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EDUCATIONAL REVIEW

Venous thromboembolism in pediatric nephrotic syndrome

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Abstract Childhood nephrotic syndrome (NS) is one of the most common pediatric kidney diseases, with an incidence of 2–7 per 100,000. Venous thromboembolism (VTE) is associated with significant morbidity and mortality, and occurs in ~3 % of children with NS, though incidence approaches 25 % in high-risk groups. VTE etiology is multifactorial, with disease-associated coagulopathy thought to be a significant contributor. Other risks include age, disease severity, and treatment-related hazards, such as the presence of central venous catheters. Non-pharmacologic preventive measures such as ambulation and compression stockings are recommended for patients with identified VTE risks. Central venous catheters should be avoided whenever possible. Symptoms of VTE include venous catheter dysfunction, unilateral extremity symptoms, respiratory compromise, flank pain, and gross hematuria. When VTE is suspected, confirmatory imaging studies should be obtained, followed by appropriate laboratory evaluation and treatment. Therapeutic goals include limiting thrombus growth, extension, and embolization by early institution of anticoagulant therapy. Anticoagulation is recommended for a minimum of 3 months, but should be continued until NS remission is achieved. Further studies are necessary to identify VTE-risk biomarkers and optimal therapeutic regimens. Observational cohort studies are needed to identify VTE-risk groups who may benefit from thromboprophylaxis and to define disease-specific treatment algorithms.

Keywords Thrombosis · Nephrotic syndrome · Proteinuria · Vascular disease

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Introduction

Childhood nephrotic syndrome (NS) is among the most common of pediatric kidney diseases with an incidence of 2–7 per 100,000 children and estimated prevalence of 16 cases per 100,000 children [1, 2]. Children with NS may develop a number of life-threatening complications during their disease course, including infections, adverse effects of therapy (such as immunosuppression and bone mineral loss from long-term corticosteroids), acute kidney injury, potential progression to end-stage renal disease (especially for steroid resistant cases), and venous thromboembolic disease (VTE), which includes deep vein thrombosis (DVT) with or without pulmonary embolism (PE) [1, 3].

The objectives of this educational review are to (1) describe the epidemiology of VTE in childhood NS, (2) examine the current understanding of the hypercoagulopathy resulting from NS, (3) review which NS patient subgroups are at elevated risk for VTE, and (4) illustrate appropriate updated, evidence-based diagnostic and treatment algorithms for established VTE. Finally, candidate biomarkers that may eventually guide appropriate thromboprophylactic therapy and other clinical/translational research opportunities in this field will be highlighted.

Epidemiology

VTE is a rare but often devastating complication of childhood NS [4]. This complication arises in approximately 3 % of childhood NS cases (Table 1) [5–15]. Venous thromboembolism is the predominate form of thromboembolic disease in children with NS, accounting for 97 % of the cases in a recent, large study [9]. In that study, arterial disease was encountered in only one of 370 (0.3 %) subjects studied.

Childhood VTE is an increasingly common complication, but is encountered predominantly in the tertiary care setting [3, 16, 17]. Over 70 % of children with VTE have a chronic underlying medical condition (e.g., cardiac disease, cancer, neuromuscular disease, etc.), with chronic renal disease (including NS) being associated with approximately 5 % of the cases [3].

Two studies suggest that the incidence of childhood NS-associated VTE may be greater (10–13 %) in children with congenital NS [7, 11]. The reasons for this are not clear. While it is possible that the higher frequency may be due to disease-specific pathophysiology, it is equally likely that this risk may derive from the fact that these children more often require the use of a central venous catheter (CVC) or because they are much less likely to achieve NS remission and are thus hypercoagulable for a longer time-frame.

