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Slow progress. How do we shift the paradigm of thinking in pediatric thrombosis and anticoagulation?

Paul Monagle*

Department of Clinical Haematology, Royal Children's Hospital, Australia
Haematology Research Murdoch Children's Research Institute, Australia
Department of Paediatrics, University of Melbourne, Flemington Rd, Melbourne, Victoria, Australia

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ABSTRACT

Since Maureen Andrew began systematically describing thrombosis in children in 1994, there has been surprisingly slow process in advancing our knowledge in terms of diagnosis, prevention and treatment of thrombosis in children. There are a variety of reasons for this slow progress. Overwhelmingly the low incidence of thrombosis in children has been a major barrier. Second, the developmental, age related, changes in haemostasis mean that the physiology of haemostasis in children, and the interaction of the haemostatic system with anticoagulant drugs is constantly changing. This presents further challenges in identifying the risk benefit ratio of therapies. In addition, the failure to adequately understand the subtleties of pathogenesis of the variety of thrombotic syndromes, and the failure to know the natural history of many types of thrombosis are also significant problems. We continue to try and solve these problems by extrapolation, not just of adult based data, but of methodologies for research founded in the adult paradigm. If we are truly going to improve our understanding of thrombosis in children and improve our ability to prevent and adequately treat thrombosis in this population, then we need multiple paradigm shifts; First, in the way we think about thrombosis and anticoagulation in children. Second in the way we design and conduct research studies to provide evidence on which to base the care of children suffering from thrombosis in the future.

1. Introduction

In 1994, Maureen Andrew led a Canadian consortium that published the first major systematic description of venous thromboembolic disease (VTE) in children [1]. The paper heralded what would be known as the new epidemic of tertiary pediatrics [2]. Despite this, almost 25 years later, one could argue that we have made little progress. Certainly in terms of the levels of evidence for treatment guidelines, there has been little advance from the first American College of Chest Physicians (ACCP) guidelines for treatment of venous thromboembolism (VTE) in children published in 1995, progressing through to the most recent published in 2012 [3–8]. Across that time there have been limited numbers of randomised clinical trials of anticoagulants in children, both for primary prophylaxis and treatment, and yet none of these trials have substantially increased the level of evidence for any guideline (See Table 1) [9–14]. Of note, there are no completed RCTs of an anticoagulant treatment for VTE in children that have ever enrolled > 200 children, and almost all completed RCTs closed early due to slow recruitment [10]. The Kidsdott study comparing duration of anticoagulation in children is ongoing and has enrolled over 300 children, but has been running for over 10 years [14]. There are a number of current trials of Direct Oral Anticoagulants (DOACS), but these shall be specifically discussed subsequently.

So why has this been so difficult? There are a number of reasons, and one could argue that each reason requires a paradigm shift to be overcome.

2. Incidence of VTE

The incidence of VTE in children at a population level is very low, reported to be 0.07–0.14 per 10,000 children [1,15,16]. However, in hospitalised children the rate is increased 100–1000 times to at least 58 per 10,000 admissions [17]. Thus, despite some exceptions, VTE should be considered a disease of sick children. The commonest age groups for VTE are neonates and teenagers, and this reflects the pattern of associated underlying diseases and interventions. Greater than 90% of pediatric VTE have > 1 risk factor, with central venous access devices (CVADs) being the most common single risk factor, accounting for >

* Department of Paediatrics, University of Melbourne, Royal Children's Hospital, 50 Flemington Rd, Parkville, Melbourne 3052, Victoria, Australia.
E-mail address: paul.monagle@rch.org.au.

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Table 1
Randomised trials of anticoagulation in children for treatment of prevention of venous thrombosis.

