

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Venous Thromboembolism in Children



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H&O How common is venous thromboembolism in children?

NG The overall incidence of venous thromboembolism (VTE)—either deep vein thrombosis (DVT) or pulmonary embolism (PE)—in children younger than 18 years is approximately 5 per 100,000 per year, according to data from the National Hospital Discharge Survey that were published in *The Journal of Pediatrics* in 2004 by Stein and colleagues.¹ More recently, data from Raffini and colleagues that were published in *Pediatrics* in 2009 found a 70% increase in the diagnoses of VTE in pediatric patients over a 7-year period from 2001 to 2007.² So even though VTE is not common in the pediatric population overall, diagnoses appear to be increasing. VTE is more common, of course, among hospitalized patients, where it occurs in approximately 1 in 200 children hospitalized with critical illnesses.

H&O Why would you say diagnoses are increasing?

NG I think that nonhematology physicians are gaining greater awareness of the signs and symptoms of VTE, which could translate into a higher rate of diagnosis. But a true increase in the incidence of VTE in children also may be occurring. We are providing invasive care to more children with critical illnesses and more children are surviving illnesses that were once fatal, which leads to more children with prolonged hospitalization in the intensive care unit with central venous catheterization and immobility, which increases the risk of VTE.

H&O In what ways is VTE different in children than in adults?

NG VTE differs between children and adults in a number of ways. First, the condition manifests differently. The proportion of upper-extremity DVT, which is increased with the use of a central venous catheter, is higher in children. Pediatric patients also are more likely than adult patients to experience cerebral sinovenous thrombosis, which occurs when a blood clot develops in the venous system bringing deoxygenated blood back toward the heart, from the head and neck.

Second, children are more likely than adults to experience provoked VTE, in which the main provoking risk factor is not chronic in nature. Provoked VTE occurs in approximately 90% to 95% of children and 60% of adults with VTE. Furthermore, among patients with provoked VTE, children typically have 2 or more clinical risk factors for VTE, whereas nonelderly adult patients tend to have fewer risk factors.

Finally, children with VTE are less likely to experience a recurrence, which is largely explained by the fact that the recurrence rate is lower in provoked VTE than in unprovoked VTE.

It is unclear whether the risk of bleeding with anticoagulants is lower in children than in adults; the most recent randomized trials suggest similar rates of major and clinically relevant nonmajor bleeding, at approximately 1% to 2% in both populations.

H&O Could you talk more about which children are at elevated risk for VTE?

NG The same general factors are at play in children as in adults: venous stasis, endothelial damage, and the hypercoagulable state—together referred to as the triad of Virchow. Children can experience venous stasis because of reduced mobility after surgery, or after casting or splinting of a limb after trauma. Dehydration can also lead to venous stasis.

Regarding endothelial damage, central venous catheterization is one of the most common risk factors for VTE in children. Many children who receive central venous catheterization never develop VTE, but it is a predisposing factor. Sepsis is another potential cause of endothelial damage.

As for hypercoagulable status, acquired thrombophilia and acquired hypercoagulable states are very common in children. These may be caused by infection or other inflammatory states. Chemotherapy can also predispose children to hypercoagulability.

One of the earliest large multicenter registry studies, which was reported in *Pediatric Research* in 2000 by Monagle and colleagues, showed that approximately 60% of pediatric patients with VTE had a central line.³ About 25% had a malignancy or a bone marrow transplant, approximately 19% had congenital heart disease, and approximately 12% had an infection. Other studies of US-based cohorts have produced similar results. We still need more evidence before we can say that these comorbidities are independent risk factors for thrombosis, however, because they are also common in children who do not develop thrombosis.

H&O When is VTE prophylaxis needed?

NG The question of when VTE prophylaxis is needed is a hot topic right now. Numerous studies have established prevalent comorbidities, but less work has been done to establish independent risk factors that could be used to create a risk score that would trigger prophylactic interventions. Right now, both single-center studies and meta-analyses have looked at risk factors and risk scores for the development of VTE among hospitalized children. Some of these studies were specific to children who were critically ill, whereas other studies looked at children who were not critically ill.

The field has been moving toward developing risk models that are more subpopulation-specific. An ongoing registry called the Children's Hospital Association Thrombosis (CHAT) project, which is led by some junior faculty mentees—Drs Julie Jaffray, Brian Branchford, and Arash Mahajerin—is aimed at developing risk models for VTE in hospitalized children based on multicenter retrospective data.⁴ So far, much of what we have seen from that registry is concordant with some of the prior single-institution studies.

