Thromboembolism in children

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Acquired and inherited prothrombotic risk factors increase the risk of thrombosis in children. This review is based on "milestone" pediatric reports and new literature data (January 2001- February 2002) on the presence of acquired and inherited prothrombotic risk factors, imaging methods, and treatment modalities in pediatric thromboembolism. After confirming clinically suspected thromboembolism with suitable imaging methods, pediatric patients should be screened for common gene mutations (factor V G1691A, prothrombin G20210A and MTHFR C677T genotypes), rare genetic deficiencies (protein C, protein S, antithrombin, and plasminogen), and new candidates for genetic thrombophilia causing elevated levels of lipoprotein(a), and homocysteine, and probable genetic risk factors (elevations in fibrinogen, factor IX, and factor VIIIC, and decreases in factor XII). Data interpretation is based on age-dependent reference ranges or the identification of causative gene mutations/polymorphisms with respect to individual ethnic backgrounds. Pediatric treatment protocols for acute thromboembolism, including thrombolytic and anticoagulant therapy, are mainly adapted from adult patient protocols. Curr Opin Hematol 2002, 9:448–453

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Abbreviations

APC-R	resistance to activated protein C
MRI	magnetic resonance imaging
MTHFR	methylenetetrahydrofolate reductase
PE	pulmonary embolism

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Venous and arterial thromboses are rare diseases but are increasingly diagnosed and recognized in infancy and childhood. Symptomatic thrombotic manifestation is recorded in 0.07/10,000 children, 5.3/10,000 admissions of children, and 24/10,000 admissions of newborns to intensive care units in Canada [1]. Within the entire childhood population, possibly because of the lower concentrations of antithrombin, heparin cofactor II, and protein C, reduced fibrinolytic capacity and elevations in hematocrit and ultralarge-molecular-weight multimers of the von Willebrand factor, neonates are at greater risk of thrombosis. The incidence of thromboembolic diseases decreases significantly after the first year of life, with a second peak during puberty and adolescence, again associated with reduced fibrinolytic activity [1]. This review is based on "milestone" pediatric reports and new literature data (January 2001- February 2002) on the presence of acquired and inherited prothrombotic risk factors, imaging methods, and treatment modalities in pediatric thromboembolism.

Clinical and acquired conditions

Thrombus formation and thrombus growth are the results of vascular injury and local coagulation activation combined with a disturbance in the balance between coagulation and fibrinolysis, leading to a prothrombotic state. Numerous conditions, such as peripartal asphyxia, fetal diabetes, neonatal infections, dehydration, the use of central lines, trauma or surgery, malignant diseases, renal diseases, autoimmune diseases, the administration of coagulation factor concentrates, or the intake of oral contraceptives in adolescent girls result in elevated thrombin generation with subsequent thrombus formation in infancy and childhood (Table 1) [2–5,6•,7–14••,15–19,].

Locations of thromboembolic events

Venous thromboembolism

In neonates, the most common manifestations of vascular occlusion are thrombosis of the renal veins and the vena cava, and peripartal thromboembolic stroke (Table 2). In addition, high rates of catheter-related thrombosis in neonates, infants, and children have been reported. Central venous lines lead to thrombus formation and thrombus growth near the catheter implantation site, especially when prothrombotic risk factors are involved. Further sources of childhood thromboembolism reported are cerebral venous thrombosis, intracardiac thrombosis,

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Table 1. Clinical risk factors for pediatric thromboembolism

Perinatal Diseases	Birth asphyxia
	Respiratory distress syndrome
	Infants of diabetic mothers
	Neonatal infections
	Necrotizing enterocolitis
	Dehydration
	Congenital nephrotic syndrome
	Polycythemia
	Demise of a fetal twin
Medical Interventions	Central lines
	Operations
	Transplantation (kidney, heart, bone marrow)
	Immobilization
	Plaster casts
	Extracorporeal membrane oxygenation
Acute Diseases	Trauma
	Sepsis
	Dehydration
	Acute rheumatic diseases
	Nephrotic syndrome
	HUS/TTP
	Acute lymphoblastic leukemia
Chronic Diseases	Malignancies
	Renal diseases
	Cardiac malformations
	Chronic rheumatic diseases
	Sickle cell disease
	Inflammatory bowel disease
Drugs	E. coli asparaginase
	Prednisone
	Activated coagulation factor concentrates
	Coagulation factor replacement: excessive levels
	Heparins
	Antifibrinolytic agents
	Oral contraceptives

HUS/TTP, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura.

portal and mesenteric vein thrombosis, vascular occlusions of the deep limb veins, and pulmonary embolism.

Arterial vascular occlusions

Arterial vascular occlusions besides thromboembolic ischemic stroke have been reported, mainly as catheter-related thrombosis in the aorta, femoral artery, mesenteric arteries, and subclavian artery, respectively [2–9].