Study title (therapeutic agents)	Study purpose	Centres involved	Total number children recruited/ target recruitment	Study outcome
REVIVE (Reviparin)	Primary prophylaxis CVL	36 centres over 2 years	78/352 patients (20%)	Closed early due to slow recruitment
Protekt (Reviparin)	VTE treatment	20 centres over < 2 years	186/600 patients (31%)	Closed early due to slow recruitment
Fontan (UFH/warfarin vs aspirin)	Primary prophylaxis post Fontan surgery	6 centres over 5 years	111/222 (50%) ? Power calculations NB 242 surgeries	Closed due to slow recruitment
PAARKA (antithrombin)	Primary prophylaxis in ALL CVAD and Asparaginase	10 centres over 2 years	109	Not powered for efficacy
KidsDott (LMWH/warfarin or fondaparinux)	6 vs 12 weeks treatment for secondary VTE in children	> 10 years. Up to 45 centres now	300 patients of target 850	

90% of neonatal and > 50% of pediatric VTE [1,18].

While CVADS are the commonest risk factor for VTE in neonates and children, the majority of pediatric patients who have a CVAD in situ do not have a thrombotic complication. A recent meta-analysis of pharmacological and non-pharmacological thromboprophylaxis for CVAD-related thrombosis in children reported that from 37 articles, the pooled frequency of thrombosis was 0.20 (95% CI 0.16 to 0.24). There was no evidence to suggest that thromboprophylaxis strategies reduced the risk of CVAD-related thrombosis [19]. However, there are clearly some pediatric populations at higher risk of CVAD-related-VTE than others. Estimates are that, if one considered a hospital wide based approach, only approximately 7% of children with a CVAD have any type of CVAD related complication, with the majority being infection. Only approximately 2% of children who had a CVAD placed as part of their medical or surgical care have a CVAD related thrombosis [20,21]. That rate might be even lower if one restricts the definition to those who have a clinical presentation of VTE, as distinct from those who have asymptomatic thrombus detected on routine imaging.

Thus, despite being “an epidemic of tertiary paediatrics”, VTE remains rare in children. The strong association of VTE events with multiple and complex underlying disease (cardiac surgery, cancer, neonatal and pediatric intensive care) makes studies even more difficult as significant variation in bleeding risk factors, vascular access, and concurrent medications is common.

In addition, pediatric VTE includes a wide range of VTE, with differing underlying pathophysiology, requiring different diagnostic imaging modalities, and with potential for differing acute and chronic complications, based on anatomic location. For example, neonatal renal vein thrombosis, the commonest spontaneous VTE in neonates has a specific pathophysiology, and specific acute and chronic complications, that are totally different to that of cerebral sinovenous thrombosis, which in turn are totally different to CVAD related VTE or pulmonary embolus. Even CVAD-related -VTE has different short and long term consequences depending on the presence or absence of right to left shunting in the child, and the underlying cardiac anatomy. Further, the risk benefit ratio of treatment, i.e. anticoagulation, also varies according to the site and type of VTE. The bleeding risk when treating a cerebral sinovenous thrombosis with cerebral infarction is likely very different to that of treating a CVAD related thrombus in a child immediately post cardiopulmonary bypass and cardiac surgery, which will be different again from a child with Cancer undergoing myeloablative chemotherapy with a CVAD related VTE.

Even within each VTE type, the pathophysiology and risk benefit ratio of therapy varies with age of the child. For example a cerebral sinovenous thrombosis in a neonate almost always has different triggering factors than the same thrombus in an older child. We assume that prematurity increases the intracerebral bleeding risk when using any anticoagulant irrespective of the site of the thrombus. CVAD related thrombosis will also be associated with different risks of bleeding depending on the underlying illness in the child. Obviously for post-surgical interventions, bleeding can occur at the surgical site, and in children with cancer, the bleeding risk can vary with the platelet count and the requirement for frequent bridging for invasive procedures such as lumbar punctures.

