Venous thromboembolism (VTE) is a rare disease that is increasingly diagnosed and recognized in pediatrics in the past decade, usually as a secondary complication of primary severe underlying diseases. Apart from acquired thrombophilic risk factors, such as lupus anticoagulants, inherited thrombophilias (IT) have been established as risk factors for venous thromboembolic events in adults. In children with idiopathic VTE and in pediatric populations in which thromboses were associated with underlying medical diseases, IT have been described as additional prothrombotic risk factors. Follow-up data for VTE recurrence in children are available and suggest a recurrence rate of approximately 3% in neonates and 8% in other children.

Here we present a review of the impact of IT on early onset of VTE and recurrence in children. Statistically significant associations between the IT traits investigated, e.g. factor V G1691A, factor II G20210A, protein C-, protein S- antithrombin deficiency, elevated lipoprotein (a), combined IT and VTE onset were reported. In addition, statistically significant associations with recurrent VTE were calculated for protein S-, antithrombin-deficiency, and the factor II variant and combined IT. The absolute risk increase for VTE recurrence associated with IT ranged from 9.8% for children carrying the factorII variant to 26% and 29% in children with combined IT and protein S-deficiency, respectively. Data obtained gave evidence that the detection of IT is clinically meaningful in children with VTE and underlines the importance of a paediatric thrombophilia screening program.

Based on these data, treatment algorithms have to be discussed.

Keywords
Venous thromboembolism

Summary
Venous thromboembolism (VTE) is a rare disease that is being increasingly diagnosed and recognized in pediatrics in the past decade, usually as a secondary complication of primary severe underlying diseases. Apart from acquired thrombophilic risk factors, such as lupus anticoagulants, inherited thrombophilias (IT) have been established as risk factors for venous thromboembolic events in adults. In children with idiopathic VTE and in pediatric populations in which thromboses were associated with underlying medical diseases, IT have been described as additional prothrombotic risk factors. Follow-up data for VTE recurrence in children are available and suggest a recurrence rate of approximately 3% in neonates and 8% in other children.

Here we present a review of the impact of IT on early onset of VTE and recurrence in children. Statistically significant associations between the IT traits investigated, e.g. factor V G1691A, factor II G20210A, protein C-, protein S- antithrombin deficiency, elevated lipoprotein (a), combined IT and VTE onset were reported. In addition, statistically significant associations with recurrent VTE were calculated for protein S-, antithrombin-deficiency, and the factor II variant and combined IT. The absolute risk increase for VTE recurrence associated with IT ranged from 9.8% for children carrying the factorII variant to 26% and 29% in children with combined IT and protein S-deficiency, respectively. Data obtained gave evidence that the detection of IT is clinically meaningful in children with VTE and underlines the importance of a paediatric thrombophilia screening program.

Based on these data, treatment algorithms have to be discussed.
Thrombotic events in paediatric patients

Locations

The most common sites of thrombus formation in neonates are the renal veins (1, 5, 40, 47, 49), venae cavae occlusion, and peripartal thromboembolic stroke (5, 11, 12). In addition, high rates of catheter-related thrombosis in neonates, infants and children have been reported (2–4, 11, 12). Central venous lines lead to thrombus formation and thrombus growth near the catheter implantation site, especially when prothrombotic risk factors are involved. Further locations of childhood thromboembolism reported are cerebral venous thrombosis (37, 39, 41, 43, 45, 54, 55), and portal or mesenteric vein thrombosis (25, 44).

Purpura fulminans is a life-threatening event characterized histologically by microvascular thrombosis in the dermis followed by perivascular hemorrhage. Haemorrhagic necrosis of the adrenal glands (Waterhouse-Friederichsen syndrome), or renal cortical necrosis may also occur. Clinically, progressive purpuric skin lesions and diffuse oozing from skin puncture sites are observed, often within hours after birth. The lesions are initially red and flat, they quickly become indurate and necrotic, and may result in gangrene formation. The known underlying causes of Purpura fulminans are disseminated intravascular coagulation (DIC), for example in response to bacterial sepsicaemia, e. g. B β-haemolytic streptococcal disease, Neisseria meningitides or Streptococcus pneumoniae. In addition, in neonates congenital absence of protein C or protein S, or the presence of homozygous or heterozygous factor V G1691A mutation, have been reported.

Imaging

Duplex sonography, venography, computed tomography and magnetic resonance (MR) imaging can be used to diagnose VTE in children. However, venography in combination with Doppler ultrasound is mandatory to confirm suspected thrombosis in the upper venous system (57). MR imaging and MR angiography are recommended to confirm the diagnosis of thromboembolic ischemic stroke. Ventilation/perfusion scan or MR angiography are suitable methods for diagnosing pulmonary embolism in children.