Most epidemiologic studies on this topic are retrospective in nature. Therefore, most reported VTE were clinically symptomatic enough to justify diagnostic imaging [18]. To date, only two studies have objectively evaluated children with NS for VTE without regard to symptomatology [8, 15]. In the first of these, 26 children in NS remission were imaged with radioisotope ventilation-perfusion scans. Seven of these children (27 %) had evidence of PE and another ten (38 %) had evidence of previous PE. It should be noted that, in adult studies, radioisotope ventilation-perfusion scans are only moderately sensitive (41–83 %) and specific (52–97 %) for PE, and have been supplanted by CTPA (computerized tomography pulmonary angiography), which has similar sensitivity (77–81 %) and better specificity (91–98 %) [19]. However, a recent CTPA study of children with NS who were without respiratory symptoms revealed a similarly high rate of subclinical PE (28.1 %) [15]. Thus, these data suggest that subclinical VTE may be far more common in childhood NS than is commonly appreciated. At least one pediatric VTE study suggested that subclinical VTE may have important long-term consequences [20], although the potential consequences of subclinical VTE in childhood NS have not been well studied.

Although the morbidity and mortality of VTE in childhood NS has not been clearly established, most inferences from the pediatric VTE literature are likely to apply. Overall, childhood VTE is associated with an approximate sixfold increase in the likelihood of in-hospital death (relative risk 6.27; 95 % CI 5.41–7.25) [3]. Both mean and median length of hospital stays are also significantly increased [16], likely resulting in greater healthcare expenditures [21, 22]. Long-term morbidity may be significant, with an estimated 6–21 % of children suffering from recurrent VTE [23]. Perhaps the best estimate comes from a recent large cohort study in which 1,401 (12 %) of 11,337 children with VTE developed recurrence [16]. Additionally, a significant proportion of children with VTE subsequently develop post-thrombotic syndrome (PTS), which results from post-VTE venous insufficiency [21]. PTS symptoms may be minor, such as mild chronic extremity edema and sensation of heaviness, but in severe cases may include chronic pain, poor wound healing, and in extreme cases non-healing venous ulcers. Effective therapies for established VTE are

Table 1 Summary of reported incidence of NS-associated TE

Senior author	Publication year	Study type	Notes	*n*	TE	TE (%)
Stalder [6]	1973	Retrospective	Probably only symptomatic TE	3,377	60	1.8
Vernier [11]	1984	Retrospective	Only congenital NS	41	4	9.8
Brodehl [8]	1986	Retrospective	V•Q evidence of PE	26	7	26.9
Ritz [12]	1987	Retrospective	Primarily only symptomatic TE	204	9	4.4
Sheu [14]	1991	Retrospective	Only symptomatic TE reported	193	2	1.0
Schlegel [13]	1997	Not Stated	Primarily only symptomatic TE	360	11	3.0
Nayir [5]	2000	Prospective	Only symptomatic TE reported	49	2	4.1
Topalov [10]	2000	Retrospective	Only symptomatic TE reported	447	9	2.0
Shomaf [7]	2001	Retrospective	Only congenital NS	30	4	13.0
Smoyer [9]	2009	Retrospective	Only symptomatic TE reported; included secondary causes of NS	326	30	9.2
Lu [15]	2012	Prospective	Dual Energy CT Angiogram evidence of PE; all subjects were asymptomatic at time of imaging	32	9	28.1
	Total			5,085	150	2.9

NS nephrotic syndrome; *TE* thromboembolism; *CT* computerized tomography

lacking, thus primary prevention is key—including prevention of VTE and early, effective anticoagulation for established VTE. A recent prospective cohort study revealed that PTS is highly prevalent, occurring in ~63 % of childhood VTE survivors, with approximately 10 % of the children having debilitating disease [24].

Pathophysiology

The pathophysiology of NS-related VTE in children is likely multifactorial in nature. These include the patient's underlying thrombophilic tendency, treatment-related hazards, and disease-related hypercoagulopathy.

The influence of heritable thrombophilia, including single-nucleotide polymorphisms known to moderately increase the likelihood of thrombophilia (i.e., F5 G1691A or F2 G20210A) as well as deficiencies of anticoagulant proteins (e.g., protein C, protein S, or antithrombin [AT]), on childhood NS-related VTE have not been well studied. Several studies have retrospectively reported the findings of thrombophilia panels among children with VTE [5, 8, 9, 12, 25], but no study to date has comprehensively studied thrombophilia in a de novo prospective cohort of childhood NS to accurately determine their potential influence on subsequent VTE development.

