Venous thromboembolic disease in childhood epidemiology, risk factors and outcome
van Ommen, C.H.

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Chapter 1

Venous thromboembolic disease in childhood: general introduction

In part adapted from:

GENERAL INTRODUCTION

Venous thromboembolic disease (VTE), the formation of a solid mass from constituents of blood in the venous circulation, is a serious disorder because of its potential complications such as pulmonary embolism (PE), which may be fatal, and the postthrombotic syndrome (PTS). It is a common disorder in adults with an annual incidence in the general population of about 1 in 1000 individuals. In children, venous thrombosis is relatively rare. However, in the past 10 years pediatric thrombotic events have increasingly been recognised, usually as complications of diagnostic and therapeutic modalities in children with severe primary illnesses. In that time, our knowledge about many aspects of venous thrombosis in children has increased and an outline of this development can be found in this chapter. Nevertheless, many questions do remain and this thesis tries to give answers to the some of them: What is the incidence of pediatric VTE in the Netherlands and which children are at risk? What is the clinical presentation of VTE in childhood? What is the role of prothrombotic disorders in the etiology of pediatric VTE and which subgroups of children with VTE are at increased risk of positive congenital prothrombotic testing? What is the possible underlying mechanism leading to VTE in girls using estrogen for tall stature? What is the clinical outcome of pediatric VTE, including death, recurrence and PTS? And finally, what is the risk of PTS in children with congenital heart disease?

Hemostatic system in infancy and childhood

The pediatric hemostatic system differs from the adult system in many aspects, offering some protection to the development of VTE.

Plasma concentrations of the four contact factors (factor XI, factor XII, high molecular weight kininogen, and prekallikrein) and vitamin K dependent coagulation proteins (factor II, VII, IX and X) are low at birth, at approximately 50% of adult values. In both premature and full-term neonates, plasma concentrations of these proteins gradually increase toward adult values over the first six months of life. However, in childhood they are still 10 to 20 percent less than adult values. As a consequence, the capacity of plasmas of new-borns and older children to generate thrombin is approximately 50% and 20% of adult values, respectively. This does not seem to increase the risk of bleeding complications, but may provide a mechanism for protection against thrombotic events during childhood.

In addition to decreased thrombin generation, increased thrombin inhibition may also contribute to the lower risk of thrombosis in children. The inhibition of thrombin is regulated by several mechanisms. Direct inhibitors of thrombin include antithrombin, \( \alpha_2 \)-macroglobulin and heparin cofactor II. Thrombin itself is a indirect inhibitor of coagulation by binding to the endothelial cell surface receptor thrombomodulin. After binding to thrombomodulin, thrombin is not able to perform its procoagulant tasks. Furthermore, the thrombin-thrombomodulin complex activates protein C which, together with its cofactor protein S inactivates factor Va and factor VIIIa and thus inhibits coagulation. In children plasma concentrations of protein C and protein S are lower than
those in adults. The lower limits of these plasma concentrations reach adult values in puberty, a factor of importance when assessing children for congenital deficiencies of these anticoagulants.\textsuperscript{4,5}

Plasma concentrations of antithrombin and heparin cofactor II are about 50\% of adult values during the first weeks of life. This may impair thrombin inhibition and lead to increased risk of thrombosis.\textsuperscript{6} However, plasma concentrations of $\alpha_2$-macroglobulin are higher in neonates than those in adults, which partly compensates for the decreased plasma concentrations of antithrombin.\textsuperscript{7} Antithrombin reaches adult values at 3 months of age, while $\alpha_2$-macroglobulin remains high throughout childhood. This may add to the decreased risk of thrombotic disease in childhood, including children with congenital heterozygous antithrombin deficiency.\textsuperscript{8,9}

The fibrinolytic system probably does not contribute to the lower risk of thrombotic disease in childhood. On the contrary, some data suggest that fibrinolysis is suppressed in children. In the neonatal period, in vitro studies showed a decrease in plasmin generation capacity due to decreased plasma concentrations of plasminogen. This observation may explain the prolonged thrombolysis times observed in neonates after therapeutic thrombolysis.\textsuperscript{10,11} Furthermore, one study showed reduced activity of the fibrinolytic system after venous occlusion because of higher plasminogen activator inhibitors activities in teenage girls compared to adult women.\textsuperscript{12}

Thrombin formation can be quantitated by measuring activation peptides, such as prothrombin fragment 1 and 2 ($\text{F}_1+2$), and thrombin-antithrombin complexes (TATs).\textsuperscript{13} In healthy children, plasma concentrations of $\text{F}_1+2$ and TATs are similar to those found in young adults.\textsuperscript{4} In children with chronic diseases, such as sickle cell disease, elevated $\text{F}_1+2$ have been found, indicative of enhanced thrombin generation.\textsuperscript{14} With increasing age (over 40 years), $\text{F}_1+2$ increases, suggesting impaired thrombin generation in older adults.\textsuperscript{15}

In healthy children, then, hemostatic differences compared to adults seem to contribute to the low incidence of VTE. In sick children, however, disturbances may develop in the balance between procoagulant factors and anticoagulant factors, leading to a prothrombotic state with increased thrombin generation and subsequent thrombus formation.

**Incidence of pediatric venous thromboembolic disease**

In prospective registries, the annual incidence of symptomatic venous thrombotic events was estimated to be 0.07 per 10,000 children or 5.3 per 10,000 hospital admissions of children and 24 per 10,000 admissions of new-borns to neonatal intensive care units.\textsuperscript{17,18} The annual incidence of asymptomatic VTE is unknown. A number of studies have reported the presence of asymptomatic VTE in specific patient groups, such as neonates with central venous catheters on the neonatal intensive care unit. Prospective screening with echocardiography revealed an incidence of catheter-related VTE ranging from 2\% to 14\%.\textsuperscript{19,21} Most of these thrombi were asymptomatic.