Inherited thrombophilias

Onset and recurrent VTE

The distribution of prothrombotic risk factors varies in different countries with respect to the ethnic background and the number of patient/controls investigated. Thus, to estimate the individual patient risk in paediatric patients suffering from thromboembolism, it is recommended that symptomatic patients should be investigated in comparison to age- and gender-matched healthy controls from the same geographic area.

In a recent metaanalysis including 56 studies (2560 patients) from 15 countries more than 70% of patients had at least one clinical risk factor (58). The summary odds ratios/95% confidence intervals of studies under a fixed-effects and random-effects model showed statistically significant associations between factor V V1691A, factor

Fig. 1 Typical age distribution of thrombotic onset in childhood venous thromboembolism
II G20210A, protein C-, protein S-, or antithrombin deficiency, elevated lipoprotein (a), combined IT and VTE onset (58) (Tab. 2). For VTE recurrence, data of 1490 patients (11 studies) were available and a statistically significant association with recurrent VTE was found for protein S-, or antithrombin-deficiency, the factor II variant and combined IT. Of note, the absolute risk increase for VTE recurrence associated with IT ranged from 10% for children heterozygous for the factor II variant to 26% and 29% in children with combined IT and protein S-deficiency, respectively (Tab. 2). The odds ratios reported for recurrent VTE in children are consistent with results obtained from adult cohort studies not receiving long-term anticoagulation (59–64):

- 4.8 (protein C),
- 7.7 (protein S),
- 4.7 (antithrombin),
- 1.8 (factor V),
- 3.7 (factor II), and
- 5.1 for ≥2 traits.

Data evidenced that the detection of IT is clinically meaningful in children with VTE and underlines the importance of a paediatric thrombophilia screening program. Based on these data treatment algorithms have to be discussed.

### Screening

Follow-up data for VTE recurrence in children are available from a few reports, and those suggest a recurrence rate of approximately 3% in neonates and 8% in older children. However, in the paediatric age group it still remains a controversial issue as to whether children with thrombosis or offspring from thrombosis-prone families benefit from screening for IT (65–68).

Based on the data obtained from the recent metaanalysis (58) at least the symptomatic propositus should be screened in a specialized coagulation unit for prothrombotic defects. In addition, since a second VTE after a first episode of spontaneous VTE, i. e. thrombosis in the absence of further secondary causes, has indicated a subgroup of paediatric patients suffering from combined prothrombotic risk factors (36) to be at high risk of recurrent thrombosis, a search for multiple risk factors is justified in selected patient groups.

With respect to the Mendelian laws of inheritance, approximately 50% of siblings of a symptomatic propositus suffering from a combined prothrombotic defect carry one single risk factor, while 25% carry two or more gene mutations/polymorphisms. Thus, based on the fact that an effective prophylactic anticoagulant therapy is available in risk situations, a screening IT evaluation has to be discussed also in non-symptomatic siblings and further first degree family members.

### Treatment modalities

Adult patients with a first thrombotic episode will receive oral anticoagulation (usually a vitamin K antagonist) for at least three months after venous thrombosis, six to 12 months when the deep venous thrombosis was idiopathic, and at least six to 12 months after pulmonary embolism. Decisions on extending anticoagulant therapy are individually based on the perceived risks of VTE recurrence and anticoagulant-related bleeding. Whether long-term continuation of anticoagulant treatment should be considered after a first VTE in carriers of a thrombophilic trait is still a matter of debate (69).

In children with a first VTE randomized therapeutic trials are missing and treatment guidelines are mainly adapted from adults (70). More than in adults, the prolonged use of anticoagulant treatment in a physically active age group must be weighted against the risk of bleeding. Data of the meta-analysis already mentioned (58) will help physicians to decide along with parents and patients in which cases a prolonged anticoagulant treatment may be justified, or practically, if paediatric patients additionally carry a genetic trait with chronic conditions associated with VTE might require secondary anticoagulant in high risk situations (e. g. postoperatively, prolonged immobilization, or dehydration). The findings based on the analyses of absolute risk increase underline the hypothesis that in cases in which the temporary risk factor recur the risk of a second VTE in children is probably less likely if IT is absent (54, 58).

### Summary ORs/CIs (meta-analysis) for genetic traits associated with a first VTE onset in children and with recurrent VTE (58)