Only after we have prospective validation of risk scores can we initiate interventional trials that evaluate the safety and efficacy of thromboprophylaxis. That is still a few steps away. In the meantime, the data to date suggest that children who have a central venous catheter, those who are anticipated to have a prolonged stay in the hospital, and those who have significant infections or systemic inflammatory states are the ones at greatest risk for developing VTE.

H&O How should VTE be treated in children?

NG We have more evidence and a greater consensus regarding VTE treatment than prevention in children. For example, randomized trials from the 1960s in adults showed that anticoagulation is superior to placebo in preventing PE in patients who have proximal-limb DVT. The US Food and Drug Administration (FDA) approvals for more recent anticoagulants in VTE treatment in adults have been based on comparing the efficacy and safety of new agents with those of prior agents such as warfarin and low-molecular-weight heparin. We have extrapolated from the adult experience to use anticoagulation in children for initial treatment of VTE, meaning the first 5 to 7 days or so, with either low-molecular-weight heparin or an unfractionated heparin drip. In certain patient subgroups, such as those with a high risk of bleeding, clinicians might choose a short-acting agent like bivalirudin or unfractionated heparin. In contrast, physicians typically choose low-molecular-weight heparin for initial treatment in patients at relatively low bleeding risk.

For the subacute treatment period, lasting through at least 3 months, the most commonly used regimen for VTE in children is probably low-molecular-weight heparin. In children who are receiving an extended course of treatment because their VTE was either unprovoked, or was provoked but a risk factor remains, warfarin should be considered.

One of the challenges with warfarin is the need for frequent venipuncture—weekly or monthly—in order to monitor the international normalized ratio. Another challenge with warfarin is dietary adherence, because vitamin K intake must be consistent. The newer direct oral anticoagulants (DOACs) have the potential to overcome some of these feasibility concerns, and ongoing studies are evaluating the efficacy, safety, and appropriate dosing of these newer agents in pediatric populations.

H&O How long should treatment last after a blood clot?

NG The duration of therapy depends on whether the DVT is provoked or unprovoked. One of the key questions in

pediatric VTE that is being addressed in a large, multinational, randomized controlled trial funded by the National Institutes of Health—the Kids-DOTT trial (Evaluation of the Duration of Therapy for Thrombosis in Children)—is the optimal duration of anticoagulation for provoked VTE in patients younger than 21 years. The American Society of Hematology 2018 guidelines on treatment of pediatric venous thromboembolism, published in *Blood Advances* by Monagle and colleagues, give 30 recommendations on treatment of pediatric VTE.⁵

One of the key recommendations from these guidelines is the duration of anticoagulation for provoked VTE, which is less than or equal to 3 months. This is a conditional recommendation because of the relatively low level of evidence. Until the Kids-DOTT trial is completed and published, we have only observational studies in children and randomized, controlled trials from the 1990s in adults that address the question of duration.

H&O Should dosing be based on accelerated pharmacokinetics in children?

NG The dose findings for multiple low-molecular-weight heparins have been published for VTE treatment in children, with the greatest depth of data being for enoxaparin. A recently completed but unpublished study also looked at dosing, safety, and efficacy of dalteparin in pediatric VTE treatment (NCT00952380). The weight of the evidence indicates that throughout the pediatric age range, children require a higher dose per kg than adults to achieve a targeted level of anti-Xa activity. In the late teen years, the dosing becomes similar to that in adults. For example, evidence suggests that the therapeutic dose of enoxaparin is approximately 1.1 mg/kg twice daily for adolescents vs 1 mg/kg twice daily for adults.

Regarding the experience with DOACs, phase 2a studies of dabigatran that were published by Halton and colleagues in 2016 and 2017 have spanned the infant, adolescent, and in-between age ranges.⁶⁻⁸ The total size of the population for dabigatran dose finding in that phase 2a series of publications is 35 children, which is a very small trial population, but the study provides information on the pharmacokinetics, pharmacodynamics, and safety of both the single-dose and multiple-dose regimens. Phase 2 data on rivaroxaban for pediatric VTE treatment that have not yet been published involve approximately 110 patients and address the pharmacokinetics and pharmacodynamics of a multiple-dose regimen of this agent (NCT01684423 and NCT02309411).