Acquired antiphospholipid antibodies (APL) may be seen in childhood NS, especially NS resulting from autoimmune glomerulopathies (e.g., systemic lupus erythematosus, Henoch-Schönlein purpura) [9, 26]. However, non-pathologic, transient APL detection is not uncommon in children [27]. No studies to date have adequately evaluated the relevance of pathologic APL (i.e., antiphospholipid syndrome) to childhood NS-VTE risk using well-defined parameters and a sound study design [28, 29]. In our recent retrospective study, subjects with secondary NS (including autoimmune glomerulopathies) were more likely to develop VTE than those with primary NS (17.0 vs. 6.6 %) [9]. It is thus possible that this increased risk may be biologically mediated by acquired APL and/or inflammation associated with the primary disease.

Treatment of the underlying nephropathy may also impart VTE risk. For instance, CVC are considered by many experts to be one of the strongest risk-factors for pediatric VTE [30–32]. In fact, in a recent large study of childhood NS-associated VTE, nearly 45 % of the VTE cases were associated with catheter use [9]. Catheters may irritate the vessel wall via direct mechanical means, disrupted laminar blood flow, or catheter-associated infection and local inflammation; all of which may activate the coagulant system, predisposing to VTE [33]. Unfortunately, catheters are often an unavoidable necessity for the provision of care to critically ill children, including some with NS.

Both corticosteroids and diuretics have also been linked to VTE risk in childhood NS [1, 10]. Nearly all nephrotic children are exposed to these therapeutic agents prior to VTE diagnosis. Thus, it is difficult to confirm whether these medications actually play a role in the pathophysiology of NS-related VTE development. Importantly, neither of these medication categories has been identified as a major risk factor for pediatric VTE in non-NS clinical settings [30, 32].

The most important risk factor for VTE in NS is likely the hypercoagulopathy that results from the underlying disease process, which has been recently reviewed in detail [13, 18, 34]. The coagulation defect in NS is highly complex and includes dramatic but variable shifts in the plasma concentrations and activities of nearly all proteins and enzymes involved in the natural procoagulant, anticoagulant, profibrinolytic, and antifibrinolytic systems. These changes are likely related to the pathologic loss of these proteins in the urine combined with dysregulated compensatory protein synthesis. In addition, some investigations have demonstrated increased adherence or aggregation properties of both red cells and platelets, which may potentiate coagulation system activity. Finally, endothelial dysfunction has been described in adult NS, but has not been well studied in childhood NS [35–37].

Risk stratification and diagnostic approach

The likelihood of VTE is elevated in several groups which have been identified mostly through retrospective cohort studies. Age is an important VTE risk modifier for children, in general. Several pediatric VTE studies have demonstrated a bimodal age distribution, with infants and adolescents at greatest risk for VTE [3, 16, 38, 39]. As mentioned above, children with congenital NS are more likely to develop VTE, which may be explained, at least partially, by this known age distribution. Similarly, recent data demonstrate that adolescents with NS are significantly more likely (adjusted OR 18.9; 95 % CI 5.7–63.2) to develop VTE than are younger children [9].

NS disease severity also appears to play a major role in thrombotic risk. In both pediatric and adult studies, worsening proteinuria is directly correlated with increasing VTE probability [9, 40]. In fact, even sub-nephrotic proteinuria has been identified as a prothrombotic risk marker [41–43]. Hypoalbuminemia, which is closely correlated to proteinuria severity, has been identified as an additional significant VTE risk marker in some adult studies [44, 45], but not in all [40], and was reported not to be a significant marker in a recent large pediatric cohort [9].

In addition to secondary NS, it should be noted that children with histologic evidence of membranous disease (e.g., membranous nephropathy and/or class-V lupus

nephritis) are substantially more likely to develop VTE [9]. Membranous nephropathy is rare in children [2], but is associated with the greatest risk for VTE (37 %) among adults with NS [18]. Thus, it is not surprising that these forms of NS are associated with a higher proclivity for VTE in children.