<table>
<thead>
<tr>
<th>VTE onset</th>
<th>inherited thrombophilia</th>
<th>odds ratio/95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients/controls</td>
<td>2470/4119</td>
<td>2470/4119</td>
</tr>
<tr>
<td>protein C-deficiency</td>
<td>13.35/8.66–20.56</td>
<td>23.22/12.28–43.89</td>
</tr>
<tr>
<td>protein S-deficiency</td>
<td>7.1/3.9–13.2</td>
<td>6.8/3.7–12.7</td>
</tr>
<tr>
<td>antithrombin-deficiency</td>
<td>13.51/6.86–26.60</td>
<td>19.5/11.84–30.85</td>
</tr>
<tr>
<td>factor V G1691A</td>
<td>3.13/2.65–3.70</td>
<td>3.1/2.36–3.95</td>
</tr>
<tr>
<td>factor II G20210A</td>
<td>1.60/1.15–2.21</td>
<td>1.87/1.28–2.72</td>
</tr>
<tr>
<td>lipoprotein (a)</td>
<td>3.93/2.98–5.19</td>
<td>3.62/1.99–6.58</td>
</tr>
<tr>
<td>≥two parameters</td>
<td>17.63/10.79–28.81</td>
<td>22.69/12.31–41.84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VTE recurrence</th>
<th>inherited thrombophilia</th>
<th>odds ratio/95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients &amp; recurrence/ patients no recurrence</td>
<td>168/1288 [Σ 1490]</td>
<td>168/1288 [Σ 1490]</td>
</tr>
<tr>
<td>protein C-deficiency</td>
<td>4.4/1.68–11.47</td>
<td>4.8/0.94–24.36</td>
</tr>
<tr>
<td>protein S-deficiency</td>
<td>5.1/1.95–13.41</td>
<td>7.6/2.04–28.92</td>
</tr>
<tr>
<td>antithrombin-deficiency</td>
<td>3.73/1.40–9.88</td>
<td>4.65/1.38–15.69</td>
</tr>
<tr>
<td>factor V G1691A</td>
<td>2.6/1.47–4.43</td>
<td>1.83/0.78–4.29</td>
</tr>
<tr>
<td>factor II G20210A</td>
<td>3.0/1.41–6.42</td>
<td>3.7/1.47–9.34</td>
</tr>
<tr>
<td>lipoprotein (a)</td>
<td>1.73/0.90–3.36</td>
<td>1.75/0.86–3.56</td>
</tr>
<tr>
<td>≥two IT</td>
<td>5.9/3.26–10.99</td>
<td>5.1/1.58–16.10</td>
</tr>
</tbody>
</table>

IT: inherited trait; VTE: venous thromboembolism
Until results from randomized trials are available for anticoagulant treatment and duration of symptomatic children, paediatric patients with symptomatic VTE are treated according to recommendations based on small-scale studies in children and guidelines adapted from adult patient protocols (70). The MPTS* score (Tab. 3) based on a positive or negative family history, idiopathic versus triggered VTE, results of thrombophilia testing, thrombotic locations and extension, and short-term patency rates will help physicians to classify children at risk and to estimate the duration of anticoagulant following a first event and secondary prophylactic anticoagulation in any clinical risk situations prone to thrombosis in later life. We suggest that children with a

- low-risk score (≤2) receive anticoagulation over three months,
- with a medium risk score (3–5) should be treated for 6 to 12 months, and
- high-risk score (>6) should be treated for at least 12 months or life-long with risk adapted dosages.

In addition, there is an urgent need for each paediatric patient with an early VTE manifestation to receive secondary anticoagulation prophylaxis in clinical risk situations prone to thromboembolism, for example catheterization, dehydration, haematologic malignancies, or prolonged immobilization respectively. Since randomized treatment trials are lacking doses and durations of secondary anticoagulation should be individually adapted to patient’s risk.

**Conclusions**

Apart from a risk stratification based on clinical acquired circumstances along with genetic thrombophilias for the onset and course of VTE diseases in children as a basic step for future evidence-based prospective anticoagulant/antithrombotic treatment trials, a world-wide paediatric expert consensus on standardized clinical outcome measurements, imaging methods to be used, and determination of follow-up intervals are urgently requested. The effective prevention of thrombosis-related complications in children will considerably reduce the burden and the costs associated with the disease.

**References**

27. Toumi NH, Khalidi F, Ben Becher S et al. Thrombosis in congenital deficiencies of AT III, protein

**Tab. 3** MPTS Score in acute paediatric venous thromboembolism

<table>
<thead>
<tr>
<th>risk</th>
<th>points</th>
</tr>
</thead>
<tbody>
<tr>
<td>factor</td>
<td></td>
</tr>
<tr>
<td>positive family history</td>
<td>1</td>
</tr>
<tr>
<td>spontaneous/idiopathic DVT</td>
<td>2</td>
</tr>
<tr>
<td>single inherited thrombophilia</td>
<td>1</td>
</tr>
<tr>
<td>combined factor/APS</td>
<td>2</td>
</tr>
<tr>
<td>calf/leg &amp; pelvis or PE/cerebral DVT</td>
<td>0/1/2/3</td>
</tr>
<tr>
<td>patency: complete/partial/none</td>
<td>0/1/2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>score</th>
<th>risk</th>
<th>Σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>≤2</td>
<td>3</td>
</tr>
<tr>
<td>medium</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>high</td>
<td>&gt;6</td>
<td></td>
</tr>
</tbody>
</table>

DVT: deep venous thrombosis, I: inherited thrombophilia; APS: antiphospholipid syndrome; PE: pulmonary embolism

* Münster Paediatric Treatment Severity