# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Thrombosis and Thrombophilia in Children

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**H&O** How common is thrombosis in children?

**NG** Approximately 1 in 10,000 children in the community get blood clots. Thrombosis is between one-tenth and one-hundredth as common in children as in adults. When we look at children who are hospitalized, however, approximately 1 in 200 develop blood clots. So thrombosis is an important problem in children, especially in those who are hospitalized. The most common times for young people to develop blood clots are during infancy and adolescence.

**H&O** How is thrombosis diagnosed?

**NG** Typically, the diagnosis is made because there are signs and symptoms of a blood clot. In deep vein thrombosis (DVT), in which a blood clot forms in one of the deep veins in the body (such as in the leg or arm), the person usually develops a painful swelling in that extremity. In cerebral sinovenous thrombosis, in which a blood clot occurs in the veins that drain blood flow from the brain back to the heart, the person generally develops an unusually severe headache that may include blurred vision. In a pulmonary embolism (PE), in which a blood clot travels to a pulmonary artery, the person typically experiences chest pain that worsens with deep breathing and sometimes has a cough with some blood in the sputum. Many of these signs and symptoms are the same in children and adults, although we think that children probably develop cerebral sinovenous thrombosis more often than do adults. If a patient has these signs or symptoms and we suspect a blood clot, we use imaging such as a computed tomography scan, a magnetic resonance imaging scan, or ultrasound to confirm the diagnosis.

**H&O** Are the same agents that are used to treat thrombosis and thrombophilia in children used in adults?

**NG** The anticoagulant medications we use to treat blood clots in children are, to a great extent, the same ones we use in adults—with unfractionated heparin, low-molecular-weight heparin, and warfarin being the historical conventional agents. Our standard of care in children is to use these drugs off-label, because (in contrast to the adult setting) they are not specifically approved for venous thromboembolism (VTE, which encompasses DVT and PE) treatment in children. Warfarin is especially challenging to use in children because its anticoagulant effect is greatly influenced by diet and other medicines, which means that frequent blood draws must be done. In addition, research shows that optimal pediatric dosing of warfarin depends largely on age and weight, both of which change over the pediatric continuum from infancy into late adolescence.

An exciting development is the wave of oral direct anticoagulant medicines, such as the direct thrombin inhibitor dabigatran (Pradaxa, Boehringer Ingelheim),

and direct factor Xa inhibitors including apixaban (Eliquis, Bristol-Myers Squibb), and rivaroxaban (Xarelto, Janssen), which have been approved for VTE treatment and/or thromboembolism prevention in adults, and are being studied in children. The potential advantage is that these newer drugs will require less monitoring than warfarin does, being less affected by diet and other medicines. However, it will be important to demonstrate that these agents are at least as safe and effective as the conventional alternatives in children, via clinical trials that in a number of instances have already been proposed or are ongoing. Because this is a new class of agents and we still need data about the benefits and risks, my personal opinion is that, in patients under 18 years of age (ie, the pediatric setting), these agents should be prescribed within the context of clinical trials whenever possible. We want to ensure vigilant patient monitoring for safety and efficacy, and acquire data on safety and efficacy as well.

**H&O** Have there been any other recent advances in treatment?

**NG** Some of the other advances include efforts to determine the optimal intensity and duration of treatment. We are also studying thrombolysis using catheters to break through or suck out a large and completely occlusive clot in a proximal limb or vena cava. The idea is to reduce the risk of post-thrombotic syndrome (PTS) by restoring blood return from the limb(s) more rapidly. In PTS, signs and/or symptoms of chronic venous insufficiency (eg, painful arm or leg swelling) develop following a DVT that occurred in the pathway of blood drainage back to the heart from a leg or arm. A trial is being planned to look at the effects of interventional thrombolysis in children with occlusive iliofemoral DVT. There is also an ongoing, large clinical trial designed to provide the first evidence for how long we should be treating children with provoked clots, and how long we should be using anticoagulants.

These studies—along with having some new anticoagulants available for study—mean that the care of these children is likely to improve significantly over the next several years.

**H&O** What are the causes of pediatric blood clots?

**NG** The causes fall into 3 categories, and this holds true for both children and adults. This system of categorization, known as the triad of Virchow, has been used for many years to think about how blood clots form. The first category is venous stasis (alterations in normal blood flow), the second is damage to the endothelium, and the third is hypercoagulability.

Venous stasis is generally caused by reduced mobility, such as from being confined to bed in the hospital, or having paralysis of a limb from an injury or stroke. A rare cause of poor blood flow is vascular abnormalities, such as the May-Thurner anomaly and Paget-Schroetter syndrome. In May-Thurner, there is a focal narrowing of the iliac vein on the left. In Paget-Schroetter syndrome, the anatomic space where a portion of the subclavian vein resides is congenitally narrow. In combination with hypertrophy of the subclavius muscle, such as can occur with competitive swimming, upper-body weight training, or pitching in baseball, the vein becomes "squeezed" and scars down to a narrow channel where a blood clot can more readily occur.

