Blood Reviews (2004) 18, 75–84

ELSEVIER

www.elsevierhealth.com/journals/blre

Neonatal thrombosis and its treatment

A. Greenway[a], M.P. Massicotte[b], P. Monagle[a,*,1]

[a]Division of Laboratory Services, Royal Children's Hospital, Department of Paediatrics, University of Melbourne, Melbourne, Vic., Australia
[b]Department of Paediatrics, Stollery Children's Hospital, Edmonton, Alberta, Canada

KEYWORDS
Neonatal thromboembolism;
Arterial thrombosis;
Venous thrombosis;
Portal vein thrombosis;
Renal vein thrombosis;
Anticoagulation

Summary Thromboembolic disease (TE) has been described as the new epidemic of tertiary paediatrics, and no where is this more evident than in the neonatal population. As survival of premature and sick newborns has improved, the frequency of complications associated with intensive supportive therapy and monitoring has increased. Clinically significant thrombosis is emerging as one of the more common complications associated with improved neonatal outcome. The long-term implications of neonatal thrombosis are only just being realised. This systematic review will consider the epidemiology, diagnostic strategies, and outcome for both arterial and venous TE in neonates. The role of inherited thrombophilic abnormalities, and the evidence for anticoagulation therapy will also be considered. The lack of high level evidence in determining optimum therapy is obvious. Further research regarding diagnostic strategies, and optimal therapies is urgently needed.

Introduction

Neonatal thromboembolic disease (TE) is a unique entity, that must be considered differently to thrombosis in older children and adults. The epidemiology of neonatal TE is significantly different to the other age groups. The incidence of symptomatic neonatal TE (including central nervous system (CNS) disease) is reported to be 0.51 per 10,000 livebirths, with approximately half of the cases being venous TEs and half arterial. Almost 90% of TEs in neonates are associated with arterial or venous access devices. Additional risk factors include asphyxia, maternal diabetes, polycythaemia, sepsis, poor cardiac output, and dehydration. The majority of non-iatrogenic TEs are spontaneous renal vein thrombosis.

A potential reason for the vastly different epidemiology of TE in neonates is the thromboprotective nature of the haemostatic system in neonates. Compared to adults and children, neonates have altered concentrations of pro- and anticoagulant factors, and components of the fibrinolytic system. The result is an overall reduction in thrombin potential, along with altered fibrinolytic pathways. In addition to altering the likelihood of developing TE, these developmental changes in the haemostatic system impact on treatment of neonatal TE. The pharmacokinetics of the commonly used anticoagulants is significantly different in neonates. Despite this, most treatment guidelines continue to be extrapolated from the experience of childhood and adult regimes.

The following review will discuss the major aspects of TE in neonates including venous and

*Corresponding author. Tel.: +61-3-9345-5914; fax: +61-3-9349-1819.
E-mail address: paul.monagle@wch.org.au (P. Monagle).
[1] Associate Professor Paul Monagle is supported by a research fellowship from Murdoch Children's Research Institute.

0268-960X/$ - see front matter
doi:10.1016/S0268-960X(03)00042-0

arterial thrombosis associated with central lines, renal and portal vein thrombosis. Anticoagulation therapy in neonates will also be considered. Purpura fulminans and thrombosis of the CNS will not be discussed in this article. The reader is referred to a number of recent reviews.[1–3]

Venous thrombosis

Catheter related venous thromboembolic disease

An international registry of symptomatic venous TE in neonates reported an incidence of 0.24 per 10,000 admissions to neonatal intensive care units, almost all of which are secondary to central venous lines (CVLs).[4] The mechanisms by which CVLs cause TE include damage to vessel walls,[5] disrupted blood flow, infusion of substances such as total parenteral nutrition that damage endothelial cells,[6] and thrombogenic catheter materials.[7] The true frequency of CVL related TE is difficult to determine. Clinical studies estimate the incidence of umbilical vein catheter (UVC)-related TE to be approximately 13%,[8] while autopsy studies estimate that 20—65% of infants who die with an UVC in situ have evidence of TE.[8–11] The difficulty in determining the true incidence of venous TE is reflected in the dilemma of determining the optimal diagnostic strategy. No studies to date compare precision and accuracy of the commonly employed non-invasive techniques such as ultrasound, with invasive modalities such as venogram or magnetic resonance venography (MRV). Studies in older children suggest that ultrasound is poorly sensitive (20%) for upper system CVL-related venous TE compared to venography.[12] The low pulse pressure in premature newborns can make ultrasound more difficult to interpret. Similarly, the presence of CVLs makes compressibility difficult to assess, which greatly reduces the sensitivity of ultrasound. Where venogram may be considered the gold standard for diagnostic imaging of venous TE, inherent difficulties with this population, such as poor peripheral venous access, limitation to contrast dose due to lower neonatal glomerular filtration rate (GFR) in premature infants, and rapid dispersion time due to relatively increased cardiac output may limit the use of this modality in the neonatal population.

Venous TE may present acutely as swelling, pain, and discolouration of the related limb, swelling of the face and head with superior vena cava syndrome,[13] CVL dysfunction, and CVL-related sepsis. Clinically overt symptoms of right atrial thrombosis include cardiac failure, persistent sepsis, and appearance of a new cardiac murmur.

