



eNeonatal Review

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In this issue... Volume 2, Number 6

Although thromboembolic disease in the neonate is relatively uncommon, its management remains a challenge. Over 80% of thrombotic events in neonates are associated with venous or arterial catheters(1), ensuring that this problem will continue to confront neonatologists. Despite the fact that indwelling catheters are a significant risk factor for thrombus formation, the majority of babies with lines do not have clots. What is different about the patients who ultimately develop clots? In this issue, we review several papers that find a high frequency of biochemical and genetic risk factors in those children who develop thrombus-both venous clots as well as arterial clots, such as ischemic stroke.

The development of guidelines for the management of thromboembolic disease in the neonate has been hampered by the lack of controlled trials of anticoagulation in infants. The most comprehensive discussion of recommendations for antithrombotic therapy in children and neonates is reported from the 7th American College of Chest Physicians Conference on Anticoagulation and Thrombolytic Therapy(2). As acknowledged in these guidelines, many of our anticoagulation treatment practices are extrapolated from large studies in adults, or based on uncontrolled studies in infants. Given the differences in the pharmacokinetics, coagulation system, and bleeding risks between neonates and adults, this is an imperfect approach. While the development of large randomized controlled trials of anticoagulants may present challenges in neonates, data on the safety, efficacy, and pharmacology are sorely needed. The papers reviewed in this issue begin to address these questions for low molecular weight heparin and thrombolytic therapy.

Commentary by:
Clifford M. Takemoto, MD

Reviews by:
John J. Strouse, MD

→ [COMMENTARY](#)
Our guest editor opinion

→ [RISK FACTORS FOR THROMBOSIS:
UMBILICAL ARTERIAL CATHETERS](#)

→ [RISK FACTORS FOR CEREBROVASCULAR
ACCIDENTS: THROMBOPHILIA 1](#)

→ [RISK FACTORS FOR CEREBROVASCULAR
ACCIDENTS: THROMBOPHILIA 2](#)

→ [RISK FACTORS FOR RENAL VEIN
THROMBOSIS \(RVT\): THROMBOPHILIA](#)

→ [TREATMENT MODALITIES:
ANTICOAGULATION WITH ENOXAPARIN 1](#)

→ [TREATMENT MODALITIES:
ANTICOAGULATION WITH ENOXAPARIN 2](#)

→ [TREATMENT MODALITIES: LOW-DOSE
THROMBOLYSIS](#)

Guest Editors of the Month

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Guest Faculty Disclosure

John J. Strouse, MD
Faculty Disclosure: No relationship with commercial supporters

Clifford M. Takemoto, MD
Faculty Disclosure: No relationship with commercial supporters

Unlabelled/Unapproved Uses

The following faculty members have disclosed that their presentation will reference unlabeled/unapproved use of drugs or products.

John J. Strouse, MD
Has indicated that the presentation includes information on uses of enoxaparin and tissue plasminogen activator that are not approved in children.

Clifford M. Takemoto, MD
Has indicated that the presentation includes information on uses of enoxaparin and tissue plasminogen activator that are not approved in children.

COMMENTARY

The hemostatic system of the infant differs from adults - a fact that significantly impacts the epidemiology, natural history, and treatment of thromboembolic disease in neonates. In addition, many anticoagulant and procoagulant proteins are at a physiologic nadir during the neonatal period, affecting thrombus risk and increasing the difficulty of managing the condition. Further, the volume of distribution in neonates, as well as their renal and liver function, also differs from that of adults, potentially affecting the clearance and metabolism of antithrombotic agents. These issues cannot be solely extrapolated from adult data, and require study specifically in infants.

Thromboembolic events are most commonly associated with indwelling vascular catheters in neonates, but the reported risk varies widely. The prospective study by Coleman reports a 3% incidence of thrombi associated with short-term umbilical artery catheter use(3). Despite this relatively low incidence, and although routine imaging for thrombi may not be warranted with short-term catheter use, practitioners should remain vigilant for signs and symptoms of thrombi.