Practitioners should be aware that the majority of clinically apparent VTE are diagnosed within the first 3 months after NS diagnosis [9, 46]. Thus, a particularly high index of suspicion for thrombosis should be maintained early in the disease course. Common signs and symptoms associated with acute VTE in children include a swollen, painful extremity, which is sometimes plethoric, loss of CVC patency, superior vena cava syndrome, and/or respiratory compromise in cases with PE [23, 30, 32, 47].

When VTE is suspected clinically, appropriate imaging studies should be obtained to confirm the diagnosis [48]. In most situations, this can be accomplished in a non-invasive manner, without radiation exposure through the use of Doppler compression ultrasonography. Magnetic resonance imaging is increasingly useful in situations where ultrasound images are suboptimal. As discussed above, CTPA is now the preferred modality for children with cardiorespiratory compromise suspicious for PE. Laboratory evaluation should include platelet count, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and quantitative D-dimers [21]. In severe cases, this profile may be supplemented with AT, protein C, and protein S levels to determine if therapeutic supplementation of these natural anticoagulants may be useful (see Prevention and treatment). Comprehensive thrombophilia testing for uncomplicated pediatric VTE is controversial and does not alter current therapeutic recommendations, thus this approach is not endorsed outside of a research setting [49, 50].

Prevention and treatment

There are no randomized controlled trials demonstrating the safety and efficacy of pharmacologic thromboprophylaxis for the prevention of NS-related VTE in either adults or children [18, 51]. Despite the lack of robust evidence, several authors have suggested prophylactic strategies for children based upon known risk factors, NS severity markers, or coagulation abnormalities [13, 52, 53]. Among these strategies, some authors have advocated aspirin prophylaxis [54]. However, nonsteroidal anti-inflammatory drugs may be associated with an increased risk for acute renal failure [55] and the in vitro observations suggest that antiplatelet therapy is less likely to be beneficial than anticoagulant therapy [56]. Strong recommendations for or against pharmacologic prophylaxis await definitive trials, perhaps limited to children in high-risk groups [18]. However, there are several non-pharmacologic strategies to limit the likelihood of VTE in childhood NS including regular ambulation, adequate hydration, avoidance of CVC whenever possible, and the use of graduated compression stockings and/or sequential compression devices for bedridden children [53].

Although NS-specific guidelines for pediatric VTE treatment have not been developed, they have been incorporated, along with other disease-specific indications, into the ACCP (American College of Chest Physicians) evidence-based clinical practice guidelines, which are revised by an expert panel and published on a 4-year cycle [49]. Upon VTE diagnosis, several therapeutic goals become a priority. Acutely, the goals are to limit thrombus growth, extension, and embolization. This is usually adequately achieved with therapeutic anticoagulation. Children with life- or limb-threatening VTE may benefit from thrombolysis or thrombectomy, followed by anticoagulation to prevent recurrence of the thrombus. In children with a first VTE, an initial 3-month course of anticoagulation is recommended, followed by thromboprophylactic anticoagulation until the underlying chronic disease (e.g., NS) is in remission or resolved. If the thrombus is CVC-related, the CVC may be removed after an initial 3 to 5-day period of anticoagulation. This allows time for the thrombus to stabilize, hypothetically limiting the likelihood of inducing a paradoxical embolism. Alternatively, if the CVC is still functional, despite the thrombus, and central venous access remains therapeutically desirable, the CVC need not be removed. The duration of therapy should remain unchanged.

Anticoagulation is typically initiated in children with low molecular weight heparin (LMWH). This is likely because the pharmacokinetics are more predictable than with standard heparin, and intravenous access is not necessary for administration. In clinical situations where a short half-life and ease of anticoagulant reversibility are favored, standard heparin may be utilized. There are published weight- and age-based nomograms for heparin and LMWH dosing in children, which are summarized in Fig. 1 [21, 49].