The frequency of life threatening complications such as stroke and pulmonary embolus[4,14] are unknown, and are likely to be underestimated due to the frequency of coexistent primary respiratory and CNS diseases in the neonatal population. Diagnostic confirmation of pulmonary embolism in particular is extremely difficult, due to the inability to perform ventilation/perfusion scans and the frequent radiological changes of underlying lung disease.

The risk of embolic stoke as a complication of venous TE is likely to be higher than that seen in the adult population due to persistence of neonatal circulation, with right to left intracardiac shunting.

The long-term clinical complications of venous TE include chronic venous obstruction with prominent cutaneous collateral circulation, chylothorax,[15,16] and chylopericardium[17] and hypertension. Recurrent venous TE may result in loss of venous access, with significant limitation to ongoing treatment. Anticoagulant and in particular thrombolytic therapy are associated with a risk of bleeding.[18]

Postthrombotic syndrome (PTS), a serious long-term outcome of venous TE, has been recently recognised in a number of children with a history of neonatal thrombosis.[19,20] Up to 20% of adults with

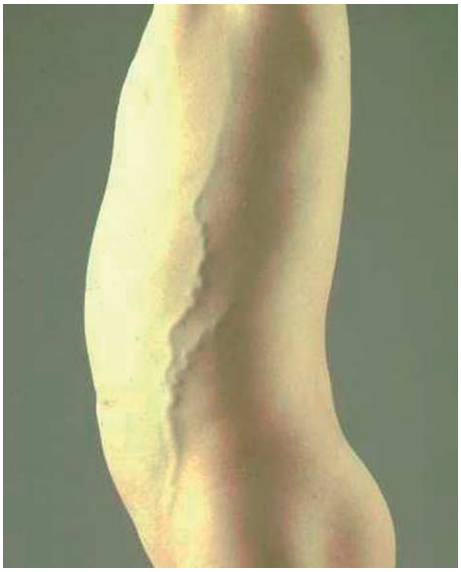

Figure 1 Extensive superficial venous collaterals in a 10 year old with complete inferior vena cava obstruction secondary to a central venous line during neonatal period. The boy had no clinical signs of thrombosis during neonatal period and collateral development commenced at 10 years of age associated with increased rate of height growth.

venous TE may develop symptoms of PTS, the onset of which can be delayed for up to 10 years post the thrombosis. Features of PTS include chromic edema, skin discolouration, poor wound healing/impaired tissue viability, pain and limitation of limb function. Neonates may potentially be at increased risk of this complication due to impaired fibrinolytic degradation of clot, where the fibrinolytic pathways are physiologically suppressed in this age group. Of particular concern are the increasing frequency with which children who had no documented clinical thrombotic episode during their neonatal care are presenting later in life with clinically significant chronic venous obstruction and PTS (see Fig. 1). Long-term surveillance studies of neonates with CVLs are required to determine the frequency and severity of PTS.

Renal vein thrombosis

Renal vein thrombosis (RVT) is the most common spontaneous (non-catheter related) TE in neonates, and accounts for approximately 10% of all venous TE. Increased risk of RVT is associated with primary neonatal disorders which result in hyperviscous, hyperosmolar, and hypercoagulable states in association with reduced renal blood flow.[21] These include sepsis, dehydration, acidosis, hypotension, congenital cardiac disease, hyperinsulinism, asphyxia, polycythaemia, and asphyxia.

Clinical findings include a palpable flank mass, haematuria, proteinuria, consumptive thrombocytopenia, and renal impairment. Bilateral RVT occurs in approximately 24% of cases. In unilateral RVT the right and left renal veins are equally affected.[21]

Current diagnostic modalities include ultrasound (most commonly used due to accessibility, adequate sensitivity to renal enlargement and minimal side effects),[22,23] magnetic resonance imaging (MRI) and computed tomography (CT).[24]

Clinical findings of edematous lower limbs with temperature variation and cyanosis may suggest thrombus propagation with inferior vena cava (IVC) occlusion. Extension into the IVC has been noted to be as frequent as to occur in 52% of cases in one retrospective analysis.[25] Ongoing venous obstruction results in dilatation of superficial collateral veins over the abdominal wall and lower limbs. Again, the paucity of long-term surveillance prevents estimation of the incidence of PTS following neonatal RVT. A recent small retrospective case series suggests the incidence of long-term complications is significant. Seventeen percent of patients were hypertensive at followup. Impairment of renal function as defined by abnormal residual function on nuclear medicine scan or renal atrophy on ultrasound was detected in 100% of patients who did not receive anticoagulation as compared to 33% in the treated group.[25] Despite these long-term sequelae, survival in the acute phase of RVT has improved significantly over recent years in association with medical management including observation, anticoagulation and thrombolysis, as opposed to previous surgical therapy such as nephrectomy/embolectomy.

Portal vein thrombosis

The incidence of neonatal portal vein thrombosis (PVT) is unknown, and may be under estimated as thrombosis at this site is often clinically silent. Risk of PVT related to the use of UVCs remains controversial as incidence has been reported to vary between 1% and 43% in recent prospective studies.[26] Portal vein thrombosis is also associated with umbilical sepsis/oomphalitis.

