, infusion of TPN and blood products, and misplaced umbilical vein catheters were identified as significant risk factors, without relevant role of inherited thrombophilia. Current recommendations state that prophylactic heparin may decrease CVL occlusion, although not consistently preventing thrombosis. Infections and TPN infusion were confirmed as concomitant conditions in CVL-related thromboembolism. However, only a minority of centers referred routine use of prophylactic heparin in CVL. Regarding another acquired risk factor, such as the presence of APLA, it has been rarely reported in neonates; the majority of studies describe transplacental passage of maternal antibodies, with stroke being the prevalent event and clinical manifestations being associated with pre/perinatal events. Also, the few reports of de novo neonatal APLA all had an additional prothrombotic risk factor, either inherited or acquired. Age-related deficiency of anticoagulants, overproduction of procoagulants and deficiency/dysfunction of fibrinolysis may lead to the transient prothrombotic phenotype in neonates, representing a concomitant risk factor for thromboembolism. A significantly lower plasmatic activity of PC and PS was found among screened patients with arterial events, probably related both to their lower GA and to earlier birth age at time of event. As for the role of inherited thrombophilia, a positive family history for thromboembolism was extensively reported among neonates with “early onset” event, including paternal thrombophilia. Thrombophilia screening performed in the present cohort was found positive mainly among cases with “early onset” thromboembolism. Recommendation for routine testing for inherited thrombophilia in all neonates with thrombosis is still controversial. The recruitment of thrombotic events in RITI is on a voluntary basis; thus, it is not possible to extrapolate data on the incidence or prevalence of thrombosis in the Italian pediatric population. This modality also explains the yet incomplete coverage of the entire Italian territory. However, in the present study, a significant number of cases were recruited by the 2 centers that provided additional information on number of live births and on number of admissions.
to NICU, allowing us to extrapolate local epidemiologic data. However, conclusions on risk factors or the nature of the causality of thrombotic events in newborns require evidence from prospective case control studies.

**Declaración de conflictos de interés:**
Los autores declaran que no poseen conflictos de interés.

**Bibliography**