Thus, while VTE in neonates and children are often spoken about as a single entity, perhaps a better construct would be to consider each anatomical site of VTE in each different age group as an individual “rare disease” (which is born out by considering the numbers published related to each individual entity) that are merely linked by the use of common therapies in their treatment. This could be the first paradigm shift. Rather than designing treatment trials or even observational cohorts that encompass all types of VTE across all age groups and then try to amalgamate some kind of common outcome measures, we should truly adopt a rare disease mindset. We should establish registries with highly detailed comparisons of specific types of VTE in specific age groups. Treatment trials should consider the specific outcome measures of relevance to each of the specific entities. For example studies of renal vein thrombosis must include outcomes of renal function and hypertension. Studies of cerebral vein thrombosis must include neurological outcomes. Prophylaxis trials must carefully balance the risk of over treatment with anticoagulant prophylaxis against the benefits. Using concepts such as Numbers needed to treat (NNT) will focus pharmacological prophylaxis to true high baseline risk groups. If pediatric centres apply an adult based insurance type approach to thromboprophylaxis (hospital acquired thrombosis viewed as preventable complications that insurers will not pay for unless pharmaceutical thromboprophyalxis was in use), then the risk is that they may do more overall harm than good. We must adjust our strategies to the low baseline risk facing hospitalised children. This approach requires three major features. First, international collaboration that embraces a willingness to contribute data to multiple data sets covering the spectrum of venous disease. The newly established International Paediatric Thrombosis Network (IPTN) under the auspices of International Society of Thrombosis and Haemostasis (ISTH) pediatric subcommittee may be the appropriate model. Second, a common classification system and language such that any neonate, child or adolescent with a VTE is classified into the right subgroup for analysis. Similarly so that children at risk of VTE are classified appropriately, so true subgrouping of baseline risk can be established. This will require considerable collaborative work and potentially some arbitrary decisions. Finally, and especially in terms of prophylaxis studies, it will require regulators, insurers and health care authorities to accept that children are different and must be considered as such. No less important, but different, and requiring specific rational approaches that are different to those being used in adult populations. Exactly the same approach could be applied to arterial thrombosis in children.

3. Natural history of VTE

The natural history of VTE in children remains unclear in many

circumstances. The reported VTE mortality from registry data is approximately 3%, in the context of approximately 16% of children dying from their underlying illness [1]. The recurrence risk is variably reported up to 10–15%. Reports of post thrombotic syndrome (PTS) vary from 10 to 60% depending on the tools used to assess for PTS, and there remains great controversy as to the clinical implications of PTS in many children [22].

In particular the significance of asymptomatic CVAD associated VTE is unclear [23].The rates of transient VTE reported by two studies conducted by Rudd et al. are 22% (4 of 18) and 62.6% (10 of 16), all of which had resolved by the time of follow up imaging five to six months later. None of the patients identified in these two studies received treatment for their asymptomatic CVC-related thrombosis [24,25]. Other studies have traced the outcome of CVAD-associated-VTE but only with treatment [26].

If asymptomatic CVAD-associated-VTE were clinically important, it would make sense to routinely screen all patients for the presence of such VTE. However, this is not routine practice and indeed many guidelines actively recommend against this practice [8].

Given that routine screening is not practiced, and asymptomatic CVAD-related-VTE is much more common than symptomatic (most studies suggest asymptomatic rates of up to 20% depending on the subpopulation of children compared to approximately 5% symptomatic), then it stands to reason that many children have asymptomatic VTE that is never detected and they remain asymptomatic into the future without any complications. There are obviously case reports of children who present with long term complications after asymptomatic VTE, but these numbers are small.

Similarly for cerebral sinovenous thrombosis, pulmonary embolus especially subsegmental, unilateral renal vein thrombosis, there is little data to demonstrate the natural history and hence the need for acute or chronic therapy.

If we also accept that one of the drivers behind the ever increasing incidence of VTE in children is improved diagnosis due to improved quality of imaging (improved Doppler ultrasound technology, improved access to Magnetic resonance imaging facilities), then it also seems likely that previously many children did not have their VTE diagnosed and yet suffered no adverse effects.

So here is the second paradigm shift. We need to address the question of natural history of VTE in neonates, children and adolescents, as it may be different in each age group. The question of whether treatment is required to prevent either short or long term adverse events for the patient is fundamental to determining whether the risks of treatment are worthwhile. In many circumstances the adult data supports that asymptomatic VTE do not require treatment [23], and clinicians are right to argue that children might be different, especially given the increased frequency of right to left shunts and the spectre of paradoxical emboli. However, until formally studied, we cannot assume that all VTE visualised on imaging requires therapy, especially given the vagaries of imaging techniques that will be discussed subsequently. This requires a real shift from defensive- rather do something than nothing approach- to an evidence based – first do no harm approach. There is no doubt this is challenging, for a multitude of reasons, and will only be achieved with active inclusive dialogue with children and parents about the decision making involved.