Diagnosis of PVT is usually made by ultrasound. Findings of cavernous transformation of the portal vein subacutely, followed by splenomegaly with reversal of portal flow are used similarly in neonates, as in adults to indicate significant PVT. Computed tomography and MRI are likely to provide similar information to ultrasound, with no additional clinical benefit associated with the increased anaesthetic risks of these procedures. Difficulty with diagnosis of PVT includes the apparent increased rate of detection (43%) with prospective ultrasound surveillance. The effect of smaller, non-occlusion thromboses detected with the umbilical catheter in situ on subsequent prognosis for portal hypertension is also unresolved. Several prospective studies suggest that spontaneous resolution of asymptomatic PVT is common.[26,27]

The most important clinical consequence of UVC associated PVT is portal hypertension,[28] which may not manifest until years later as splenomegaly without liver disease, reversal of portal vein flow and gastric/oesophageal varices,[29] if severe. Ascites is less common in this group. Major bleeding related to the varices[14,30] is a potentially life threatening outcome, however, tends to be less severe following PVT than that seen in the groups with intrahepatic/posthepatic portal hypertension, where coagulopathy often contributes to the haemorrhage risk. With time, increasing development of collateral venous drainage may lower

portal pressure, with subsequent reduction in frequency and severity of bleeding episodes.

Arterial thromboses

Arterial thromboses account for approximately half of all thrombotic events in neonates. Arterial TE arise almost exclusively as iatrogenic complications of in situ arterial devices such as umbilical artery catheters (UAC) and peripheral arterial catheters (PAC) (predominantly used for monitoring purposes), or femoral arterial catheters used during cardiac catheterisation. Spontaneous arterial thrombosis are usually aortic and usually catastrophic.[1,31]

Similar to venous TE, the reported incidence of UAC related TE varies greatly depending on the diagnostic test used. Studies using clinical signs UAC related TE rate of 1—3%,[32] while ultrasound based studies report an incidence between 14 to 35%. This increases further to 64% in studies based on angiographic findings.

Arterial site of PACs, along with variables such as catheter material, duration of placement, diameter, length, and solutions infused also impact on the reported incidence of arterial TE.[33–35] The potential for ischaemic damage is reduced at arterial insertion sites where dual blood supply exists, such as the radial/ulnar arteries or posterior tibial/dorsalis pedis, compared to single arteries such as the brachial artery. There is no definitive evidence that position of the UAC (high aortic placement versus low placement) effects the incidence of UAC related TE.

Clinical presentation of arterial TE varies also with anatomic site of intravascular catheter, extent of thrombosis, and potential for collateral arterial supply. A significant number of arterial TEs are asymptomatic or are indicated by minor features such as line dysfunction. Larger thrombosis, however, can present with catastrophic trunk and limb ischaemia necessitating urgent treatment. Specific complications related to UAC include necrotising enterocolitis due to mesenteric artery occlusion, renal failure with hypertension due to renal artery occlusion, and peripheral limb ischaemia due to embolic events.[36,37]

Angiography, the gold standard for diagnosis in adults and older children is rarely used in routine diagnosis due to the risk of further procedure related TE. Non-invasive techniques, such as doppler ultrasound are often employed to confirm clinical suspicion, however, these modalities have not been validated, and anecdotally may underdiagnose clinically significant arterial TE, particularly with complete vessel occlusion.[38]

Use of prophylactic unfractionated heparin (UFH) has been shown to prolong patency of PACs[39–41] and UACs.[31] However, the role of UFH in preventing obstructive arterial thrombosis remains questionable.[42,43] There are three studies that assessed the relationship between low dose UFH infusions and intracranial haemorrhage (ICH).[44–46] In the first study, a retrospective case control study, UFH was implicated as a risk factor for ICH in low birth weight newborns.[44] However, this study was retrospective, the 95% confidence interval around the odds ratio of 3.9 was large (1.4—11.0), and the magnitude of the risk uncertain.[44] In a second study, the association of UFH exposure with ICH among very low birth weight newborns was assessed in a clinical trial that was designed to assess UAC placement.[45] The authors reported that newborns with ICH received increased concentrations of UFH (83.5 units/kg/day) compared to those without ICH (59.4 units/kg/day).[45] An odds ratio of 1.96 with a 95% confidence interval of 1.32 and 2.91 was reported. A recent randomised controlled trial (RCT) trial of 113 newborns who received either 1 unit/ml UFH ($n = 55$) or no UFH ($n = 58$) in their infusate, reported that there was no difference in the incidence of ICH.[46] In the same study, the influence of UFH on the coagulation system was also assessed and no differences detected due to UFH.[46]

Treatment for acute arterial TE in neonates is difficult. The affected neonates are usually sick, often with concurrent coagulopathies or preexisting ICH. The removal of the arterial catheter is almost always required. The risk/benefit ratio for anticoagulation and thrombolytic therapy is unknown and must be assessed on a case by case basis. Embolectomy is technically difficult, and in general less successful due to re-occlusion in tiny vessels. Often the benefits of limb salvage must be weighed against the systemic risk of bleeding. Umbilical artery catheter related aortic thrombosis are often life threatening due to impaired renal function, and so there is little choice but to try thrombolytic therapy, which has been reported to have variable success.

The mortality related to arterial TE usually results from multiorgan ischaemic dysfunction.

Long-term morbidity in survivors may manifest as hypertension,[47,48] abnormal renal function,[37,47,49] discrepancies in leg length,[48,50] claudication,[51] and paraplegia.[52,53] Further surveillance is needed to determine the frequency of these complications and the impact of different treatment options on long-term outcome (see Fig. 2).