The current incidence of PE in children is unknown. A number of retrospective autopsy studies have estimated the overall incidence of PE in children to be 0.05-4.2\%.\textsuperscript{22,26}
The variation in results of autopsy studies probably reflects patient selection and the range of techniques used to detect PE. Large macroscopic emboli were unlikely to be missed at post mortem examination, but the rate of PE rose considerably if microscopic techniques were used. In the Canadian prospective registry, the annual incidence of PE was estimated to be 0.86 per 10,000 pediatric admissions. The decreased index of clinical suspicion for PE in children and absence of standardised diagnostic techniques suggest that clinical studies provide a minimal estimate of the incidence of PE in pediatric patients.

Pathophysiology

In 1856, Virchow postulated three main causes of thrombosis: damage to the vessel wall, stasis of the blood, and increase in blood coagulability ("Virchow’s triad"). Nowadays, risk factors for thrombosis are usually classified into congenital and acquired risk factors. In most children with VTE, several of these congenital and/or acquired risk factors can be found.

**Congenital risk factors** In 1965, Egeberg introduced the term thrombophilia to describe an increased risk of venous thrombosis in a Norwegian family which appeared to have congenital deficiency of naturally occurring anticoagulant antithrombin. Thrombophilic families with deficiencies of the anticoagulants protein C and protein S were first reported in 1981 and 1984, respectively. In 1993, Dalhöök reported a thrombophilic family with resistance to activated protein C. Addition of activated protein C did not cause prolongation of the activated partial thromboplastin time in some members of this family. One year later, resistance to activated protein C appeared to be usually caused by a point mutation in the gene of factor V, at position 506, one of the three cleavage sites of factor V by activated protein C. At the present factor V R506Q mutation is the most common known congenital thrombophilic risk factor for venous thrombosis in the Caucasian adult population. The frequency of this mutation is 2 to 15% in the general population, up to 50% in selected patients with VTE. A large case-control study estimated that the risk for a first thrombotic event was increased by a factor of 7 in heterozygous carriers and by a factor of 80 in homozygous carriers compared to non-carriers. A mutation in another coagulant factor gene, the prothrombin gene (prothrombin G20210A), is also associated with a tendency to venous thromboembolism. In adults, one or more of these established congenital prothrombotic disorders can be found in about 30% of patients with a first episode of venous thrombosis (Table 1). As many congenital risk factors are common in the general population, a combination of these risk factors may occur in an individual. Individuals with a combination of congenital defects have a higher risk of thrombosis than those who carry one of the defects.

In children, the role of congenital prothrombotic disorders in the pathogenesis of venous thromboembolism is not completely elucidated. The reported prevalences of congenital prothrombotic disorders in children vary enormously, depending on the age and size of the study population, on the type of prothrombotic disorders studied and on the study design. Table 2 and 3 summarize the most recent studies dealing with the
Table 1. Estimates of prevalence of congenital thrombophilic risk factors in general population and in unselected adult patients with confirmed venous thromboembolic disease.\(^{1,9,15}\)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>General population (%)</th>
<th>Adult patients with VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V R506Q</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2-0.4</td>
<td>3</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>unknown</td>
<td>1-2</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02</td>
<td>1</td>
</tr>
</tbody>
</table>

Prevalences of the five established congenital prothrombotic disorders in children with venous thrombosis in general and in specific organ sites and pediatric diseases.

**Acquired risk factors** Currently, the presence of a central venous catheter is the most important acquired risk factor for VTE in children, especially in neonates.\(^{15,16}\) Several other acquired conditions associated with an increased risk for venous thrombosis are reported in children. Examples are heart disease, malignancy, trauma and surgery, renal disease, the presence of lupus anticoagulant, oral contraceptives and the use of high dose estrogen for tall stature. These conditions may be transient or persist over time. Some of them are known to be associated with acquired prothrombotic disorders.\(^{15,16}\)

**Other risk factors** Recently, several prothrombotic risk factors were identified as potential thrombophilic in adults. Examples are hyperhomocysteinemia, and high levels of factor VII, VIII, IX, XI, fibrinogen, lipoprotein (a) and thrombin activatable fibrinolysis inhibitor (TAFI).\(^{4,17}\) These risk factors may be congenital or acquired. The increased thrombotic risk is usually mild. In children, the role of these factors in the etiology of thrombosis needs to be established.