Moreover, this will require uniformity of definition of outcome measures. Post Thrombotic syndrome (PTS) is considered an important outcome of VTE to be potentially mitigated. However there remains no uniformity in measurement or reporting of PTS in children [27–29]. Two tools are often referred to: the Manco Johnson Instrument (MJI) and the modified Villalta (MV) score. A study by Polen et al. (2015) reported differences in the diagnosed rates of PTS by the MV compared to the MJI, with the MJI identifying less cases of all PTS but more patients with clinically significant PTS [30].The differences in how the tools score PTS can be attributed to the value placed on subjective symptoms as opposed to the measure of objective signs. To understand natural history, we need uniform definitions of outcome measures. As discussed previously, these measures are likely going to have to be VTE site specific.

4. Diagnosis of VTE

If we make the first two paradigm shifts, that is we consider each type of VTE in each different age group as a separate rare disease that needs individual consideration in terms of pathogenesis, potential outcomes and treatments, and we agree that we need to understand the natural history of symptomatic and asymptomatic VTE in that context, then clearly accurate diagnosis and classification of VTE becomes paramount. This is another area that therefore requires a paradigm shift. The ongoing use of imaging techniques that are either unvalidated, or worse, have been shown to have unacceptable false positive or false negative rates in specific circumstances remains problematic. Often driven by pragmatics such as availability of vascular access or requirements for anaesthetic, inaccurate diagnosis remains a major challenge in children.

Diagnostic algorithms, and considerations of pretest probabilities have not been validated in children [31]. VTE is a radiological diagnosis and ancillary tests (e.g. the presence or absence of thrombophilia, elevated d-dimers) should never be used as part of the diagnostic strategy. Objective radiological studies must be used. There are numerous anecdotes of an apparent VTE being actually a mechanical obstruction or even an extravascular haematoma compressing the vessel.

Venogram is considered as the gold standard in the diagnosis of VTE [32–34]. This test is not operator dependent and has high specificity and sensitivity in predicting the incidence of thromboembolism as compared to other imaging techniques. However, difficult intravenous access, radiation exposure, lower glomerular filtration rate and inaccessibility to perform at bedside in sick children make this test impractical in most circumstances. Magnetic resonance venography (MRV) has recently been used for the diagnosis of VTE. It provides accurate non-invasive venographic imaging and highly sensitive for the detection of thrombus [35]. However, the usage is limited as it requires sedation and difficult to perform at bedside in sick children. Hence, ultrasound doppler (US) is the most widely and safely used modality. However, it's validity should be carefully considered. The low pulse pressure in premature newborns likely makes US more difficult to interpret. Similarly, the presence of CVADs makes compressibility difficult to assess, which greatly reduces the sensitivity of US. In the upper system, compressibility is not possible for veins below the clavicle and the PAARKA study demonstrated US to have a sensitivity of 20% for intrathoracic VTE; yet diagnosed jugular thrombi that were missed on venography [13]. Linograms (contrast injected through the CVAD) should never be used to diagnose suspected VTE, most of which occur at the insertion site of the CVAD rather than the CVAD tip [32].

The imaging of Pulmonary embolus in children is no less challenging. There are a number of potential difficulties with interpreting ventilation/perfusion (V/Q) scans in children at risk from PE have been identified. In children following specific cardiac surgeries such as Fontan surgery, total pulmonary blood flow is not assessed by isotope injected into an upper limb. Injection into both upper and lower venous systems is required, but even then the impact of intrapulmonary shunting may make interpretation difficult. In addition, there are concerns about the safety of perfusion scanning in children with significant right to left cardiac shunts, as likely significant amounts of macroaggregated albumin will lodge in the cerebral circulation, and the impact of this is unknown. Reducing doses of isotope may be important in such children. In theory, pulmonary angiography remains the gold standard, but most pediatric radiologists have little or no practical experience in performing this test. Computerised tomography (CT) pulmonary angiography is increasingly used but CT may miss small peripheral pulmonary emboli. Further, repeated CT angiogram may cause

significant radiation exposure to breast tissue in young female patients.