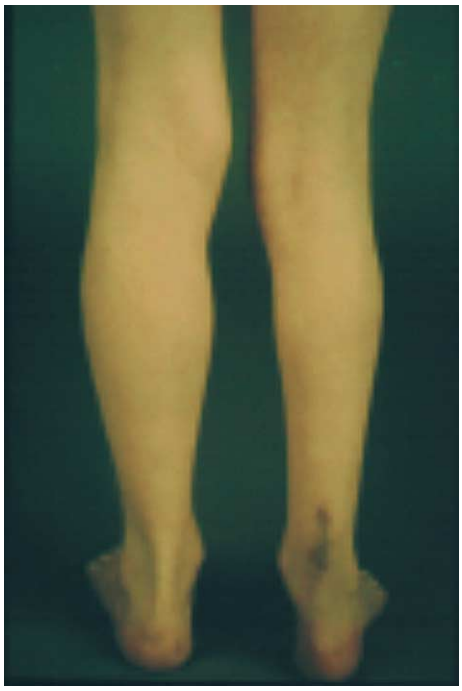

Figure 2 Chronic arterial insufficiency. Note the reduced muscle bulk in the affected right leg, which is associated with significant limb shortening. Scars reflect previous tendon releases. This child had a diagnostic cardiac catheter via the right femoral artery as a neonate.

Role of thrombophilic conditions

The role of screening for thrombophilic conditions in neonatal TE is controversial for a number of reasons. In the setting of catheter related thrombosis, screening for prothrombotic markers is unlikely to effect treatment decisions with respect to duration of therapy and future prophylaxis. This reflects the lack of data on the incidence of recurrent thromboses in neonates.

Lack of normative data regarding levels of anticoagulant proteins such as protein C, S, and antithrombin makes interpretation of baseline investigations in neonates difficult. Physiological levels are reduced compared to older children and adults.[54–56] Acquired deficiency states due to anticoagulant consumption at the time of acute thrombosis also limits the impact of these investigations on clinical treatment decisions. Other than for cases of homozygous or compound heterozygous protein C/S deficiency, which is likely to present with severe thromboses/purpura fulminans, there is currently insufficient evidence to justify thrombophilic screening of the neonatal population. The role of genetic markers such as PT20210A and factor (F)V Leiden mutation in TE is again not yet established in the neonatal group. The rare clinical scenario of neonatal TE in association with maternal systemic lupus erythematosus or antiphospholipid syndrome has been documented, however, case numbers are insufficient to establish the implications of screening. Currently clinical monitoring only of these infants would appear to be best practice.

Antithrombotic therapy

Antithrombotic therapy in newborns with TEs is difficult due to altered physiology and metabolism of anticoagulants, poor knowledge of bleeding risks associated with treatment,[57] and minimal information on long-term morbidity and outcome of untreated thromboses. Unfortunately, results from clinical trials in adults and older children cannot be simply extrapolated to newborns because the risk/benefit ratio with regards to efficacy and bleeding likely differs significantly. The decisions to use or to with hold antithrombotic therapy are both active decisions. The site of the TE, the presence or possibility of organ or limb impairment as well as the bleeding risk will influence the use and choice of antithrombotic agents.

The following section describes some specific aspects of anticoagulation therapy to be considered with respect to their use in neonates.[4,14,58]

Unfractionated heparin

The studies of UFH in newborns are limited but show that the clearance of UFH is faster than for older children due to a larger volume of distribution,[59] and that the dose of UFH required to achieve a therapeutic activated partial thromboplastin time (APTT) is also increased compared to older children.[57] Whether the target therapeutic APTT range used for children and adults is optimal for newborns remains unknown. Similarly the optimal duration of therapy with UFH in newborns is also unknown.

The clinically important side effects of UFH include major bleeding, heparin induced thrombocytopenia (HIT), and osteoporosis.[60] In one prospective study, 13% of neonates had significant bleeding (95% CI: 0—25%).[57] However, in this series, many patients had sub-therapeutic APTT values. Although HIT has been reported in newborns[61] the exact incidence, remains unclear. If anticoagulation is needed when HIT is diagnosed alternative agents include danaparoid or lepirudin, however, there is a marked paucity of data on the use of

these agents in neonates. Osteoporosis associated with UFH has been reported in older children, but there is no information for newborns. Other problematic issues with UFH include the need for venous access, and frequent venous or arterial monitoring.

Low molecular weight heparin

The studies of low molecular weight heparin (LMWH) in newborns are more extensive than for UFH and show that the clearance of LMWH is faster in newborns than for older children again due to a larger volume of distribution.[62] Doses of Enoxaparin (the most commonly used LMWH in newborns) and Reviparin required to achieve anti-FXa levels in the adult therapeutic range from 0.5 to 1.0 units/ml is increased compared to older children.[63–65] (See Table 1.) One limitation of these studies is that they are not entirely limited to newborns but include infants less than 3 month of age.

The potential advantages of LMWH compared to UFH include a more predictable pharmacokinetic profile, minimal monitoring, subcutaneous administration, and potentially less bleeding and osteopenia compared to UFH.

The risk of major bleeding is not precisely known in newborns, however, there are studies reporting the risk of bleeding in newborns as part of larger patient populations. One pilot study reported no bleeding documented in seven infants less than 2 months of age (0%, 95% CI: 0—47%).[64] In a larger series, 4 out of 37 infants had major bleeding (10.8%, 95% CI: 3—25.4%).[65] Location of bleeding complications included subcutaneous injection sites, and CNS bleeding into preexisting CNS abnormalities. Subcutaneous catheters should be used with caution in newborns with little subcutaneous tissue, due to the risk of local bleeding.