**Clinical presentation**

The clinical presentation of VTE depends on the location of the thrombi. The majority of pediatric venous thrombi are catheter related and situatet in the upper venous system. The clinical symptoms of these thrombi include swelling, pain and discoloration of the upper extremity, superior vena cava syndrome (swelling of the face and neck, distended veins in the skin over the chest), chylothorax, and chylopericardium.\(^{7,12}\) VTE in the lower extremity usually causes abdominal, inguinal or leg pain, swelling of the abdomen or leg, and reddish or blue-purple discoloration of the lower extremity. In general, sepsis and repeated loss of patency of the catheter raise suspicion of catheter-related thrombosis. Chronic catheter-related thrombosis often presents with collateral circulation.\(^{7,12}\) In some neonates, thrombocytopenia appears to be the only sign of VTE due to consumption of platelets.
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Study design</th>
<th>Type of VTE</th>
<th>Protein C deficiency factor</th>
<th>Factor V R506Q factor</th>
<th>Antithrombin deficiency factor</th>
<th>Age (year)</th>
<th>Type of VTE</th>
<th>Protein C deficiency factor</th>
<th>Factor V R506Q factor</th>
<th>Antithrombin deficiency factor</th>
<th>Age (year)</th>
<th>Type of VTE</th>
<th>Protein C deficiency factor</th>
<th>Factor V R506Q factor</th>
<th>Antithrombin deficiency factor</th>
<th>Age (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Ahmadzadeh et al.</td>
<td>prospective</td>
<td>extremely VTE</td>
<td>0.21</td>
<td>0.05</td>
<td>0.15</td>
<td>0</td>
<td>extremely VTE</td>
<td>0.21</td>
<td>0.05</td>
<td>0.15</td>
<td>0</td>
<td>extremely VTE</td>
<td>0.21</td>
<td>0.05</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>Hussain et al.</td>
<td>prospective</td>
<td>VTE / ATE</td>
<td>0.18</td>
<td>0.03</td>
<td>0.14</td>
<td>0</td>
<td>VTE / ATE</td>
<td>0.18</td>
<td>0.03</td>
<td>0.14</td>
<td>0</td>
<td>VTE / ATE</td>
<td>0.18</td>
<td>0.03</td>
<td>0.14</td>
<td>0</td>
</tr>
<tr>
<td>1996</td>
<td>Archard et al.</td>
<td>prospective</td>
<td>VTE</td>
<td>0.23</td>
<td>0.02</td>
<td>0.23</td>
<td>0</td>
<td>VTE</td>
<td>0.23</td>
<td>0.02</td>
<td>0.23</td>
<td>0</td>
<td>VTE</td>
<td>0.23</td>
<td>0.02</td>
<td>0.23</td>
<td>0</td>
</tr>
<tr>
<td>1996</td>
<td>Silates et al.</td>
<td>prospective</td>
<td>non CNS VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>non CNS VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>non CNS VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
</tr>
<tr>
<td>1997</td>
<td>Nowak-Grau et al.</td>
<td>prospective</td>
<td>catheter-related VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>catheter-related VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>catheter-related VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
</tr>
<tr>
<td>1997</td>
<td>Ukena et al.</td>
<td>prospective</td>
<td>VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
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<tr>
<td>1998</td>
<td>Ukena et al.</td>
<td>prospective</td>
<td>non CNS VTE</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0</td>
<td>non CNS VTE</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0</td>
<td>non CNS VTE</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0</td>
</tr>
<tr>
<td>1998</td>
<td>Hengstlein et al.</td>
<td>retrospective</td>
<td>VTE</td>
<td>0.23</td>
<td>0.23</td>
<td>0.23</td>
<td>0</td>
<td>VTE</td>
<td>0.23</td>
<td>0.23</td>
<td>0.23</td>
<td>0</td>
<td>VTE</td>
<td>0.23</td>
<td>0.23</td>
<td>0.23</td>
<td>0</td>
</tr>
<tr>
<td>1999</td>
<td>Juncker et al.</td>
<td>prospective</td>
<td>VTE / ATE / stroke</td>
<td>0.18</td>
<td>0.15</td>
<td>0.15</td>
<td>0</td>
<td>VTE / ATE / stroke</td>
<td>0.18</td>
<td>0.15</td>
<td>0.15</td>
<td>0</td>
<td>VTE / ATE / stroke</td>
<td>0.18</td>
<td>0.15</td>
<td>0.15</td>
<td>0</td>
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<tr>
<td>1999</td>
<td>Ewert et al.</td>
<td>prospective</td>
<td>VTE / ATE / stroke</td>
<td>0.18</td>
<td>0.15</td>
<td>0.15</td>
<td>0</td>
<td>VTE / ATE / stroke</td>
<td>0.18</td>
<td>0.15</td>
<td>0.15</td>
<td>0</td>
<td>VTE / ATE / stroke</td>
<td>0.18</td>
<td>0.15</td>
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<td>1999</td>
<td>Lawrence et al.</td>
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<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
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<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>extremely VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>extremely VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
</tr>
<tr>
<td>2000</td>
<td>Solimane et al.</td>
<td>prospective</td>
<td>VTE / ATE / stroke</td>
<td>0.13</td>
<td>0.10</td>
<td>0.10</td>
<td>0</td>
<td>VTE / ATE / stroke</td>
<td>0.13</td>
<td>0.10</td>
<td>0.10</td>
<td>0</td>
<td>VTE / ATE / stroke</td>
<td>0.13</td>
<td>0.10</td>
<td>0.10</td>
<td>0</td>
</tr>
<tr>
<td>2000</td>
<td>Bondde et al.</td>
<td>prospective</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
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<tr>
<td>2001</td>
<td>Kasch et al.</td>
<td>prospective</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
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<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
<td>spontaneous VTE</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: VTE, Venous thromboembolic disease; ATE, Arterial thromboembolic disease; CNS, Central nervous system.
Table 3. Summary of most recent studies investigating the prevalence of congenital prothrombotic disorders in children with venous thrombosis in specific organ sites and pediatric diseases (some children have more than one risk factor)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Specific organ sites and diseases</th>
<th>Age (y)</th>
<th>Antithrombin deficiency</th>
<th>Protein S deficiency</th>
<th>Protein C deficiency</th>
<th>Factor V R506Q</th>
<th>Factor II G20210A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohliase*</td>
<td>1996</td>
<td>retrospective</td>
<td>cardiac disease</td>
<td>0-18</td>
<td>0/9 (33%)</td>
<td>0/9</td>
<td>3/9 (33%)</td>
<td>5/9 (56%)</td>
<td>0/9</td>
</tr>
<tr>
<td>Seixas*</td>
<td>1997</td>
<td>prospective</td>
<td>portal vein VTE</td>
<td>0-11</td>
<td>-</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
</tr>
<tr>
<td>Dubuisson*</td>
<td>1997</td>
<td>prospective</td>
<td>portal vein VTE</td>
<td>3-18</td>
<td>0/20</td>
<td>2/20 (10%)</td>
<td>0/20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fabri*</td>
<td>1998</td>
<td>cross-sectional</td>
<td>nephrotic syndrome</td>
<td>2-21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nowak-Gössl*</td>
<td>1999</td>
<td>prospective</td>
<td>ALL</td>
<td>0.5-18</td>
<td>2/32 (6.3%)</td>
<td>4/32 (13%)</td>
<td>6/32 (19%)</td>
<td>7/32 (22%)</td>
<td>0/32</td>
</tr>
<tr>
<td>Münchow*</td>
<td>1999</td>
<td>prospective</td>
<td>caval vein VTE</td>
<td>0.1-18</td>
<td>1/27 (4%)</td>
<td>0/27</td>
<td>0.27</td>
<td>6/27 (22%)</td>
<td>0/27</td>
</tr>
<tr>
<td>Werndt*</td>
<td>1999</td>
<td>prospective</td>
<td>catheter-related VTE and malignancy</td>
<td>1-20</td>
<td>0/10</td>
<td>1/10 (10%)</td>
<td>0/10</td>
<td>1/10 (10%)</td>
<td>0/10</td>
</tr>
<tr>
<td>Knoller*</td>
<td>1999</td>
<td>prospective</td>
<td>catheter-related VTE and ALL</td>
<td>1-18</td>
<td>0/11</td>
<td>1/11 (9%)</td>
<td>1/11 (9%)</td>
<td>4/11 (36%)</td>
<td>0/11</td>
</tr>
<tr>
<td>Heller*</td>
<td>2000</td>
<td>prospective</td>
<td>abdominal VTE</td>
<td>0-1</td>
<td>2/65 (3%)</td>
<td>0/6</td>
<td>3/65 (5%)</td>
<td>14/65 (22%)</td>
<td>1/65 (2%)</td>
</tr>
<tr>
<td>Mauz-Körholz*</td>
<td>2000</td>
<td>prospective</td>
<td>ALL</td>
<td>1-18</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
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</tr>
</tbody>
</table>