So, in terms of diagnosis, we need to bite the bullet, and perform rigorous studies that demonstrate the validity of differing diagnostic modalities, in different age groups of children with VTE at the various anatomic sites. We need to understand the operator dependence, and whether improvements in technology over the last decade have truly improved the utility of some methods. Such studies do not need to be randomised trials. Cohorts, and cross sectional studies may be more appropriate. If the studies are restricted to homogenous patient groups, then higher quality data will be achievable. Until we can accurately diagnose VTE in children, we run the risk of continued over or under treatment, which is bad enough at an individual level, but at a population level plays havoc with our desire to classify VTE properly and enable consideration of true natural history.

5. Treatment of VTE

There are currently no anticoagulant drugs approved for use in children, with very little specific research in children. Much of the evidence for treatment is extrapolated from adult practice, despite the major differences between adults and children in the epidemiology and pathophysiology of thrombosis, the physiology of the coagulation system and the impact of this on the pharmacology of antithrombotic agents [8].

Developmental haemostasis, a concept which was again pioneered by the work of Dr. Maureen Andrew [36–39], has a significant impact on the use and monitoring of current anticoagulants [40–54] and is likely to also have an impact on the use of DOACS in children as well [55].

This concept again supports developing a paradigm that classifies VTE in different age groups as different entities, because of the different interactions of the developing haemostatic system with anticoagulant agents, that would appear to impact on dosing, monitoring and the adverse event rates.

As mentioned previously, there are currently a multitude of industry sponsored phase III studies of Direct oral anticoagulants (DOACs) being performed at multiple centres around the world. These trials all extrapolate efficacy from adult data (Rivaroxaban NCT02234843; Apixaban NCT02464969; Dabigatran NCT02197416; Edoxaban- NCT02798471). This is for a variety of reasons. First, good efficacy estimates in children of standard of care anticoagulation versus either placebo, or even no treatment are unknown, as no such trials have been performed. Second, the heterogeneity of the pediatric population and the clinical entities involved makes estimation of baseline data from currently available observational studies extremely difficult. Third, a properly powered study would require likely several thousands of children which seems impossible due to the low incidence of VTE in childhood, and would be even less likely if we shifted to the paradigm of VTE being considered a series of separate rare diseases. To allow extrapolation of efficacy and safety data from adults, the studies are designed such that the plasma exposure/concentration in the children matches the plasma exposure/concentration of the drug achieved in the adult trails. This assumes that children require the same exposure for effective therapy. The studies assume that the clinical course (i.e. incidences of symptomatic recurrent VTE, major bleeding and mortality) of VTE is similar in children and adults, which seems unlikely to be true given the heterogeneity of the disease in children. Finally, the studies assume that the response to the therapy as compared to standard of care anticoagulation should be similar in children and adults. This method of designing trials in children which extrapolate efficacy based on these conditions is frequently supported by regulators such as the FDA [56]. While the DOAC studies will undoubtedly give us much useful information, (arguably more information than exists for the currently used anticoagulants), we must remember the assumptions on which they are based. Hence the final paradigm shift. We must understand the limitations for accumulating evidence under the current research paradigms and continually be asking how we can perform these studies differently to provide better child specific evidence. For example, one could argue that following appropriate dose finding studies, rather than the aforementioned underpowered RCTs, it would be more useful to construct multi centre long term cohort studies of DOACS, with broad based clinical, and neurodevelopmental outcome measures. Only such a paradigm shift will enable the early recognition of any potential off target effects of these new drugs, in addition to providing probably equally useful efficacy and bleeding safety data. This would require cooperation of industry and regulators alike. At the very least, we must understand the limitations of our current paradigm and accept uncertainty rather than be dogmatic about our current understanding, which will surely change with time.

Conflict of interest statement

I have no financial conflicts to declare. I am on steering committee of industry sponsored trials of Rivaroxaban and apixaban.

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