Oral anticoagulation

Warfarin is a vitamin K antagonist and functions as an anticoagulant by reducing the functional plasma concentration of vitamin K-dependent factors (FII, FVII, FIX, FX). The vitamin K-dependent factors are decreased physiologically in newborns to levels that are frequently achieved in adults receiving therapeutic amounts of warfarin with target international normalised ratios (INRs) of 2—3.

Warfarin is problematic in newborns for several other reasons. First, infant formula is supplemented with vitamin K to prevent haemorrhagic disease of the newborn, therefore formula fed newborns are relatively resistant to warfarin. In contrast, breast milk has low concentrations of vitamin K, making breast fed newborns very sensitive to warfarin.[66] The latter can be compensated for by feeding breast fed newborns 1—2 ounces of formulae each day. Second, warfarin is only available in tablet form. Although the tablets can be dissolved in water for administration to newborns, there is no stability data nor critical assessment of this practice. Third, warfarin requires frequent monitoring in newborns because of the rapidly changing physiological values of the vitamin K-dependent proteins, frequent changes in medications, and variations in oral intake. Poor venous access has previously been a major issue in the newborn population, however, increasing use of point of care capillary INR monitoring may alleviate some of these issues. Fourth, although there is substantial information on the use of warfarin in children over 3 months of age,[67] there is essentially no information on its use in newborns with the associated efficacy and safety information. Another potential complication with the prolonged use of vitamin K antagonist includes a negative impact of warfarin on bone density in growing children.[68] In summary, the use of oral vitamin K antagonist is problematic and should be avoided

Table 1 Therapeutic and prophylactic doses of reviparin—sodium and enoxaparin in pediatric patients[58]

	Dose	Interval
Reviparin—sodium		
Weight <5 kg	Therapeutic 150 U/kg/dose	12 h
	Prophylactic 50 U/kg/dose	12 h
Enoxaparin		
Age <2 months	Therapeutic 1.5 mg/kg/dose	12 h
	Prophylactic 0.75 mg/kg/dose	12 h

Abbreviations: kg, kilograms; U, units; mg, milligram.

when possible in the neonatal period. In the event of warfarin induced bleeding, vitamin K, with or without factor replacement can be used depending on the clinical situation.

Antiplatelet therapy

Platelet function is reduced in neonates relative to that of adults and older children due to reduced aggregation to usual agonists such as thrombin, adenosine diphosphate, epinephrine and thromboxane A2. To counter this increased levels of high molecular weight von Willebrand multimers, higher haematocrit, and increased red cell size may all contribute to shortened bleeding time in this group. Antiplatelet agents such as aspirin are traditionally used for primary prophylaxis of arterial shunts such as Blalock Taussig shunts. There is no good evidence to support the use of this agent in venous TE, or as prophylaxis for arterial catheters. The association of aspirin use (high dose) with Reye's syndrome, an almost universally fatal complication, has in the past made this a less popular agent in the management of TE, although Reye's syndrome has never been reported at antiplatelet aspirin doses (5 mg/kg/day). Clearly aspirin can only be used when oral intake is tolerated and administration of appropriate doses requires manipulation of adult preparations.

Thrombolytic therapy

Thrombolytic agents all act by converting plasminogen to plasmin which in turn cleaves fibrinogen and fibrin leading to the formation of fibrinogen/fibrin degradation products. Decreased concentrations of plasminogen at birth limit the in vitro thrombolytic effects of the three most commonly used thrombolytic agents, streptokinase (SK), urokinase (UK), and tissue plasminogen activator (TPA)[69] and may limit their efficacy in newborns. Supplementation of plasminogen (with fresh frozen plasma (FFP)) may be preferable to increasing the dose of thrombolytic agents in order to optimise thrombolysis.[69]

Tissue plasminogen activator is currently the agent of choice in neonates due to increased fibrin specificity and improved in vitro clot lysis in plasma from newborns compared to either UK or SK.

The incidence of bleeding secondary to thrombolytic agents, based upon red cell transfusions requirements, is 20% in the pediatric population.[70] In another review, Zenz et al.[71] reported that 1 of 83 term neonates (1.2%, 95% CI: 0.3—6.5%) and 11 of 86 premature neonates (13.8%, 95% CI: 6.6—21.7%) had ICH. However, premature neonates in an RCT were included in this review, and the incidence of ICH was the same for the control and treatment group at 15%. A retrospective analysis of 16 neonates treated with TPA reported one death from bleeding.[72] Based upon the reported literature, the bleeding risk associated with the use of thrombolytic agents in neonates remains unclear. Because of the potential for major bleeding, and the general lack of information, thrombolytic therapy should likely be reserved for newborns with life, organ, or limb threatening situations.[58] Prior to thrombolytic therapy, both an ultrasound of the brain to determine if there is a pre-existing haemorrhage, and coagulation screening tests to detect a concurrent coagulopathy are recommended.

New anticoagulants

Numerous new anticoagulants are being tested in adults but none have been tested in newborns. Of particular interest is a direct oral thrombin inhibitor (Melagatran) that appears to fulfil many of the above requirements.[73] Another area of ongoing research is improving the biocompatibility of vascular access devices.[74] No trial has demonstrated efficacy of anticoagulant bonded catheters in the neonatal population.[42] New catheter materials in the clinical and preclinical stage of development, such as hyulorinic acid coated catheters and antithrombin—heparin covalent complex coated catheters may prove to be useful in the future. The latter is of particular interest in newborns who have decreased levels of AT.