All heparins are dependent on AT for their mechanism of action. Thus, regardless of which compound is utilized, AT supplementation may rarely be necessary to achieve an adequate anticoagulant effect in children with NS [4, 10]. Although there is no published childhood NS-specific evidence regarding optimal AT levels, the dosing guidelines for subjects with congenital AT deficiency target levels in the 80–150 unit/dl range [57]. Both plasma-derived and recombinant AT are clinically available; however, the pharmacokinetics and thus the dosing strategy differ [57]. The expected pharmacological peak effect of plasma-derived and recombinant AT is similar (1.4–2.1 units/dl per administered unit/kg for plasma-derived vs. ~1.7 for recombinant AT). However, the biologic half-life of plasma-derived AT (56.8–68 h) is substantially longer than that of recombinant AT (~10.5 h). Thus, it would be reasonable to hypothesize

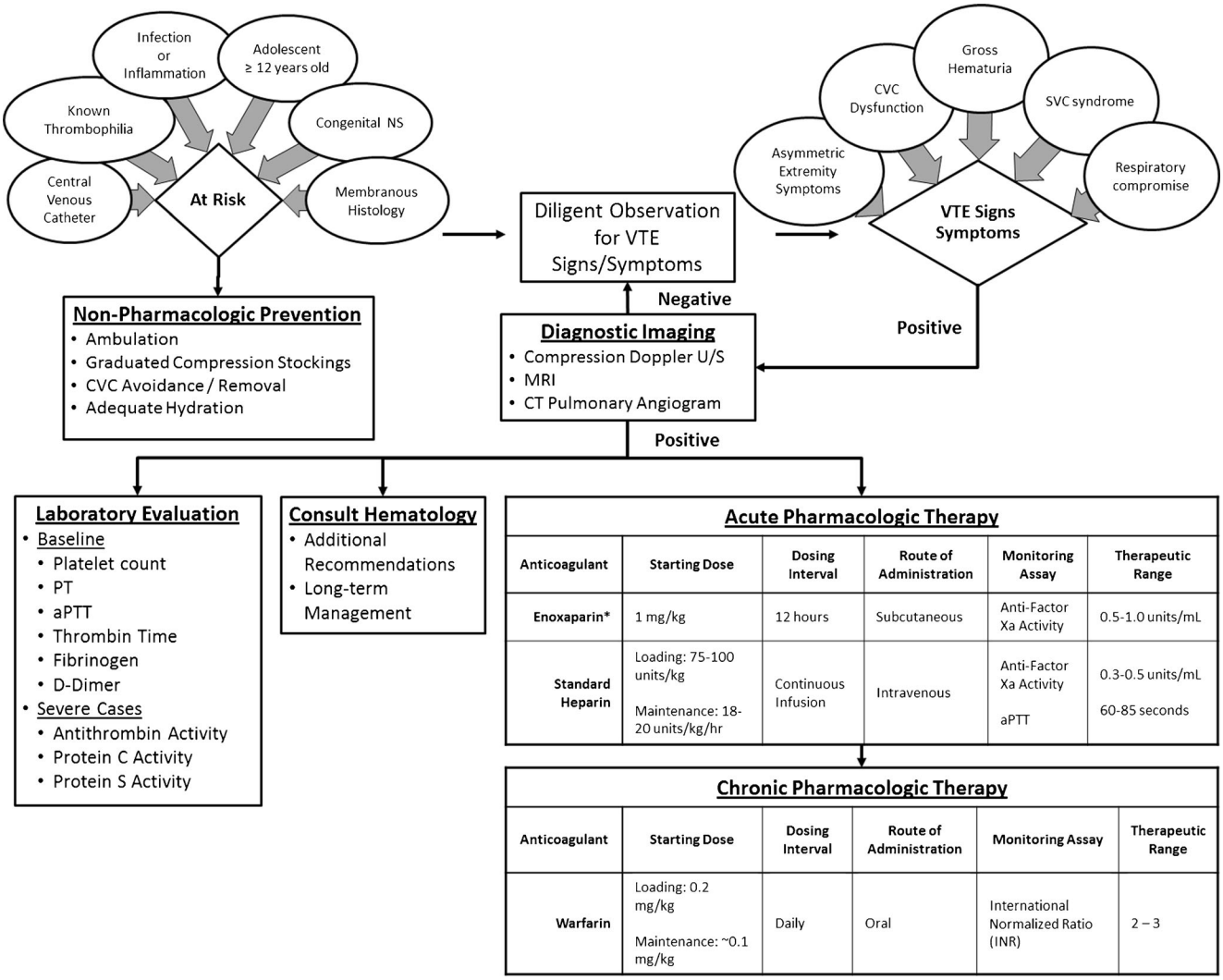

Fig. 1 Suggested algorithm for childhood nephrotic syndrome (NS) associated venous thromboembolism (VTE) prevention and management. *Enoxaparin is an example of a low molecular weight heparin (LMWH). Nomograms for dosing other LMWH compounds in children are available in reference #49

that the plasma-derived formulation, with its longer half-life, would be preferable in the setting of childhood NS, since urinary protein loss is driving the acquired AT deficiency. However, there are no published studies comparing them in an NS population.

Children may complete their course of anticoagulation with LMWH or may be bridged to a vitamin K antagonist, typically warfarin [49]. Warfarin has many drug–drug interactions and poorly predictable pharmacokinetics in children, but it is not AT-dependent. Thus, warfarin may be preferable for children who do not rapidly go into remission and continue to require antithrombin supplementation. There are established warfarin dosing algorithms to maintain the international normalized ratio (INR) in the desired range of 2.0–3.0 during the course of therapy (Fig. 1) [21, 49].