Abbreviations: VTE Venous thromboembolic disease, ALL Acute lymphoblastic leukemia, PE Pulmonary embolism
Chapter 1

Renal vein thrombosis usually presents within the first month of life. Symptoms of renal vein thrombosis are hematuria, proteinuria, thrombocytopenia, nonfunction of the involved kidney and the presence of an abdominal mass.41,43

Homozygous protein C and S deficiency may lead to neonatal purpura fulminans, a disorder characterised by rapidly progressive purpura and ecchymosis, which often develop into large areas of skin necrosis with bulla formation. Histologic examination reveals thrombosis of the dermal capillaries and venules.44

Portal vein thrombosis may occur after umbilical vein catheterization with or without infection in new-borns and after liver transplantation, intra-abdominal sepsis and splenectomy in older children.45-48 It may present as an acute abdomen, especially in adolescents. In some patients the thrombus is asymptomatic for years, finally presenting with symptoms of chronic obstruction, such as splenomegaly and gastrointestinal bleeding.

The clinical presentation of sinovenous thrombosis depends on age, extent of the thrombosis and underlying diseases. In new-borns, it frequently presents with seizures, lethargy, and jitteriness.49-51 Manifestation in older children include headache, vomiting, seizures, hemiparesis and altered levels of consciousness.52

PE may be clinical silent or with minimal symptoms which can be explained by other co-morbid conditions.52 In a retrospective series by Buck et al, only 50% of children with clinically significant PE had clinical symptoms which were attributable to PE.53 The clinical diagnosis was considered in only 15% of these children. In teenagers the most classic complaint was chest pain (mainly pleuritic), noted in 84%. Other frequently occurring complaints included dyspnoe, cough and hemoptysis.54 In children, receiving artificial ventilation, the most obvious indication of PE is a marked increase in oxygen requirements.55 Other signs which have been reported to occur in children with acute PE are acute right heart failure, cyanosis, hypotension, arrhythmia, pallor, syncope, tachycardia and sweating.56-58 Although many of the clinical features of PE in children are similar to those in adults, the diagnosis is often unnecessarily delayed. The clinical symptoms of PE are often confused with the clinical symptoms of the underlying disorder, or thought to represent cardio-respiratory deterioration due to other causes, such as sepsis or cardiac failure in critically ill children.59,60

Diagnosis

As the clinical diagnosis of VTE might be difficult in children, radiographic tests are necessary to confirm clinical suspicion of VTE. Registry studies showed that objective diagnosis of VTE in children in either the upper or lower venous system was most frequently made by non-invasive radiographic techniques, especially ultrasonography.17,18 However, the gold standard diagnostic test is venography. The most reliable venographic criterion is the presence of an intraluminal filling defect that is constant in all films and is seen in at least two different projections. Other criteria are (1) non-filling of the deep venous system above the knee despite adequate technique and (2) non-filling of a segment of the deep venous system with abrupt termination of the contrast agent at a constant site.
below the segment and reappearance of the contrast agent at a constant site above the segment. A major drawback of venography is invasiveness. Furthermore, it might be difficult to detect a vessel for the injection of the contrast agent, especially in sick neonates. In adults compression ultrasonography appears to be as sensitive and specific as venography for detection of venous thrombosis in the proximal venous system of the lower extremity compared to venography. With compression ultrasonography, VTE is diagnosed when residual lumen of the vein is observed after gentle probe pressure. It is probable that ultrasonography is sufficiently sensitive and specific to diagnose proximal-vein thrombosis of the lower extremity in children as well, but there are no studies in children to confirm this hypothesis.

With duplex ultrasonography blood flow characteristics may be evaluated. In normal veins the blood flow is spontaneous, phasic with respiration, can be increased by manual compression distal to the ultrasound transducer and can be interrupted by Valsalva manoeuvre. Absence of one or more of these characteristics may result from VTE. Colour Doppler ultrasonography is an combination of compression and duplex ultrasonography. In addition, Doppler detected flow signals can be shown in colours (red or blue) according to its forward or reverse direction. The criterion for an abnormal colour Doppler test is a focal intraluminal filling defect or the absence of colour in a vein after increase of the flow.

Venography is mandatory for the diagnosis of venous thrombosis in the upper venous system in children. The limitations of ultrasonography in the detection of thrombosis in the upper venous system are caused by the impossibility of compressing the veins due to the thoracic cage and by the presence of the clavicles, which limits the view of distal subclavian veins. Furthermore, it may be difficult to distinguish large collateral vessels from the normal vasculature.

Lineography may be useful for diagnosing catheter-tip thrombosis, but it may miss thrombosis along the intravascular length of the catheters.

Other diagnostic radiographic techniques for venous thromboembolic disease include spiral computed tomography (CT), magnetic resonance imaging (MRI) and angiography (MRA). These techniques are mainly used to detect sinus venous thrombosis. On a contrast-enhanced CT, an empty triangle or 'delta-sign' represents bright contrast enhancement of the dura surrounding a clot in the sinus venous system. CT scans may easily miss the presence of sinus venous thrombosis and may underestimate the extent of the thrombus and the presence of infarcts. MRI with MRA has a better sensitivity and specificity. MRI and MRA signs of sinus venous thrombosis include an absence of flow-related signal and visualisation of the thrombus, which appears as an increased signal on T1-weighted and T2-weighted images in a cerebral vein or dural sinus.