Conclusion

Neonates are the paediatric group most commonly affected by thromboembolic disease. Lack of well-designed clinical trials considering optimal diagnostic tools, best treatment (efficacy and safety) or longer term followup for outcome and morbidity continue to make clinical management of these patients difficult. Until improvements in current therapies can be developed in large scale cooperative clinical trials, we may expect to see increasing burden of disease due to the acute and long-term complications of TE as the survival of premature neonates continues to improve.

Practice points

- Almost 90% of neonatal Thrombosis are secondary to vascular access devices.
- A High Index of clinical suspicion is required to detect thrombosis in neonates with CVAD in situ.
- Angiography remains the gold standard diagnostic test for thrombosis in neonates.
- Bilateral renal vein thrombosis or unilateral thrombosis with extension into the IVC likely benefit from antithrombotic therapy.
- Thrombophilic workup rarely influences acute management of vascular access related thrombosis.
- The pharmacokinetics of antithrombotic agents is vastly different in neonates compared to adults, and age specific dosing protocols need to be used.

Research agenda

- Long-term outcome of thromboembolic disease in neonates.
- Validation of non-invasive diagnostic techniques.
- Safety and efficacy of thromboprophylaxis for central venous and arterial vascular access devices.

Acknowledgements

The authors thank Lu Ann Brooker for her assistance in editing the manuscript.

References

1. Andrew ME, Monagle P, deVeber G, Chan AK. Thromboembolic disease and antithrombotic therapy in newborns. *Hematology (Am Soc Hematol Educ Program)* 2001:358—74.
2. Andrew M, Monagle P, Brooker L. Stroke, thromboembolic complications during infancy and childhood. Hamilton, BC: Decker Inc; 2000. p. 201—30.
3. Andrew M, Monagle P, Brooker L. Congenital prothrombotic disorders: presentation during infancy and childhood, thromboembolic complications during infancy and childhood. Hamilton, BC: Decker Inc; 2000. p. 47—110.
4. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics* 1995;**96**:939—43.
5. Chidi CC, King DR, Bales Jr ET. An ultrastructural study of the intimal injury by an indwelling umbilical catheter. *J Pediatr Surg* 1983;**18**:109.
6. Wakefield A, Cohen Z, Rosenthal A, Craig M, Jeejeebhoy KN, Gotlieb A, Levy GA. Thrombogenicity of total parenteral nutrition solutions: II. Effect on induction of endothelial cell procoagulant activity. *Gastroenterology* 1989;**97**:1220—8.
7. Pottecher T, Forrler M, Picardat P, Krause D, Bellocq JP, Otteni JC. Thrombogenicity of central venous catheters: prospective study of polyethylene, silicone and polyurethane catheters with phlebography or post-mortem examination. *Eur J Anaesthesiol* 1984;**1**:361—5.
8. Tanke RB, van Megen R, Daniels O. Thrombus detection on central venous catheters in the neonatal intensive care unit. *Angiology* 1994;**45**:477—80.
9. Khilnani P, Goldstein B, Todres ID. Double lumen umbilical venous catheters in critically ill neonates: a randomized prospective study. *Crit Care Med* 1991;**19**:1348—51.
10. Roy M, Turner-Gomes S, Gill G. Incidence and diagnosis of neonatal thrombosis associated with umbilical venous catheters. *Thromb Haemostas* 1997;**78**:724 (abstr).
11. Schmidt B, Zipursky A. Thrombotic disease in newborn infants. *Clin Perinatol* 1984;**11**:461—88.
12. Mitchell L, Chait P, Ginsberg J, Hanna K, Andrew M. Comparison of venography with ultrasound for the detection of venous thrombosis in the upper body in children: results of the PARKAA study. *Blood* 1999;**94**(Suppl 1(pt 1 of 2)):588a (abstr).
13. Bertrand M, Presant CA, Klein L, Scott E. Iatrogenic superior vena cava syndrome. A new entity. *Cancer* 1984;**54**:376—8.
14. Nowak-Gottl U, Von Kries R, Gobel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal Ed* 1997;**76**:F163—7.
15. Le Coultre C, Oberhansli I, Mossaz A, Bugmann P, Faidutti B, Belli DC. Postoperative chylothorax in children: differences between vascular and traumatic origin. *J Pediatr Surg* 1991;**26**:519—23.
16. Kramer SS, Taylor GA, Garfinkel DJ, Simmons MA. Lethal chylothoraces due to superior vena caval thrombosis in infants. *AJR Am J Roentgenol* 1981;**137**:559—63.
17. Kurekci E, Kaye R, Koehler M. Chylothorax and chylopericardium: a complication of a central venous catheter. *J Pediatr* 1998;**132**:1064—6.
18. Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, Bernstein M, Brisson L, Cairney B, DeSai D. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian registry of VTE. *Blood* 1994;**83**:1251—7.
19. Marzinotto V, Choi M, Massicotte MP, Chan AKC. Post-thrombotic syndrome in children with previous deep vein thrombosis. *Thromb Haemostas* 2001;(Suppl):OC962 (abstr).
20. Barnes C, Newall F, Monagle P. Post-thrombotic syndrome. *Arch Dis Child* 2002;**86**:212—4.
21. Andrew M, Monagle P, Brooker L. Thromboembolic complications in specific organ sites and pediatric diseases, thromboembolic complications during infancy and childhood. Hamilton, BC: Decker Inc; 2000. p. 231—76.
22. Hibbert J, Howlett DC, Greenwood KL, MacDonald LM, Saunders AJ. The ultrasound appearances of neonatal renal vein thrombosis. *Br J Radiol* 1997;**70**:1191—4.
23. Cremin BJ, Davey H, Oleszczuk-Raszke K. Neonatal renal venous thrombosis: sequential ultrasonic appearances. *Clin Radiol* 1991;**44**:52—5.
24. Greene A, Cromie WJ, Goldman M. Computerized body tomography in neonatal renal vein thrombosis. *Urology* 1982;**20**:213—5.
25. Zigman A, Yazbeck S, Emil S, Nguyen L. Renal vein thrombosis: a 10-year review. *J Pediatr Surg* 2000; **35**:1540—2.
26. Kim JH, Lee YS, Kim SH, Lee SK, Lim MK, Kim HS. Does umbilical vein catheterization lead to portal venous thrombosis? Prospective US evaluation in 100 neonates. *Radiology* 2001;**219**:645—50.