As for endothelial damage, a common cause is central venous catheters. Based on published cohorts and registries of children with blood clots, the presence of a central venous catheter is among the provoking factors for a blood clot in at least 30% (and often a majority) of cases. On the other hand, most children who have catheters do not develop blood clots, so clearly other factors are at work. That is an active question for research right now: What makes the children who develop clots different from those who do not? Other causes of endothelial damage include certain medications, toxins, and sepsis.

Regarding the third component of the causal triad, hypercoagulability can be genetic—so-called inherited thrombophilia—or can be acquired. Illness or medications, for example, can serve as acquired causes of a hypercoagulable state. Some children are predisposed to develop blood clots from a combination of these factors. For example, oral contraceptives with standard-dose estrogen can cause users to become resistant to the natural blood-thinning effects of protein C. If a user of oral contraceptives also has the factor V Leiden mutation, an inherited cause of resistance to activated protein C, the combination can greatly multiply the risk for a blood clot—there is a synergistic effect.

We do know that the risk for recurrent VTE is very different in a child whose blood clot occurred out of the blue vs a child who had a clear provoking factor. We use the term *provoked VTE* to refer to the latter case, such as when someone develops a blood clot during hospitalization, especially if a catheter is placed in a central vein. The risk of recurrence is lower in children with provoked VTE than in those with unprovoked blood clots—much as is the case in adults. As a result, people with an unprovoked blood clot require longer courses of treatment with anticoagulant medication.

**H&O** What are the risks when a blood clot does occur in a child?

**NG** There are a number of potential sequelae in children who experience VTE, most of which mirror what

occurs in adults. These include the risk of bleeding while on anticoagulant therapy and the risk of recurrent VTE, including PE. A third major issue of concern is PTS.

There is also a risk of death from blood clots, although fortunately this is not common in children. The mortality rate that is directly attributable to blood clots is approximately 2%.

**H&O** Could you talk more about these risks and how they relate to children?

**NG** We know that approximately 20% of children who receive a course of an anticoagulant for treatment of a blood clot will have bleeding. This is a high number, but it reflects both minor bleeds—a brief nosebleed or prolonged oozing from a small cut—and so-called major bleeds, which include bleeds that occur in the brain or other critical organ areas, and/or require hospitalization and possibly medication or surgical intervention to halt the bleeding. These represent 2 extremes of the spectrum of bleeding severity, and bleeds that may not be "major" can still be very important clinically in that they are brought to medical attention and are a cause for concern to the parents and care provider alike. We are always dealing with a balance between risk of bleeding and risk of new blood clot formation/embolism when we think about how long a child needs to be on an anticoagulant. The equation is different in children compared with adults, particularly given that children tend to be more active than most adults treated with anticoagulants. As most parents can attest, there is a big difference between a 60-year-old adult and a toddler or school-aged child in terms of developmentally appropriate types and levels of physical activity. So, it is usually very stressful to have a child on a blood thinner.

We use anticoagulants to reduce the risk of recurrent VTE (including PE) following a first VTE in a child. The risk of recurrent VTE after 1 year of follow-up is approximately 6% to 10% in children, which is a bit lower than in adults. Most of these children have been treated with a 3-month course of anticoagulants, and some have been treated for longer periods, such as 6 months.

We know that most of these recurrent blood clots occur after the children discontinue anticoagulants, although blood clots can occur while anticoagulants are being taken. As a result, it is very important to try to figure out who can safely stop taking an anticoagulant and who is at high risk of developing another clot after stopping the anticoagulant. Determining this through prognostic stratification, also called predictive modeling, is a major emphasis of research that is ongoing in pediatric VTE.

Another risk from blood clots, as mentioned earlier, is PTS. Approximately 25% of adult patients develop PTS; it has recently been clarified that the rate is roughly the same in children. This syndrome can range from mild to severe. In its mildest form, the person experiences no pain and skin changes are not noticeable, but swelling becomes apparent when we measure and compare the circumference of the limb where the DVT occurred with that of the opposite limb. In the most severe cases, the blood flow going back to the heart from an arm or a leg that had been affected by DVT is so poor that the limb can develop chronic swelling, skin breakdown, ulceration, and pain. We have a few different scales or scoring systems to evaluate PTS in children that are being used increasingly in recent clinical research studies.

We are currently studying what proportion of children has functionally significant PTS, which causes pain and prevents optimal activities. If we have a better understanding (through prognostic stratification) of who will go on to develop that kind of PTS, it can affect the way we look at treating children upfront.

**H&O** What are some of the factors you have not mentioned that make thrombosis different in children than in adults?

**NG** A key factor that differentiates children with VTE from their adult counterparts is that the average child is expected to have a much longer lifespan during which to endure any long-term sequelae (such as PTS) from VTE. As a result, we need to be especially sensitive to preventing and detecting PTS. At the same time, as noted earlier, the risk for bleeding in active children is a real concern, and affects the way we view the tradeoff between bleeding and recurrent VTE in kids vs adults when we are determining the optimal length of treatment with blood thinner medications. The risk of recurrent VTE in children with a first provoked VTE appears to be lower than in adults, so there is a real question as to whether the majority of children with VTE could be treated with anticoagulant medications for a shorter duration than their adult counterparts. This is an active area of clinical trial research in pediatric VTE.