H&O What is the effect of elevated levels of plasma, factor VIII, or D-dimer on thrombotic outcomes?

NG We first published on that in the *New England Journal of Medicine* in 2004,⁹ and it is interesting that 15 years later we know little more about prognostic markers for VTE outcome in pediatrics. One of the secondary aims of the Kids-DOTT trial is to establish a multinational biobank of plasma and genetic material from which to discover and validate additional prognostic markers for some discrete, blinded endpoints, which include recurrent VTE and the post-thrombotic syndrome (PTS). As part of that effort, we will further investigate the role of factor VIII and D-dimer levels at approximately 6 weeks and 3 months after diagnosis of VTE as prognostic markers.

In terms of treatment, the evidence to date does not warrant treating children differently based on their levels of plasma, factor VIII, or D-dimer levels alone, which was highlighted by the ASH guidelines I mentioned earlier. In my own practice, however, I tend to use D-dimer as a reassuring marker when discussing duration of therapy with pediatric patients and/or their parents in the setting of an unprovoked VTE, or a provoked VTE with a non-transient provoking factor.

H&O Do reversal agents work the same in children as they do in adults?

NG This is one of the key unanswered questions that need to be addressed in pediatric VTE. An ongoing study is looking at idarucizumab in dabigatran-associated bleeding in children (NCT02815670). One of the challenges of conducting such studies in children is adequate enrollment because bleeding rates are low with DOACs.

We need to take a thoughtful approach regarding reversal agents in management of DOAC-associated bleeding in pediatric VTE patients. We have ongoing studies on apixaban for prevention of cancer-associated VTE in children with central venous catheters (NCT02369653) and for VTE treatment in children (NCT02464969), rivaroxaban for VTE treatment (as mentioned above) as well as for thromboembolism prevention after the Fontan procedure in children with congenital heart disease (NCT02846532), and edoxaban for VTE treatment (NCT02798471) as well as prevention in cardiac disease (NCT03395639). At the same time we are learning about dosing, safety, and efficacy of DOACs, we need to keep our eye on generating evidence regarding DOAC reversal.

H&O How often does PTS occur in children?

NG Systematic review data published in *Haematologica* in 2010 suggest that approximately 26% of children with limb DVT will develop PTS, based on a mix of retrospective and prospective studies.¹⁰ More recently, unpublished blinded data from the Kids-DOTT trial thus far indicate a very similar risk of PTS among patients with limb

DVT at enrollment, of 25% at 1 year. That cumulative-incidence value is based on a definition of any objective signs of PTS using 1 of 2 validated outcome instruments for pediatric PTS assessment that are recommended by the pediatric subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.

Fortunately, the rate of PTS that limits activities of daily living or age-appropriate exercise or athletic activities is lower than 25%, and appears to be less than 5% for unselected pediatric patients who have a provoked DVT of the limbs. We still need to generate robust evidence on the natural history of PTS, however.

H&O What treatments are effective in children with PTS?

NG The optimal management of PTS is a key question in both children and adults. Most pediatric patients who are symptomatic seem to get relief of symptoms from the use of graduated compression stockings, which typically are prescribed at 20 to 30 mm Hg of pressure. I also encourage pediatric patients who have PTS of the lower extremities to undertake a treadmill exercise regimen with calf strengthening and stretching. This is based on pilot findings from a physical therapist-supervised regimen in adults with PTS that was published by Kahn and colleagues at McGill University.¹¹

H&O What questions should future studies address?

NG Future treatment trials should take into consideration not just the historical standard endpoints of recurrent thrombosis and bleeding complications, but also the long-term outcomes, particularly PTS. Addressing long-term outcomes in trial designs is important. Another important issue is the safe and effective prevention of VTE in hospitalized children, as I mentioned. In addition, future studies should aim to identify prognostic markers in children to assess the risk of thrombosis, as well as to predict thrombosis when it occurs. Risk stratification in pediatric VTE management will result in a more effective, tailored

approach to achieving optimal outcomes in particular subgroups of children.

Disclosure

Dr Goldenberg has participated in steering committees and data and safety monitoring committees in pharmaceutical industry-sponsored trials by Pfizer, Bristol-Myers Squibb, Daiichi Sankyo, and Novartis. He has participated in academia-industry collaborative designs of trials on behalf of the ATLAS Group (co-sponsored by CPC Clinical Research and Worldwide Clinical Trials). He has received research support from the National Heart, Lung, and Blood Institute.

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