27. Kooiman AM, Kootstra G, Zwierstra RP. Portal hypertension in children due to thrombosis of the portal vein. *Neth J Surg* 1982;**34**:97—103.
28. Obladen M, Ernst D, Feist D, Wille L. Portal hypertension in children following neonatal umbilical disorders. *J Perinat Med* 1975;**3**:101—4.
29. Vos LJ, Potocky V, Broker FH, Vries JD, Postma L, Edens E. Splenic vein thrombosis with oesophageal varices: a late complication of umbilical vein catheterization. *Ann Surg* 1974;**180**:152—6.
30. Monagle P, Adams M, Mahoney M, Ali K, Barnard D, Bernstein M, Brisson L, David M, Desai S, Scully MF, Halton J, Israels S, Jardine L, Leaker M, McCusker P, Silva M, Wu J, Anderson R, Andrew M, Massicotte MP. Outcome of pediatric thromboembolic disease: a report from the Canadian childhood thrombophilia registry. *Pediatr Res* 2000;**47**:763—6.
31. Andrew M, Monagle P, Brooker L. Arterial thromboembolic complications in pediatric patients, thromboembolic complications during infancy and childhood. Hamilton, BC: Decker Inc; 2000. p. 165—200.
32. Cohen RS, Ramachandran P, Kim EH, Glasscock GF. Retrospective analysis of risks associated with an umbilical artery catheter system for continuous monitoring of arterial oxygen tension. *J Perinatol* 1995;**15**:195—8.
33. Hoar PF, Wilson RM, Mangano DT, Avery GJ, Szarnicki RJ, Hill JD. Heparin bonding reduces thrombogenicity of pulmonary-artery catheters. *N Engl J Med* 1981;**305**: 993—5.
34. Downs JB, Chapman Jr RL, Hawkins Jr IF. Prolonged radial-artery catheterization. An evaluation of heparinized catheters and continuous irrigation. *Arch Surg* 1974;**108**: 671—3.
35. The AACN Thunder Project. By the American Association of Critical-Care Nurses: Evaluation of the effects of heparinized and nonheparinized flush solutions on the patency of arterial pressure monitoring lines. *Am J Crit Care* 1993;**2**:3—15.
36. Bryant BG. Drug, fluid, and blood products administered through the umbilical artery catheter: complication experiences from one NICU. *Neonatal Netw* 1990;**9**:26—7.
37. Glickstein JS, Rutkowski M, Schacht R, Friedman D. Renal blood flow velocity in neonates with and without umbilical artery catheters. *J Clin Ultrasound* 1994;**22**:543—50.
38. Vailas GN, Brouillette RT, Scott JP, Shkolnik A, Conway J, Wiringa K. Neonatal aortic thrombosis: recent experience. *J Pediatr* 1986;**109**:101—8.
39. Sellden H, Nilsson K, Larsson LE, Ekstrom-Jodal B. Radial arterial catheters in children and neonates: a prospective study. *Crit Care Med* 1987;**15**:1106—9.
40. Rais-Bahrami K, Karna P, Dolanski EA. Effect of fluids on life span of peripheral arterial lines. *Am J Perinatol* 1990;**7**:122—4.
41. Butt W, Shann F, McDonnell G, Hudson I. Effect of heparin concentration and infusion rate on the patency of arterial catheters. *Crit Care Med* 1987;**15**:230—2.
42. Jackson JC, Truog WE, Watchko JF, Mack LA, Cyr DR, van Belle G. Efficacy of thromboresistant umbilical artery catheters in reducing aortic thrombosis and related complications. *J Pediatr* 1987;**110**:102—5.
43. Horgan MJ, Bartoletti A, Polansky S, Peters JC, Manning TJ, Lamont BM. Effect of heparin infusates in umbilical arterial catheters on frequency of thrombotic complications. *J Pediatr* 1987;**111**:774—8.
44. Lesko SM, Mitchell AA, Epstein MF, Louik C, Giacoia GP, Shapiro S. Heparin use as a risk factor for intraventricular hemorrhage in low-birth-weight infants. *N Engl J Med* 1986;**314**:1156—60.
45. Malloy MH, Cutter GR. The association of heparin exposure with intraventricular hemorrhage among very low birth weight infants. *J Perinatol* 1995;**15**:185—91.
46. Chang GY, Lueder FL, DiMichele DM, Radkowski MA, McWilliams LJ, Jansen RD. Heparin and the risk of intraventricular hemorrhage in premature infants. *J Pediatr* 1997;**131**:362—6.
47. Caplan MS, Cohn RA, Langman CB, Conway JA, Shkolnik A, Brouillette RT. Favorable outcome of neonatal aortic thrombosis and renovascular hypertension. *J Pediatr* 1989;**115**:291—5.
48. Seibert JJ, Northington FJ, Miers JF, Taylor BJ. Aortic thrombosis after umbilical artery catheterization in neonates: prevalence of complications on long-term follow-up. *AJR Am J Roentgenol* 1991;**156**:567—9.
49. Payne RM, Martin TC, Bower RJ, Canter CE. Management and follow-up of arterial thrombosis in the neonatal period. *J Pediatr* 1989;**114**:853—8.
50. Boros SJ, Nystrom JF, Thompson TR, Reynolds JW, Williams HJ. Leg growth following umbilical artery catheter-associated thrombus formation: a 4-year follow-up. *J Pediatr* 1975;**87**:973—6.
51. Letts M, Blastorah B, al Azzam S. Neonatal gangrene of the extremities. *J Pediatr Orthop* 1997;**17**:397—401.
52. Munoz ME, Roche C, Escriba R, Martinez-Bermejo A, Pascual-Castroviejo I. Flaccid paraplegia as complication of umbilical artery catheterization. *Pediatr Neurol* 1993;**9**:401—3.
53. Krishnamoorthy KS, Fernandex RJ, Todres ID, De Long GR. Paraplegia associated with umbilical artery catheterization in the newborn. *Pediatrics* 1976;**58**:443—5.
54. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P. Development of the human coagulation system in the full-term infant. *Blood* 1987;**70**:165—72.
55. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Castle V, Powers P. Development of the human coagulation system in the healthy premature infant. *Blood* 1988;**72**:1651—7.
56. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. *Blood* 1992;**80**:1998—2005.
57. Andrew M, Marzinotto V, Massicotte P, Blanchette V, Ginsberg J, Brill-Edwards P, Burrows P, Benson L, Williams W, David M. Heparin therapy in pediatric patients: a prospective cohort study. *Pediatr Res* 1994;**35**:78—83.
58. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest* 2001;**119**:344S—70S.
59. McDonald MM, Jacobson LJ, Hay Jr WW, Hathaway WE. Heparin clearance in the newborn. *Pediatr Res* 1981;**15**:1015—8.
60. Warkentin TE. Heparin-induced thrombocytopenia and its treatment. *J Thromb Thrombolysis* 2000;**9**(Suppl 1): S29—35.
61. Spadone D. Heparin induced thrombocytopenia in the newborn. *J Vasc Surg* 1996;**15**:306—12.
62. Andrew M, Ofosu F, Brooker L, Buchanan MR. The comparison of the pharmacokinetics of a low molecular weight heparin in the newborn and adult pig. *Thromb Res* 1989;**56**:529—39.
63. Albisetti M, Andrew M. Low molecular weight heparin in children. *Eur J Pediatr* 2002;**161**(2):71—7.
64. Massicotte P, Adams M, Marzinotto V, Brooker LA, Andrew M. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr* 1996;**128**:313—8.