The significant role of genetic and biochemical prothrombotic risk factors in the pathogenesis of thromboembolic disease is well established in adults and children, but has not been extensively examined in neonates. Renal vein thrombosis (RVT) is the most

common manifestation of venous thrombosis in neonates; in a report from the Childhood Thrombophilia Study Group in Germany(4), the majority of babies with RVT were found to have prothrombotic risk factors, including FV Leiden and Lipoprotein(a). Two other papers reviewed herein found a high incidence of prothrombotic risk factors in neonatal stroke: Mercuri and colleagues reported an association with high FVIII activity and FV Leiden mutations(5), while Hogeveen found that high homocysteine levels are associated with both ischemic and hemorrhagic stroke(6). Taken together, these studies show that prothrombotic risk factors are common in neonates with thromboembolic events.

Anticoagulation with unfractionated heparin (UFH) is challenging in neonates with limited vascular access, as it requires both a dedicated intravenous line and frequent laboratory monitoring with aPTTs. Low molecular weight heparin (LMWH), administered subcutaneously usually twice a day, has more predictable pharmacokinetics than UFH, and so requires less frequent monitoring. Thus, in the neonate with a thrombus in whom vascular access is limited and frequent blood draws are difficult, LMWH offers a potentially attractive alternative to an UFH drip.

Despite the potential advantages of LMWH over UFH, the safety, efficacy, and pharmacokinetics of LMWH in neonates should not be assumed from adult data. Two recent trials provide important new information: the study by Streif from the Hospital for Sick Children in Toronto (7), as well as in the study by Michaels(8), found that a) infants require higher doses of LMWH to achieve therapeutic levels of anticoagulation, and b) premature infants require even higher doses. The majority of neonates treated with LMWH in both investigations showed some resolution of thrombus, but the single-arm design of these trials did not permit conclusions about the safety and efficacy of LMWH compared to UFH or other therapies. In addition, while the experience with LMWH use in neonates continues to grow, it is important to be cognizant of potential disadvantages of this therapy. These include less effective reversal of the anticoagulant activity (with protamine) in the event of significant bleeding, and longer turnaround times for monitoring (anti-Xa levels) -- potentially resulting in a delay in achieving therapeutic levels of anticoagulation if dose adjustments are needed.

Data on the use of thrombolytic therapy in neonates is sparse. The inherent risk of intraventricular hemorrhage in premature infants imposes additional caution with this treatment. For these reasons, thrombolysis is usually reserved for treatment of life-threatening, organ-threatening, or limb-threatening clots. The retrospective experience from the Pediatric Coagulation Consortium suggests that low-dose thrombolysis can be both effective and safe in neonates(9). Given the paucity of data on thrombolysis in infants, these data are important and provide a rationale to further investigate the efficacy and safety of low-dose versus standard dose thrombolytic therapy.

The management of neonatal thromboembolic disease remains a challenge, and further studies are needed to determine appropriate therapies specific for this population. The papers reviewed in this issue build on our limited knowledge base, and provide a basis for developing more rigorous investigations into safer and more effective treatment of thromboembolic disease in neonates.

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RISK FACTORS FOR THROMBOSIS: UMBILICAL ARTERIAL CATHETERS

Coleman MM, Spear ML, Finkelstein M, et al. Short-term use of umbilical artery catheters may not be associated with increased risk for thrombosis. Pediatrics 2004;113(4):770-4.

Finding that the risk of thrombosis may be lower with short-term umbilical artery catheterization.