PE is diagnosed by pulmonary angiography, ventilation/perfusion (V/Q) scanning, echocardiography and other techniques. The current reference standard for diagnosis of PE in adults is pulmonary angiography. Direct angiographic signs of PE are complete obstruction of a vessel or a filling defect. This technique has several disadvantages, such as invasiveness, high costs and limited availability. It requires selective catheterization of the pulmonary arteries and injection of radio-opaque contrast media. Catheter-placement may be technically difficult in small children or those with
complex cardiac lesions. Furthermore, critically sick children may be at increased risk of complications from the procedure. In adult patients, morbidity and mortality are 3% and 0.2% respectively. Mortality and morbidity in pediatric patients are unknown.

V/Q scanning is the most frequently used test for PE in both adult and pediatric patients. Ventilation scanning is performed by inhalation of a radioactive gas mixed with air, usually Xenon 133, Technetium 99 or Krypton 81. Older children are able to cooperate by holding their breath. In young infants and neonates, reliable images can be obtained through continuous tidal breathing with little or no co-operation. Perfusion scanning is performed by injecting particles labelled with radioactive isotope, most commonly Technetium 99. Macroaggregated Albumin is the most widely used particulate material. The classification of V/Q scans in children is extrapolated from diagnostic studies in adults and can be categorised as high, intermediate, or low probability for PE. The PIOPED-criteria consider the following lung scans as high probability for PE: (1) 2 or more large (>75%) segmental V/Q mismatches, (2) 2 or more moderate (25-75%) segmental V/Q mismatches and 1 large mismatch and (3) 4 or more moderate segmental mismatches. There are some underlying diseases that may influence the interpretation of V/Q scans in children. For example, V/Q scans may be difficult in children with congenital heart disease by imbalanced pulmonary blood flow between the left and right lungs, or even within each lung. Children with left to right shunts will have variable distribution of the isotope due to mixture of arterial blood in the pulmonary artery. Coexistent peripheral pulmonary artery stenosis may be confused with multiple PE.

Echocardiography may be helpful in diagnosing PE. Echocardiographic diagnosis of PE depends on direct imaging of PE in the central pulmonary arteries. Indirect indices of PE by echocardiography include increased right ventricular volume or pressure, which have been shown to be very sensitive in adults. In children, the presence of structural cardiac defects makes these findings less specific. Furthermore, echocardiography is of value in detecting intracardiac thrombi, which may be a source of PE, and provides indirect evidence for the diagnosis of PE.

Antithrombotic therapy

a. Treatment of venous thromboembolic disease
Anticoagulation remains the mainstay of therapy for VTE in children. The Canadian and German registry studies made it clear that children with venous thrombosis were receiving a variety of therapeutic modalities, probably because of a lack of prospective randomised trials in children. Pediatric patients with VTE are therefore treated in accordance with recommendations based on small-scale studies in children and guidelines adapted from adult patient protocols.

a1. Unfractionated heparin
Unfractionated heparin is the most frequently used anticoagulant for the initial treatment of thromboembolic disease in children. It functions as an antithrombotic agent by catalyzing the ability of antithrombin to inactivate coagulation factors, especially thrombin and factor Xa. One pediatric prospective study showed that only 39% of children
achieved adult therapeutic activated partial thromboplastin time (APTT) levels, after a bolus dose of 50 U/kg. Maintenance heparin doses appeared to be age dependent, with children less than one year having the highest requirements (28 U/kg/hr) and older children having lower requirements (20 U/kg/hr). The high heparin requirement of young children may be caused by the more rapid clearance of heparin in infants compared to adult patients. The duration of therapy with unfractionated heparin is a minimum of 5 days, and 7 to 10 days for extensive deep-vein thrombosis or PE. Treatment with oral anticoagulants can be initiated 2 to 5 days after start of heparin therapy. Guidelines for treatment of thrombosis with unfractionated heparin are given in table 4.

The most common complication of unfractionated heparin is bleeding. A prospective study reported bleeding complications in about 2% of the pediatric patients. However, many children were treated suboptimally. The bleeding risk will probably rise, when heparin concentrations reach therapeutic levels. Regular monitoring of platelets during heparin therapy is required, because some case reports mention heparin-induced thrombocytopenia. The platelet count fall usually begins 4 or more days after start of heparin therapy. There have been three case reports of heparin induced osteoporosis in children. Two received steroids also. One 15-year-old boy with pulmonary occlusive disease received 6,000 to 10,000 units for a total of 11 months and developed vertebral fractures.

Table 4. Guidelines for antithrombotic therapy with unfractionated heparin

<table>
<thead>
<tr>
<th>APTT (s)</th>
<th>Bolus (U/kg)</th>
<th>Hold (min)</th>
<th>Rate change (U/kg/h)</th>
<th>Repeat APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>50</td>
<td>0</td>
<td>+10%</td>
<td>4 h</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>+10%</td>
<td>4 h</td>
</tr>
<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>24 h</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>-10%</td>
<td>4 h</td>
</tr>
<tr>
<td>96-120</td>
<td>0</td>
<td>30</td>
<td>-10%</td>
<td>4 h</td>
</tr>
<tr>
<td>&gt;120</td>
<td>0</td>
<td>60</td>
<td>-15%</td>
<td>4 h</td>
</tr>
</tbody>
</table>

c. Regular monitoring of platelets

Abbreviations: CBC Complete blood count, PT Prothrombin time, APTT Activated partial thromboplastin time.
Low-molecular-weight heparin

Clinical trials in adults have established that low-molecular-weight heparin (LMWH) is at least as effective and safe as unfractionated heparin, but offers several advantages over standard heparin that may benefit children. First, the pharmacokinetics of LMWH are more predictable than unfractionated heparin, minimizing the frequency of monitoring. Second, LMWH can be administered subcutaneously, eliminating the need for continuous venous access. Third, the risk of heparin-induced thrombocytopenia and osteoporosis is decreased compared with unfractionated heparin. Finally, LMWH does not interfere with diet or drugs and this is the case with oral anticoagulants.