65. Dix D, Andrew M, Marzinotto V, Charpentier K, Bridge S, Monagle P, deVeber G, Leaker M, Chan AK, Massicotte MP. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000;**136**:439—45.
66. Andrew M, Monagle P, Brooker L. Oral anticoagulant therapy in pediatric patients, thromboembolic complications during infancy and childhood. Hamilton, BC: Decker Inc; 2000. p. 278—356.
67. Streif W, Andrew M, Marzinotto V, Massicotte P, Chan AK, Julian JA, Mitchell L. Analysis of warfarin therapy in pediatric patients: aA prospective cohort study of 319 patients. *Blood* 1999;**94**:3007—14.
68. Massicotte P, Julian J, Webber C, Charpentier K. Osteoporosis: a potential complication of long term warfarin therapy. *Thromb Haemostas* 1999;(Suppl):1333a (abstr).
69. Andrew M, Brooker L, Leaker M, Paes B, Weitz J. Fibrin clot lysis by thrombolytic agents is impaired in newborns due to a low plasminogen concentration. *Thromb Haemost* 1992;**68**:325—30.
70. Leaker M, Massicotte MP, Brooker LA, Andrew M. Thrombolytic therapy in pediatric patients: a comprehensive review of the literature. *Thromb Haemost* 1996;**76**:132—4.
71. Zenz W, Arlt F, Sodia S, Berghold A. Intracerebral hemorrhage during fibrinolytic therapy in children: a review of the literature of the last thirty years. *Semin Thromb Hemost* 1997;**23**:321—32.
72. Farnoux C, Camard O, Pinquier D, Hurtaud-Roux MF, Sebag G, Schlegel N, Beaufils F. Recombinant tissue-type plasminogen activator therapy of thrombosis in16 neonates. *J Pediatr* 1998;**133**:137—40.
73. Weitz JI, Hirsh J. New anticoagulant drugs. *Chest* 2001;**119**:95S—107S.
74. Barrington KJ. Umbilical artery catheters in the newborn: effects of catheter materials. *Cochrane Database Syst Rev* 2000:CD000949.