Several novel anticoagulants have recently been approved for use in adults, and are now undergoing pediatric trials [21]. Moreover, several of these agents are orally bioavailable and AT-independent anticoagulants, thus they may become preferable treatment options in the near future. Prevention of PTS may be feasible with the application of graduated compression stockings, which are recommended for the first 24 months following extremity DVT diagnosis [58, 59].

Approximately 12 % of childhood VTE subjects develop recurrent disease [16]. For these children, long-term indefinite duration anticoagulation is recommended to prevent the development of subsequent VTE and potential embolic-related mortality.

Future directions

Although the epidemiology and hypercoagulable physiology of childhood NS is now well defined, much work

remains in this field to develop appropriate VTE prevention strategies and optimal treatment guidelines. Additionally, the impact of childhood NS on vascular endothelial cell biology is not well understood, but is suspected to play a major role in VTE evolution [60].

While prevention of all VTE is an optimal goal, pharmacoprophylaxis for all children with NS is not a reasonable strategy given the overall low incidence of childhood NS-associated VTE. Only 3 % of children with NS develop clinically significant VTE while another 24–25 % are affected by subclinical VTE [8, 15, 18]. Thus, if pharmacoprophylaxis were universally applied, 75–97 % of children would receive unnecessary anticoagulation, and potentially suffer anticoagulation-related adverse events (e.g., bleeding). Since the "number needed to treat" to prevent clinically relevant VTE would be very high, a favorable cost/benefit ratio is not feasible. In this light, the most obvious strategy is to develop consensus-based VTE-risk groups based on clinical risk factors (i.e., CVC use, congenital NS, secondary NS, membranous histology, and/or adolescent age) in combination with one or more relevant VTE-risk biomarkers (e.g., proteinuria severity) and target this group for a prospective randomized controlled trial of thromboprophylaxis. Obviously, such restrictive eligibility criteria further limit study feasibility due to the rarity of qualifying study subjects. Thus, multicenter collaborative group efforts would be essential and may need to be coupled with innovative analytical methods to account for low-frequency event rates [61–63].