Few pharmacokinetic and clinical cohort studies have been performed in children using LMWH therapy. Pharmacokinetic studies assessed the doses of two LMWHs, enoxaparin and reviparin. Peak anti-factor Xa levels occurred in all children between 2 to 6 hours after the administration of enoxaparin or reviparin. The target anti-factor Xa range was 0.5 to 1.0 U/mL. The doses of both LMWHs were age-dependent, with young children requiring higher doses of LMWH per kilogram. (Table 5) The guidelines for antithrombotic therapy with nadroparin are extrapolated from adult guidelines.

Table 5. Guidelines for antithrombotic therapy with low-molecular-weight heparin (LMWH)

<table>
<thead>
<tr>
<th>Anti-factor Xa level</th>
<th>Dose change</th>
<th>Repeat anti-factor Xa level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35 U/mL</td>
<td>increase by 25%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>0.35 - 0.49 U/mL</td>
<td>increase by 10%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>0.5 - 1.0 U/mL</td>
<td>0</td>
<td>1 week later and monthly thereafter</td>
</tr>
<tr>
<td>1.1 - 1.5 U/mL</td>
<td>decrease by 20%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>1.6 - 2.0 U/mL</td>
<td>decrease by 30%</td>
<td>4 hours post next dose</td>
</tr>
<tr>
<td>&gt;2.0 U/mL</td>
<td>hold all doses until anti-Xa is &lt;0.5 U/mL. restart at 60% of previous dose</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBC Complete blood count, PT Prothrombin time, APTT Activated partial thromboplastin time
Two clinical trials using enoxaparin for the treatment of VTE in 143 and 19 children showed major bleeding in 4.9% and 0% of children, respectively.\textsuperscript{12,15}

\textbf{a3. Oral anticoagulant therapy}

Oral anticoagulants function by blocking the regeneration of vitamin K from its epoxide. Vitamin K is necessary for the addition of \( \gamma \)-carboxyglutamic acid residues to the coagulation factors II, VII, IX, and X (and protein C and S). As a consequence, plasma concentrations of these vitamin K dependent proteins are reduced in patients treated with oral anticoagulant therapy.\textsuperscript{16}

Monitoring oral anticoagulant therapy in children is difficult and needs to be frequently done because of diet, medication, and primary underlying diseases.\textsuperscript{12} Breast-fed infants are very sensitive to oral anticoagulants, as they have low concentrations of vitamin K in breast milk. By contrast, other children need high doses of oral anticoagulants as a result of impaired absorption, total parenteral nutrition or nutrient formulas containing high concentrations of vitamin K.\textsuperscript{16} Most children receive several medications to treat their underlying disease. These medications may influence the dose requirements for oral anticoagulants.\textsuperscript{18}

Monitoring can be especially difficult in neonates because of poor venous access. Whole-blood prothrombin time/INR monitors may be a solution, using blood obtained by capillary punctures instead of venipunctures. Furthermore, these monitors may be used at home. Until now, a few point-of-care monitors have been evaluated in the pediatric population. These monitors were acceptable and reliable in the outpatient laboratory and home settings.\textsuperscript{14,15} Guidelines for oral anticoagulant therapy are provided in table 6.

Bleeding is the main complication of oral anticoagulants. In a prospective study of 319 consecutive children requiring warfarin, major bleeding complications occurred in 2 children with target International Normalized Ratio (INR) range 2.0 to 3.0, resulting in an incidence of 1% per patient year in that group.\textsuperscript{15}

Little is known about the optimal duration of anticoagulant therapy in children. Paediatric patients with uncomplicated venous thrombosis are usually treated for 3 months. Long-term anticoagulant therapy may be considered in some patients, such as patients carrying combined heterozygous prothrombotic risk factors with spontaneous thrombosis, symptomatic patients with homozygous protein S or protein C deficiency and patients with recurrent life-threatening VTE.\textsuperscript{14}

\textbf{a4. Thrombolytic therapy}

In general, thrombolytic agents are plasminogen activators, including urokinase, streptokinase and tissue plasminogen activator. Decreased plasma concentrations of plasminogen in newborns slow the generation of plasmin and reduce the thrombolytic effects of all thrombolytic agents in vitro.\textsuperscript{11}

Several case reports and small case series have reported successful thrombolysis in children.\textsuperscript{16,17} The thrombolytic agents were administered either locally by catheters with their tips located close to the thrombus or systemically by intravenous infusions and were generally used in combination with heparin therapy. No studies are available assessing the efficacy and safety of thrombolytic therapy in children compared to other
Chapter 1

Table 6. Guidelines for antithrombotic treatment with oral anticoagulants

a. Start: 2 to 5 days after start of heparin treatment: in neonates: in case of total oral feeding
b. Stop vitamin K medication in breast fed new-borns and vitamin K supplementation in total parenteral nutrition
c. Be careful of other medication which may influence dose requirements of oral anticoagulants
d. Loading dose (orally in the evening):
   - **Warfarin**: 0.2 mg/kg (max. 10 mg)
   - **Phenprocoumon**: 0.15-0.2 mg/kg (max. 8 mg)
   - **Acenocoumarol**: 0.15-0.2 mg/kg (max. 10 mg)
In case of initial prolonged PT, liver dysfunction, post Fontan procedure, known protein S or C deficiency or severe illness: decrease loading dose by 25% to 50%
e. Loading doses on day 2-4 based on INR response

<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1-1.3</td>
<td>Repeat initial loading dose</td>
</tr>
<tr>
<td>1.4-1.9</td>
<td>50% of initial loading dose</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>50% of initial loading dose</td>
</tr>
<tr>
<td>3.1-3.5</td>
<td>25% of initial loading dose</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>Hold dose until INR&lt;3.5, restart at 50% of previous dose</td>
</tr>
</tbody>
</table>

f. Maintain an INR between 2 and 3 for pediatric patients with venous thrombosis and between 2.5 and 3.5 for children with prosthetic heart valves
g. Heparin therapy should be continued until the INR has reached the therapeutic level
h. Maintenance guidelines:

<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1-1.4</td>
<td>Increase by 20% of dose</td>
</tr>
<tr>
<td>1.5-1.9</td>
<td>Increase by 10% of dose</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>No change</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>Decrease by 10% of dose</td>
</tr>
<tr>
<td>4.1-4.5</td>
<td>Decrease by 20% of dose</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>Hold dose until INR&lt;4.5, restart at 80% of previous dose</td>
</tr>
</tbody>
</table>

Abbreviations: PT Prothrombin time, INR International normalized ratio
antithrombotic agents. The decision to use thrombolytic therapy should be individualised and considered in children with large, new PE, particularly, if the PE is hemodynamically compromising or in children with extensive venous thrombosis in a threatened extremity. Guidelines for treatment of venous thrombosis with thrombolytic agents are given in table 7.

Table 7. Guidelines for antithrombotic therapy with thrombolytic therapy:

a. Dosages for systemic thrombolytic therapy:

<table>
<thead>
<tr>
<th></th>
<th>Bolus</th>
<th>Maintenance</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urokinase</td>
<td>4400 U/kg IV</td>
<td>4400 U/kg/h IV</td>
<td>6-12 h</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>2000 U/kg IV</td>
<td>2000 U/kg/h IV</td>
<td>6-12 h</td>
</tr>
<tr>
<td>tPA</td>
<td>None</td>
<td>0.1-0.6 mg/kg/h IV</td>
<td>6 h</td>
</tr>
</tbody>
</table>

b. Monitoring: CBC, D-dimer, fibrinogen, plasminogen, PT and APTT
c. Start heparin therapy either during or immediately after thrombolytic therapy (10-20 U/kg/h)
d. Fibrinogen < 1.0 g/L: consider dose reduction and infusion of plasma
e. Platelets should be maintained above 100 x 10^7/L.
f. In children with prolonged thrombolytic therapy and in neonates with physiological low plasminogen concentrations, plasma supplementation should be considered.

Abbreviations: tPA Tissue plasminogen activator, CBC Complete Blood count, PT Prothrombin time, APTT Activated partial thromboplastin time, IV Intravenously

The bleeding risk depends on the underlying clinical disease and the duration of therapy. A review of the literature showed minor bleeding in 54% of the children. Another review of the literature reported intracerebral hemorrhage in 14 of 929 reported children. These results are probably optimistic due to the reporting bias.

b. Prophylactic treatment

In adults, several randomized controlled trials have shown that prophylactic antithrombotic treatment prevents thrombosis in high risk situations, such as orthopedic surgery or major trauma. In children, the very low incidence of VTE does not seem to warrant prophylactic antithrombotic treatment. However, prophylaxis is strongly recommended for children with mechanical prosthetic heart valves and may be considered in other specific pediatric patient groups, such as children after Fontan procedure, children with known congenital prothrombotic disorders in high-risk situations, and sick children with a number of risk factors. Further clinical investigation is needed before definitive recommendations for primary prophylaxis in children can be made.

LMWH is the most frequently used short-term prophylactic antithrombotic agent.
Few small cohort studies have been performed to evaluate safety and efficacy of LMWH prophylaxis (enoxaparin and dalteparin). Major bleeding complications were reported in 0% to 14% of the children and new or recurrent VTE in 0% to 3% of children. Guidelines for prophylactic antithrombotic treatment are given in Table 9. The guidelines for prophylaxis with nadroprin are extrapolated from adult guidelines.

Table 9. Prophylactic antithrombotic therapy

a. Dosages of prophylactic antithrombotic treatment (anti-factor Xa level: 0.1-0.3):

| Drug         | Dosage range
|--------------|--------------|
| Reviparin    | < 5 kg: 50 U/kg/dose q12h  
               | >5 kg: 30 U/kg/dose q12h  
| Enoxaparin   | < 2 mo: 0.75 mg/kg/dose q12h  
               | > 2 mo: 0.5 mg/kg/dose q12h  
| Nadroprin    | 20-30 kg: 950 IE/dose q 24h  
               | 30-50 kg: 1900 IE/dose q 24h  
               | >50 kg: 2850 IE/dose q 24h

Outcome

The complications of venous thromboembolic disease, such as mortality, recurrence and the PTS, have not been thoroughly investigated in children, probably because of the low incidence of pediatric thrombosis. Until now, only four studies have been published, about the outcome of symptomatic pediatric thrombosis, which are summarised in Table 10.

All-cause mortality is high in pediatric patients. This is caused by the severe underlying diseases, which are present in the majority of children with venous thromboembolic disease. Death as direct result of thrombosis was most frequently caused by extension of the thrombus into the heart causing cardiac output obstruction or by PE.

The reported incidences of recurrence might be an underestimation because of the short duration of follow-up. It is known that the frequency of recurrence increases in adults with longer duration of follow-up.

The PTS consists of pain, swelling, varicose veins, pigmentation, and sometimes ulceration of the leg. PTS is caused by persistent outflow obstruction because of residual venous thrombosis and/or valvular insufficiency, which causes reflux of blood and inefficient functioning of the calf muscle pump, leading to venous hypertension. Table 11 shows the clinical classification as developed by an international consensus conference on chronic venous disease in adults.