This prospective observational study enrolled 33 infants after umbilical artery catheter (UAC) placement for clinical indications. Only patients with severe congenital abnormalities were ineligible. The UACs were polyvinyl single-lumen 3.5 French Argyle catheters with end holes, were placed with the distal end between the second and fourth lumbar vertebrae, and were infused at 1 ml/hr with 0.2 normal saline with unfractionated heparin (1 unit/ml). Serial color flow and spectral analysis doppler ultrasound of the abdominal aorta and iliac arteries was performed within 24 hours of UAC placement and then again on day 3 and day 5 after catheter placement. At the same time as the doppler studies, complete blood counts and levels of fibrinogen 1.2 (F1.2) and thrombin-antithrombin (TAT) were measured in venous or arterial blood. (Both F1.2 and TAT measure in vivo thrombin generation and activation of coagulation).

Enrolled patients had a mean birth weight of 1133 g and mean gestational age of 27.4 weeks. Only 1 of 61 interpretable ultrasounds (31 within 24 hours, 20 on day 3, and 11 on day 5) demonstrated thrombus. This infant also had decreased aortic flow and died within 48 hours of birth. Levels of F1.2 and TAT did not vary over the 3 time points of the study, but the platelet count decreased from 210,000/ul to 160,000/ul ($p=0.08$). Birth weight and gestational age were not significantly correlated with F1.2 and TAT.

This study of neonates with UACs demonstrated a 3% prevalence of arterial thrombus. This is surprisingly low compared to the prevalence of 33% in a screening study after UAC removal and 60% in an autopsy study. The low prevalence of thrombosis may have been secondary to decreased detection by ultrasound compared to aortography, catheter location/material, or the duration of the study. There was one event in approximately 77 patient-days with an indwelling UAC. This would give a rate of 1.3 thrombi per 100 patient-days (assuming that the rate of thrombosis remained constant over time). While the levels of F1.2 and TAT did not increase after catheter placement, they remained significantly higher than the normal adult range. Note, however, that the significance of this finding is unclear because the levels were not measured in a comparable group of neonates without UACs.

Coleman MM, Spear ML, Finkelstein M, et al. Short-term use of umbilical artery catheters may not be associated with increased risk for thrombosis. Pediatrics

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RISK FACTORS FOR CEREBROVASCULAR ACCIDENTS: THROMBOPHILIA 1

Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 2001;107(6):1400-4.

Finding that prothrombotic conditions including the factor V Leiden mutation and elevated factor VIII are common in neonates with cerebral infarction.

This prospective study of neonatal cerebral infarction identified strokes in 23 infants after seizure in the first days of life and 1 infant imaged on Day 2 of life as normal control. All infants had Apgar scores ≥ 8 at 5 minutes and cord pH ≥ 7.2 . Magnetic resonance imaging from 1 to 4 weeks of age was assessed by a single observer without access to the hematological data. Lesions were classified by location and any associated hemorrhage. Laboratory assessment included a prothrombin, activated partial thromboplastin and thrombin time, platelet count, fibrinogen, von Willebrand factor antigen, factor VIII, protein C, protein S, antithrombin, and the factor V Leiden and Prothrombin G20210A mutations. Follow-up assessments (structured neurologic examination and Griffiths Mental Developmental Scales) occurred every 6 months for the first two years of life and then yearly. All children were followed until at least 24 months of age.

The majority of children (22 of 24) had cerebral infarction in the distribution of the middle cerebral artery; the remainder had border zone lesions. Eleven of 24 had evidence of hemorrhage as well. None of the children had significant thrombocytopenia or evidence of disseminated intravascular coagulation. However, 6 of 22 (27%) had abnormally elevated factor VIII and 5 of 23 (22%) were heterozygotes for the factor V Leiden mutation. Factor VIII remained elevated in 4 of 5 infants retested after 2 months to 3 years. Antithrombin, protein C, and protein S were normal in all infants and the prothrombin gene mutation G20210A was not identified. The extent and site of the lesions were not associated with prothrombotic risk factors. However, there was a strong relationship between adverse outcome (hemiplegia or developmental delay at 2 years) and prothrombotic risk factors, in that eight of 11 children with adverse outcome had a prothrombotic risk factor versus 2 of 13 with normal outcome. All 5 children heterozygous for factor V Leiden developed a hemiplegia compared to 4 of 18 children without the mutation ($p=0.003$). Hemorrhage was also more prevalent in neonates with factor V Leiden (5 of 5) and associated with adverse outcome in 8 of 11 neonates.