Disease-specific treatment strategies have not been defined for childhood VTE, despite the fact that over 70 % of VTE occur in children with an underlying chronic health condition [3]. Presumably, as with childhood NS, the hypercoagulable physiology is at least partially disease-specific [21]. Thus, it may be optimal to tailor treatment algorithms based on the underlying disease state. For instance, if a child develops VTE during their initial treatment, then later develops recurrent VTE during a NS relapse; should that child receive long-term anticoagulation as per the current ACCP guidelines, even if remission is again achieved? Thus, additional therapeutic trials for childhood VTE are desperately needed to guide improvements in clinical care. These may best be achieved through collaborative efforts among nephrologists and hematologists who both participate in the development and leadership of prospective multicenter trials.

Many additional biologic questions remain unanswered. For instance, a healthy vascular endothelium promotes quiescent hemostasis [60]. The potential role of endothelial activation in the pathobiology of childhood NS-related hypercoagulopathy remains undefined. This and other questions may best be answered in the laboratory through the use of appropriate NS animal models crossed with hyper- and hypo-coagulable transgenic animals. Such studies may lead to the development of novel biomarkers for NS-related VTE-risk and/or reveal novel therapeutic targets. Similarly, as new anticoagulant agents (with varying mechanisms of action) emerge, they could be tested in these animal models to determine which ones may have more favorable properties to control or reverse NS-specific pathobiologic derangements.

Conclusions

Over the past 30 years, much has been learned about the epidemiology and pathobiology of childhood NS-related VTE. While these events occur in only about 3 % of children with NS, they can have devastating clinical consequences. It is now well recognized that NS is associated with a variable, but oftentimes severe hypercoagulopathy. Careful synthesis of clinical and emerging laboratory data in children with NS should improve our identification of high-risk clinical groups who may benefit from pharmacologic prophylaxis, as well as identify potential novel future drug targets for thromboprophylaxis. Emerging VTE-risk biomarkers will likely also help to further refine the patient population that would benefit most from such therapy.

Key summary points

1. Venous thromboembolism (VTE) occurs in ~3 % of children with nephrotic syndrome (NS) and is associated with significant morbidity and mortality.
2. Risks for VTE development in association with childhood NS include age, disease severity, disease type, underlying thrombophilic tendency, and treatment-related hazards.
3. When VTE is suspected, appropriate imaging studies should be obtained to confirm the diagnosis, followed by appropriate laboratory evaluation and prompt initiation of treatment.
4. Preventive measures for VTE may include regular ambulation, adequate hydration, graduated compression stockings, and avoiding central venous catheters.
5. Therapeutic goals for VTE include limiting thrombus growth, extension, and embolization through the use of anticoagulation; life- or limb-threatening events may require thrombolysis or thrombectomy.

Key research points

1. Additional research is necessary to assess the impact of childhood NS on vascular endothelial cell biology, which is suspected to play a major role in VTE evolution.

2. Further laboratory research using appropriate animal models is required to identify relevant VTE-risk biomarkers and potential novel therapeutic targets.
3. Observational cohort studies are needed to validate VTE-risk groups who may benefit most from thromboprophylaxis.
4. Disease-specific treatment algorithms for NS-associated VTE await evidence from multicenter collaborative group trials.

Questions (answers are provided following the reference list)

1. Overall, childhood VTE is associated with what increase in likelihood of in-hospital death?
   a. 6 %
   b. 6-fold (RR=6)
   c. 60 %
   d. 16 %
   e. 60-fold (RR=60)
2. Approximately what percentage of pediatric VTE patients develop recurrent VTE?
   a. 3 %
   b. 52 %
   c. 12 %
   d. 71 %
   e. 32 %
3. What is the strongest risk factor for pediatric VTE?
   a. Presence of infection
   b. Immobilization
   c. Presence of anti-phospholipid antibodies
   d. Heritable thrombophilia
   e. Presence of a central venous catheter
4. For children with NS, the majority of clinically apparent VTE develop within how long after diagnosis?
   a. 1 month
   b. 6 months
   c. 9 months
   d. 3 months
   e. 12 months
5. Antithrombin supplementation may become necessary with the use of which anticoagulants?
   a. Warfarin
   b. Vitamin K antagonists
   c. Tissue-type plasminogen activator
   d. Heparin
   e. Aspirin

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Answers:
1. B
2. C
3. E
4. D
5. D