An overall key distinction between children and adults with regard to VTE is that the standard of care in pediatrics is based on much weaker evidence than what exists for treating adults. This has occurred not only because thrombosis is less common in children than adults, but also because of the challenges of conducting research in children. As a result, we need to make greater efforts to narrow the gap in evidence on the best way to treat blood clots in children. That usually means developing the resources to do large national or international clinical trials that can answer key questions about optimal ways to treat blood clots.

**H&O** Under which circumstances should children be tested for thrombophilia?

**NG** This is a very important question, and a very difficult one. There has been a lot of debate within our international committees about what testing we should do in a child who has had a blood clot. One of the most prominent guidelines on treatment of blood clots in children, which comes from the American College of Chest Physicians, states that the results of thrombophilia testing in a child with a blood clot should not have any impact on treatment. This statement is based on the lack of firm evidence that the test result makes a difference in outcome.

Despite this, many practicing physicians who treat pediatric thrombosis, such as I, do test for certain abnormalities in children. When a blood clot occurs at a young age, we are more concerned about a potential genetic disorder than if the clot first occurs late in life.

When I do testing, I look for clinically significant deficiencies in protein C, protein S, and antithrombin, because those abnormalities appear to have the most significant impact on the risk of recurrence. If such deficiencies are present, we consider whether and how to adjust our treatment accordingly. For example, we may want to treat those children longer, or at least continue them on a lower dose of preventative anticoagulant. Another possibility would be to take a more aggressive approach in preventing blood clots in other ways, such as taking extra measures to ensure that such children are highly mobile, active, and well hydrated. We might even consider using preventative anticoagulation during short-term hospitalizations, or times when mobility might be reduced. None of these steps are supported by clinical trials, but many pediatric thrombosis physicians feel that taking this information into account (and having it available on a given patient) is important when talking to parents about future risk.

In other cases, thrombophilia testing is important because a child with an unprovoked or minimally provoked clot may have family members with the same condition. Early testing of family members potentially gives us the opportunity to prevent a PE. Although this type of testing is widely debated, I believe there are scenarios in which it makes sense to do selective testing.

**H&O** What is the prognosis for children who experience a blood clot?

**NG** The prognosis is quite good for the vast majority of children with provoked VTE who have neither a severe inherited thrombophilia nor an underlying abnormal venous anomaly causing stasis. The vast majority of such children will never develop a blood clot again as long as they received an adequate course of anticoagulant therapy. However, a small percentage of these children will develop life-threatening PE despite anticoagulation, and a small percentage will also suffer life-threatening bleeding complications associated with anticoagulation. In addition, approximately 1 in 4 children with DVT of the limbs (particularly those with completely occlusive proximal limb DVT at presentation, and especially those who additionally show biochemical evidence of systemic inflammation) will develop clinically significant PTS—for which there is little knowledge of effective treatments in children or adults.

**H&O** What research are you working on?

**NG** Much of my research effort is spent as overall principal investigator for the Kids-DOTT trial (Prospective Multicenter Evaluation of the Duration of Therapy for Thrombosis in Children; NCT00687882), a large randomized clinical trial that seeks to establish key evidence on duration of anticoagulation for provoked VTE in pediatrics. I am also very involved with the planning efforts for a catheter-directed randomized controlled trial on thrombolysis called the PHLO trial (under a National Heart, Lung, and Blood Institute U34 planning grant) that is aimed at reducing the risk of PTS in kids with occlusive iliofemoral DVT. In addition, I am on oversight committees for some of the pediatric and adult VTE treatment and prevention trials using the oral direct anticoagulants. Within Hopkins and with mentees at other institutions, my research focuses on prognostic models and markers for recurrent VTE and PTS in children and young adults, and on hospital-associated VTE risk models. We hope that in our future clinical trials, and from them, we will have an even more refined approach to knowing which children will benefit from which specific therapeutic approaches in a growing armamentarium against VTE.

## Suggested Readings

ClinicalTrials.gov. Evaluation of the duration of therapy for thrombosis in children (Kids-DOTT). http://www.clinicaltrials.gov/ct2/show/NCT00687882. Identifier: NCT00687882. Accessed July 28, 2014.

Goldenberg NA, Bernard TJ. Venous thromboembolism in children. *Pediatr Clin North Am*. 2008;55(2):305-322.

Goldenberg NA, Donadini M, Kahn SR, et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. *Haematologica*. 2010;95(11):1952-1959.

Kenet G, Lütkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010;121(16):1838-1847.

Monagle P, Chan AK, Goldenberg NA, et al; American College of Chest Physicians. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e737S-e801S.

Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001-1008.