The results of this study support a relationship between two common prothrombotic risk factors: the factor V Leiden mutation and elevated factor VIII, and neonatal cerebral infarction. While factor VIII may be elevated after cerebral infarction as an acute phase reactant, there was persistent elevation in 80% of the neonates with baseline elevated factor VIII. In addition, the authors suggest an association between factor V Leiden, intracranial hemorrhage, and adverse neurological outcomes. Note, however, that possible mechanisms for the hemorrhage or adverse outcomes were not addressed in this investigation.

Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 2001;107(6):1400-4.

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RISK FACTORS FOR CEREBROVASCULAR ACCIDENTS: THROMBOPHILIA 2

Hogeveen M, Blom HJ, Van Amerongen M, et al. Hyperhomocysteinemia as risk factor for ischemic and hemorrhagic stroke in newborn infants. J Pediatr 2002;141(3):429-31.

Finding that hyperhomocysteinemia may be associated with ischemic and hemorrhagic stroke in neonates.

This retrospective case-control study identified all infants born between 1993 and 2000 with a gestational age >34 weeks and a cerebrovascular lesion in the neonatal period from a single institution. Only infants with severe organ failure or midline closure defects were excluded. All data (demographics, imaging and laboratory results) were collected from hospital records. Total homocysteine values from these cases were compared with those obtained prospectively from controls (a group of healthy neonates delivered at or near term in the same hospital in 2000). The authors defined hyperhomocysteinemia as values greater than the 80th percentile of normal infants. No criteria were provided for the classification of ischemic versus hemorrhagic events.

The study included 24 neonates with strokes (11 ischemic and 13 hemorrhagic) and 94 controls. The mean weight was similar between the group with stroke (3229 ± 488 g) and without (3143 ± 695 g) stroke, but the gestational age of patients with stroke was significantly greater than that of controls (39.3 ± 1.9 vs. 37.5 ± 3.0 weeks). Stroke was diagnosed at a median age of 8 days. The homocysteine levels were collected later in children with stroke (median 10 days) compared to the controls (median 4 days, p -value < 0.001). All patients with stroke had normal values for platelet count, partial thromboplastin and prothrombin time, protein S, protein C, and antithrombin. Homocysteine levels were significantly higher in the stroke group (geometric mean 9.3; 95% CI 9.1 - 9.6 $\mu\text{mol/L}$) than the control group (geometric mean 7.4; 95% CI 7.1 - 7.7, $p < 0.001$). Homocysteine levels were similar between the groups with ischemic (8.6; 95% CI 6.8 - 10.4) and hemorrhagic stroke (9.9; 95% CI 9.1 - 10.7). Fifty percent of the stroke group and 20% of the control group had hyperhomocysteinemia. Hyperhomocysteinemia was associated with a 3.95 (95% CI 1.5-10.2) odds ratio of neonatal stroke.

The results of this study suggest that elevated levels of homocysteine are associated with both ischemic and hemorrhagic stroke in neonates. While elevated levels of homocysteine are associated with ischemic stroke and atherosclerosis in adults, this relationship between homocysteine and hemorrhagic stroke is unique to neonates in this study. The hemorrhagic strokes may be secondary to hemorrhagic conversion of in utero ischemic strokes.

In addition, there are several possible confounders that may obscure the true relationship between homocysteine and stroke. The infants with neonatal stroke were older and had blood samples collected for homocysteine significantly later after birth than the controls. Further, 18 of the 24 children with strokes were receiving anticonvulsants at the time the blood was collected. The authors had only limited power to detect and therefore did not identify a relationship between homocysteine levels and post-conceptional age, chronological age at the time of collection, or anticonvulsant use. In addition, other potential confounders including maternal homocysteine levels and renal function in the infants were not evaluated. These issues and other criteria for causality need to be addressed before elevated homocysteinemia can be validated as a risk factor for neonatal stroke.