Table 2. Locations of venous and arterial thrombosis in children

Venous	Deep vein thrombosis of the limbs
	Pulmonary embolism
	Renal veins
	Hepatic veins
	Caval veins
	Right intracardiac thrombosis
	Portal vein
	Mesenteric veins
	Cerebral veins
	Retinal vein
Arterial	Ischaemic stroke
	Aorta
	Left intracardiac
	Renal artery
	Mesenteric artery
	Limb artery

Inherited genetic disorders

Various genetic defects, particularly those affecting the physiologic anticoagulant systems, *ie*, antithrombin-, protein C-, and protein S-deficiency; resistance to activated protein C (APC-R) mostly because of the G1691A mutation of coagulation factor V, and the prothrombin G20210A gene variant, have been established as risk factors for thrombotic events not only in adults [20] but also in venous [21–27,26•,27,25••] and cerebral thromboembolism [28–39,32•,36,39,38••] in neonates, infants, and children (Table 3). Metabolic diseases such as homozygous homocysteinuria, and moderate hyperhomocysteinemia because of malnutrition or the common homozygous TT genotype of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism have been described, as well as increased concentrations of lipoprotein (Lp)(a), fibrinogen, factor VIIIC, and factor IX, or factor XII-deficiency, which have been shown to enhance the risk of thromboembolic arterial and venous thrombosis in pediatric or adult patients. In addition, infants with acute purpura fulminans because of homozygous protein C deficiency or protein S deficiency have been reported. The prothrombotic risk factors reported are not only involved in pediatric venous or arterial thromboembolism but also in intraventricular hemorrhage in preterm infants [40•] and fetal growth restriction [41•], respectively. Interestingly, in contrast to adults, pediatric patients show a similar distribution of prothrombotic risk factors in cohorts of venous and arterial thromboembolism. Since the discovery of APC-R as a highly prevalent hereditary risk factor of thromboembolism, evidence has been accumulating that thrombophilia is a multifactorial disorder [42,43].

Moreover, besides an observed asymptomatic increase in anticardiolipin antibodies in cases of *Varicella zoster* infections [44•], anticardiolipin-/antiphospholipid antibodies play a potential role in the pediatric population with symptomatic venous thrombosis, or ischemic stroke [45••,46•]. Rare disorders of the hemostatic system, *eg,* dysfibrinogenemia, hypo-/or dysplasminogenemia, heparin cofactor II deficiency, increased levels of histidine-rich glycoprotein, or further genetic polymorphisms were also found to be associated with the risk of venous thrombosis [20].

Imaging methods

Duplex sonography, venography, computed tomography, and magnetic resonance imaging (MRI) can be used to diagnose venous thrombosis [1–9,47••,48••]. However, venography in combination with Doppler ultrasound is often necessary to confirm suspected thrombosis in the upper venous system [48••]. MRI and MR angiography are recommended to confirm the diagnosis of thromboembolic ischemic stroke. Ventilation/perfusion scan, spiral CT, or MR angiography are suitable methods for diagnosing pulmonary embolism (PE) in children.

Table 3. Inherited prothrombotic risk factors

	Prothrombotic risk factors
Common	Factor V G1691A gene mutation
	Prothrombin G20210A gene mutation
	Increased concentrations of apolipoprotein (a)
	Moderate hyperhomocysteinemia
	Homozygous C677T polymorphism in the methylenetetrahydrofolate reductase gene
Rare	Protein C deficiency
	Protein S deficiency
	Antithrombin deficiency
	Heparin cofactor II deficiency
Very rare	Dysfibrinogenemia
	Dys/Hypoplasminogenemia
	Homozygous homocystinuria
Genetic traits, probably contributed to an increased risk in thrombosis:	Increased levels of factor VIIIC, IX, or fibrinogen
	Decreased levels of factor XII

Screening for risk factors

Population background

The distribution of prothrombotic risk factors varies in different countries with respect to the ethnic background and the number of patients/controls investigated. Thus, to estimate the individual patient risk in pediatric patients suffering thromboembolism, it is recommended that symptomatic patients be investigated in comparison with age- and gender-matched healthy controls with attention to ethnicity [49–51].

Patients who should be screened

Children with symptomatic thrombosis should be treated by pediatricians with special expertise in coagulation. A recent prospective study has indicated that the subgroup of pediatric patients suffering from multiple combined prothrombotic risk factors is at risk of thrombus recurrence after an initial event of spontaneous venous thromboembolism. Therefore, laboratory testing for multiple risk factors is warranted in symptomatic children [25••]. In addition, the availability of effective prophylactic anticoagulation around high-risk events such as elective surgery supports a discussion of genetic screening in asymptomatic siblings and other first-degree relatives of an affected child [52•].