Two recent studies evaluated predictive factors for recurrence and PTS. One study showed that the risk of recurrent thrombosis in children with a first episode of spontaneous thrombosis is significantly higher in children with a prothrombotic disorder, especially a combination of various heterozygous prothrombotic disorders. Another small
Table 10. Outcome of venous thromboembolic disease in childhood

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>n=244</td>
<td>n=405</td>
<td>n=95</td>
</tr>
<tr>
<td>Age children at time of VTE</td>
<td>1 m to 18 y</td>
<td>1 m to 18 y</td>
<td>1 m to 17 y</td>
</tr>
<tr>
<td>Follow-up period</td>
<td>3 m to 7 y</td>
<td>2 w to 6 y</td>
<td>12 to 41 m</td>
</tr>
<tr>
<td>(mean 2.4 y)</td>
<td>(mean 2.86 y)</td>
<td>(mean 3 y)</td>
<td>(median 10.2 y)</td>
</tr>
<tr>
<td>Type of VTE</td>
<td>Catheter-related VTE</td>
<td>Extremity VTE</td>
<td>All VTE, including cerebral infarct, purpura fulminans</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>n=57 (23%)</td>
<td>n=65 (16%)</td>
<td>n=19 (20%)</td>
</tr>
<tr>
<td>Mortality due to VTE</td>
<td>n=9 (3.7%)</td>
<td>n=9 (2.2%)</td>
<td>n=4 (4.2%)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>n=16 (6.5%)</td>
<td>n=33 (8.1%)</td>
<td>n=3 (3.1%)</td>
</tr>
<tr>
<td>PTS</td>
<td>n=23 (9.5%)</td>
<td>n=50 (12.4%)</td>
<td>n=3 (3.1%)</td>
</tr>
</tbody>
</table>

Abbreviations: VTE Venous thromboembolic disease, PTS Postthrombotic syndrome

study investigated outcome after combination of thrombolytic and anticoagulant therapy in 32 children. At 48 hours half of the children showed substantial clot lysis, and on follow-up (range 1 to 10 years, median 4.5 years) these children had complete resolution without recurrence and PTS. Recurrence and PTS were present in three and four children, respectively, with poor early clot lysis. Two children had minor bleeding complications as result of the thrombolytic therapy. However, no comparison group was used in this study.

Table 11. Clinical classification of chronic lower extremity venous disease in adults

| Class 0 | No visible or palpable signs of venous disease |
| Class 1 | Telangiectases, reticular veins, malleolar flare |
| Class 2 | Varicose veins |
| Class 3 | Edema without skin changes |
| Class 4 | Skin changes ascribed to venous disease (e.g., pigmentation, venous eczema, lipodermatosclerosis) |
| Class 5 | Skin changes as defined above with healed ulceration |
| Class 6 | Skin changes as defined above with active ulceration |
Chapter 1

OUTLINE OF THE THESIS

This thesis tries to give answers to the questions listed above: What is the incidence of pediatric VTE in The Netherlands and which children are at risk? What is the clinical presentation of VTE in childhood? What is the role of prothrombotic risk factors in the etiology of pediatric VTE and which subgroups of children with VTE have increased risk of positive congenital prothrombotic testing? What is the possible underlying mechanism, leading to VTE in girls using estrogen for tall stature? What is the clinical outcome of pediatric VTE, including death, recurrence and PTS? And finally, what is the risk of PTS in children with congenital heart disease?

The first part of this thesis, chapter 1, describes how the incidence of venous thromboembolic disease in children aged 0 to 18 years in The Netherlands was estimated in a prospective registry in cooperation with the Dutch Pediatric Surveillance Unit. This registry revealed two patients groups that appeared to be at risk for venous thrombosis.

The second part of the thesis deals with some clinical presentations of pediatric VTE. Chapter 3 describes three children with PE. For many years, deep vein thrombosis and PE have been regarded as separate entities. Many studies have shown that the majority of patients with confirmed deep vein thrombosis of both lower and upper extremities have asymptomatic or symptomatic PE, and vice versa. Therefore, PE and deep vein thrombosis are therefore now regarded as a single clinical entity. Although many of the clinical features of PE in children are similar to those in adults, the diagnosis is often unnecessary delayed in children. The clinical symptoms of PE are often confused with the clinical symptoms of the underlying disorder, or thought to represent cardiorespiratory deterioration because of other causes, such as sepsis or cardiac failure in critically ill children. The children in chapter 3 presented with tachypnea. Other causes of tachypnea were diagnosed and treated before PE was considered.

In chapter 4, a boy with borderline cognitive impairment and cerebellar hypoplasia is described, who developed VTE of the lower extremity after a stroke-like episode and a period of immobilisation. Several coagulation disturbances were present. The clinical and coagulation abnormalities suggested carbohydrate-deficient glycoprotein syndrome.

A special presentation of thrombosis is purpura fulminans. Purpura fulminans is histologically characterised by thrombosis of the dermal capillaries and venules. It may occur after mild infectious diseases, such as streptococcal infection and varicella. Post-varicella purpura fulminans is caused by severe acquired protein S deficiency resulting from anti-protein S antibodies. Chapter 5 describes the search for the epitopes of these autoantibodies in a 5-year-old girl with post-varicella purpura fulminans.

Risk factors for venous thrombosis in children are the subject of the third part of this thesis. Chapter 6 describes the clinical and prothrombotic risk factors determined in a prospective cohort of 100 consecutive children with VTE in the Emma Children's Hospital/AMC. This study identified predictors of positive testing for the presence of
congenital prothrombotic risk factors.

One of the clinical risk factors for VTE in children, particularly in tall girls, is high doses of estrogens. Oral contraceptives containing ethinyl estradiol doses of 20 to 50 μg. are known to increase the risk of venous thrombosis as much as 4-fold in women. Much higher doses of 100 to 1000 μg of ethinyl estradiol are used to reduce final height of tall girls. The effect of these high doses on coagulation and fibrinolytic parameters is studied in chapter 7.

The final part of this thesis addresses the sequelae of VTE in childhood, such as mortality, recurrence and the PTS. Data about outcome of VTE in children is scarce. In order to supply more data, a prospective follow-up study was performed in the cohort of 100 consecutive children with VTE (Chapter 8).

Furthermore, the incidence and severity of PTS was investigated in 28 children with congenital heart disease. The majority of children with congenital heart disease undergo cardiac catheterization and/or surgery, requiring the insertion of central venous catheters, most often into the femoral veins. One of the complications of these diagnostic and interventional procedures is venous thrombosis, which usually develops without showing any sign or symptom in the acute phase. The long-term complications of the thrombotic event, however, may be considerable (Chapter 9).

In chapter 10, the results are summarised and discussed and recommendations are given for further investigations in the field of pediatric VTE.

References


General introduction


Chapter 1


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Chapter I


Genera l introduction