Hogeveen M, Blom HJ, Van Amerongen M, et al. Hyperhomocysteinemia as risk factor for ischemic and hemorrhagic stroke in newborn infants. J Pediatr 2002;141(3):429-31.

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RISK FACTORS FOR RENAL VEIN THROMBOSIS (RVT): THROMBOPHILIA

Kosch A, Kuwertz-Broking E, Heller C, et al. Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up. Blood 2004;104(5):1356-60.

Finding that prothrombotic risk factors are frequent in infants with idiopathic renal vein thrombosis

This case-control study included 59 white neonates with RVT (cases) and 118 healthy neonates (controls) consecutively recruited between January 1996 and June 2003 from multiple centers in Germany. Inclusion criteria for cases were a RVT objectively confirmed by standard imaging methods and age <28 days. Only patients without parental consent were excluded. Controls were healthy neonates presenting for evaluation before minor surgery (circumcision or hernia repair) or bone marrow donation. Information was collected on underlying clinical conditions including infections, vascular trauma, surgery, macrosomia, jugular or central lines, solid tumors, autoimmune or renal disease, metabolic disorders, birth asphyxia, cardiac malformations, and administrations of steroids, sympathomimetics, or coagulation factor concentrates. RVT was considered idiopathic in neonates without underlying clinical conditions. All cases and controls were tested for the factor V Leiden and prothrombin G20210A mutations, activated protein C resistance, and the concentration of lipoprotein(a), protein C, protein S, antithrombin, total fasting homocysteine, and anticardiolipin antibodies. The testing was repeated at a central reference laboratory 3 to 6 months after the initial event.

The 59 cases included 24 females and 35 males with 45 term and 14 premature neonates (median gestational age 31 weeks). Seven of the parents (5.9%) had symptomatic venous thrombosis before 35 years of age. Findings at presentation included hematuria and thrombocytopenia in 29 (49.1%), anuria in 16 (27.1%), palpable abdominal mass in 9 (15.3%), and adrenal hemorrhage in 5 (8.5%). The RVT was limited to the left side in 23 (38.9%), right side in 20 (33.9%), and bilateral in 16 (27.2%). The thrombus extended to the inferior vena cava in 15 of the neonates with bilateral RVT. RVT was idiopathic in 27 children (47.8%) and associated with sepsis in 10, central lines in 9, birth asphyxia in 7, maternal use of betamethasone in 4, and diabetic fetopathy in 2. At least one established prothrombotic risk factors was identified in 40 (67.8%) of the 59 cases compared to 14 (11.9%) of the controls (odd ratio (OR) 15.6; 95% CI, 4.2-29.5). Cases had significantly higher prevalence (37.3%) of the factor V Leiden mutation (OR 11.1; 95% CI 4.2-29.5) and elevated lipoprotein(a) (28.8%; OR 9.2; 95% CI 3.2-26.4). Also protein C deficiency (5.0%), antithrombin deficiency (5.0%), and anticardiolipin antibodies (5.0%) were significantly more common (p=0.04 for each comparison) in cases than controls (0%). The 27 children with "idiopathic" RVT were even more likely (22 or 81.5%) to have a prothrombotic risk factor. Long-term follow-up by ultrasound showed significant morbidity from RVT. Fifty-three (89.8%) develop renal atrophy, unilateral in 42 cases and bilateral in 11. Thirteen patients developed severe arterial hypertension, 3 patients received renal transplants, and one had a nephrectomy at age 2 for difficult to control hypertension.