Laboratory investigation and interpretation of results

To identify prothrombotic risk factors and underlying conditions responsible for thrombosis diseases in children, in addition to a comprehensive personal and family history a laboratory work-up (Table 3) is indicated. Besides genotyping at the onset of the thrombotic disease, a step-wise diagnostic procedure is recommended for plasma-based parameters. In pediatric patients with a reduced protein activity, total protein concentration and free antigen (protein S only) should be determined. To prevent results of protein-based assays from being affected by the acute thrombotic onset, plasma samples should be obtained at least 3 to 6 months after the thrombotic episode. In addition, oral anticoagulant medication also influences protein-based assays. Therefore it is recommended that fresh plasma samples for coagulation analyses be drawn at least 14 to 30 days after withdrawal of oral anticoagulation. Data interpretation is based on age-dependent reference ranges or the identification of causative gene mutations/polymorphisms with respect to individual ethnic backgrounds [49–54].

Treatment modalities

In pediatric patients with thromboembolism, detailed patient management is seriously hampered by the lack of appropriate clinical trials. In addition, long-term outcome of pediatric thromboembolism has rarely been reported to date [55–57,57•]. Thus, until data are available for the treatment of symptomatic children, pediatric patients with thrombosis are treated according to recommendations based on small-scale studies in children and guidelines adapted from adult patient protocols.

Acute thrombotic therapy

Standard heparin, low-molecular weight heparin [58,59•,60•], heparinoids [61•], and thrombolytic agents [62–69,65•,66•,68••] are used to manage acute thromboembolism in children. Besides specific treatment of acute thromboembolism with anticoagulant or thrombolytic therapy (catheter- and non–catheter-related thrombosis), infants with acute purpura fulminans caused by homozygous protein C deficiency or protein S deficiency should receive fresh frozen plasma or, if available, protein C concentrate [70]. In addition, to prevent pulmonary embolism in selected cases the use of cava filters has been reported [71•]. The latter, however, is difficult and risky in small neonates, infants, and children. As in adults, it must be kept in mind that heparin administration and the use of thrombolytic agents can lead to major bleeding episodes or acute thrombus rupture with subsequent pulmonary embolism or thromboembolic stroke in neonates (patent foramen ovale). In addition, heparin-induced thrombocytopenia type II has not only been reported in adults but also in pediatric patients, creating the potential need to substitute heparin with an alternative anticoagulant emergently [61•]. Whereas the man-

agement of neonates and infants with life-threatening thrombosis possibly leading to organ or limb damage necessitates acute thrombotic treatment, *eg*, thrombolytic therapy, patients during late puberty with venous thrombosis and underlying clinical conditions should be treated according to adult guidelines, which is to the current state of knowledge heparin administration.

Long-term anticoagulation

According to the current state of knowledge only a few authors reported on outcome of pediatric patients with venous thromboembolism. Until prospective randomized data on chronic anticoagulation in pediatric patients are available, pediatric patients should be treated on an individual basis. Pediatric patients with venous thromboembolism found to have a single prothrombotic trait (one heterozygous allele: factor V 1691GA; prothrombin 20210GA; deficiencies of protein C, protein S, or antithrombin; elevated lipoprotein (a)) should receive oral anticoagulation or low-dose heparin, usually administered for 3 to 6 (-12) months after the acute thrombotic onset. Three months anticoagulation is suggested when the thrombus is resolved, the provoking factor is gone, and there is no further underlying prothrombotic tendency, whereas 6 to 12 (or maybe 24) months may be considered for children with ongoing underlying prothrombotic conditions, such as genetic risks, infections, inflammations, or malignancies, respectively. Symptomatic children with severe or multiple genetic thrombotic traits (protein C-, protein S-, antithrombin deficiency) with spontaneous thrombosis, *ie*, without further underlying prothrombotic triggering factors, or with a history of life-threatening recurrent thrombosis, long-term anticoagulant therapy with vitamin K-antagonists [72] is considered on an individual patient basis. In these individuals, secondary preventive anticoagulant therapy, *ie*, low-molecular-weight heparin, may be given in situations known to provoke thrombosis.

For selected pediatric patients under long-term coumadin therapy INR home monitoring is available. In pediatric patients with arterial vascular occlusion or ischemic stroke we suggest the use of low-dose ASA or LMWH [73••].

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The use of tissue plasminogen activator at an average of 0.5 mg/kg/h for a median duration of 6 hours is retrospectively described in a cohort of eighty consecutively treated children with thrombosis: 65% of children showed complete patency, partial patency was observed in 20%, whereas 15% did not show any effect. Major complications occurred in 40% of patients. The authors conclude that tPA in children can be effective but is associated with a low margin of safety and unknown risk-benefit ratio in the dosage and duration administered.

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The successful use of vena cava filters in children is reported.

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73 •• Straeter R, Kurnik K, Heller C, et al.: Aspirin versus low-dose low-molecular-weight heparin: Antithrombotic therapy in pediatric ischemic stroke patients: A prospective follow-up study. Stroke 2001, 32:2554–2558.
Children with ischemic stroke received secondary anticoagulation with either aspirin or low-dose low-molecular-weight heparin. The re-stroke rate reported was 9.3% but was no different in children treated with aspirin or heparin. No bleeding complications were observed.