This rigorous prospective case control study clearly demonstrated the greatly increased prevalence of prothrombotic conditions in children with RVT. The authors identified factor V Leiden and elevated lipoprotein(a) as common risk factors in children with RVT. Protein C and antithrombin deficiency and anticardiolipin antibodies were also associated with RVT, but were much less common (5% of the cases). However, other predisposing conditions especially sepsis, central lines, and birth asphyxia were also found to be strongly associated with RVT.

Kosch A, Kuwertz-Broking E, Heller C, et al. Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up. *Blood* 2004;104(5):1356-60.

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TREATMENT MODALITIES: ANTICOAGULATION WITH ENOXAPARIN 1

Streif W, Goebel G, Chan AK, et al. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003;88(5):F365-70.

Finding that neonates require higher doses (in mg/kg) of enoxaparin than older children to achieve similar levels of anticoagulation

The pediatric thromboembolism program at the Hospital for Sick Children (Toronto) prospectively enrolled 62 consecutive infants (age <2 months) receiving enoxaparin for primary prophylaxis (8) or treatment of thromboembolism (54). They prospectively collected information on baseline characteristics, risk factors for thrombosis, enoxaparin dose, anti-factor Xa levels, bleeding, and thromboembolism. Bleeding was classified as major (clinically overt bleeding associated with >2 g/dl drop in hemoglobin in < 24 hours, transfusion of red blood cells, or any central nervous system or retroperitoneal bleed) or minor (all other bleeding events). A standardized nonogram was followed for dose adjustments to achieve a target anti-factor Xa level of 0.1 - 0.3 units/ml for prophylaxis and 0.5 - 1 units/ml for treatment.

The cohort included 54 infants with documented thromboembolism of the lower venous system (25), upper venous system (11), aorta and other major arteries (9), central nervous system (4), heart (3), small arteries (1), and Blalock-Taussing shunt (1). Congenital heart disease was the major underlying disorder in 46 (74%) of the infants. The thrombosis was catheter-associated in 37 of 54 infants (69%). Fifteen of the infants were premature (mean gestational age = 33.5 weeks); this group required significantly higher doses of enoxaparin (1.9 ± 0.6 mg/kg/dose) than the 47 full term infants (1.5 ± 0.3 mg/kg/dose) to achieve an anti-factor Xa level in the target range. The average time to achieve a therapeutic level was 6 days for the premature infants versus 2 days for the full term infants. Serious bleeding occurred in 4 infants (2 from the enoxaparin administration site and 2 with intracranial hemorrhage) and minor bleeding in 4 infants for an incidence rate of 1.2 events per patient-year of treatment for both. Additional thrombotic events occurred in 3 infants, with one infant dying from obstruction of a modified Blalock-Taussing shunt. Complete (15) or partial (17) resolution of the thrombus was achieved in 32 (59%) of the infants.

This study provides prospective data on the safety and efficacy of enoxaparin in infants. By the use of a standardized nonogram, the authors rapidly achieved anti-factor Xa levels known to be therapeutic in adults with thromboembolism. It supports the use of higher doses of enoxaparin in premature infants. Unfortunately, the single-arm design of this study does not permit the comparison of enoxaparin to other interventions for thromboembolism including unfractionated heparin, thrombolysis, or observation.

Streif W, Goebel G, Chan AK, et al. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. Arch Dis Child Fetal Neonatal Ed 2003;88(5):F365-70.

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TREATMENT MODALITIES: ANTICOAGULATION WITH ENOXAPARIN 2

Michaels L, Gurian M, Hegyi T, et al. Low Molecular Weight Heparin in the Treatment of Venous and Arterial Thromboses in the Premature Infant. Pediatrics 2004;114(3):703-7.

Finding that neonates require higher doses (in mg/kg) of enoxaparin than older children to achieve similar levels of anticoagulation

This retrospective study included 10 premature infants treated at a single institution over a 6 year period. Infants receiving enoxaparin were identified from pharmacy records; only premature infants with documented thrombosis were included in the series. The primary outcome measures were the dose of enoxaparin necessary to achieve therapeutic levels, anti-factor Xa levels, bleeding complications, response of initial thrombosis, additional thromboembolic events, and death from all causes. Therapeutic levels of anti-factor Xa were defined as 0.1 to 0.4 units/ml for prophylaxis and 0.5 to 1.0 units/ml for treatment.

The 10 premature infants had a mean estimated gestation age of 26 weeks (range 24 to 34 weeks) and all had a central venous or arterial catheter at or shortly before the diagnosis of thrombosis. The infants had atrial (4), superior vena caval (3) aortic (2), or innominate vein and pulmonary artery (1) thrombus. Nine infants were thrombocytopenic at diagnosis; 8 of the 9 received platelet transfusions to maintain the platelet count >50,000/ul during treatment. Five infants had intracranial hemorrhage (3 intraventricular, 1 retinal, and 1 subependymal) at diagnosis. Eight of the 10 infants had resolution of the thrombus after 15 to 126 days. Two infants had extension of the original thrombus; both died from complications of thrombosis. Bleeding complications, limited to 3 patients, included oozing at an operative site (enoxaparin was held for 36 hours), mild epistaxis, and a small subependymal hemorrhage. Of the 9 infants with anti-factor Xa levels, only 5 achieved therapeutic treatment levels at any time. The mean dose required to achieve an anti-factor Xa level of >0.5 units/ml was 2.27 mg/kg (range 2 - 3.5).

The results of this retrospective series show that higher doses of enoxaparin are needed in premature infants to achieve the levels of anti-factor Xa activity that are therapeutic in adults. However, the therapeutic range in infants is unknown and will require a multicenter trial to determine. This small study and the larger Strief study (see above) suggest that higher starting doses are necessary in full term and especially premature neonates.

Michaels L, Gurian M, Hegyi T, et al. Low Molecular Weight Heparin in the Treatment of Venous and Arterial Thromboses in the Premature Infant. Pediatrics 2004;114(3):703-7.

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[↑ back to top](#)

TREATMENT MODALITIES: LOW-DOSE THROMBOLYSIS

Wang M, Hays T, Balasa V, et al. Low-dose tissue plasminogen activator thrombolysis in children. J Pediatr Hematol Oncol 2003;25(5):379-86.

Finding that low-dose thrombolysis with tissue plasminogen activator is effective for pediatric arterial and venous thromboembolism.

This retrospective study from the Pediatric Coagulation Consortium described 35 children with thrombosis treated with low-dose or standard dose tissue plasminogen activator (TPA). All patients had imaging to document the extent and site of thrombus and complete information on dose, duration, complications, and outcome. Exclusion criteria for thrombolysis were: major surgery or central nervous system bleeding within 10 days, birth asphyxia within 7 days, an invasive procedure within 72 hours, seizures within 48 hours, platelet count <50,000/ul, or fibrinogen of <100 mg/dl. TPA dose, route (systemic or by selective catheterization) and the concurrent use of heparin were at the discretion of the treating physician. Outcome measures included major bleeding (intracranial, retroperitoneal, leading directly to death, drop of hgb >2 g/dl, or requiring transfusion), minor bleeding, clot lysis (complete >95%, partial 50-95%), and post-thrombotic syndrome.

Four neonates received standard dose TPA infusions (0.1-0.5 mg/kg/hr) for 3 to 16 hours for acute femoral artery (2), renal and hepatic arteries (1), or pulmonary artery thrombosis (1). All had complete resolution of the thrombosis without bleeding complications. Four preterm neonates received low-dose infusions of TPA (0.03 - 0.06 mg/kg/hour) for 12 to 60 hours for left atrium (2), left pulmonary artery (1), and aorta and bilateral iliac artery thrombosis. Two required increased doses of 0.1 mg/kg/hr and 0.24 mg/kg/hr to achieve complete clot lysis. One infant, a 28 week estimated gestational age girl with endocarditis receiving 0.24 mg/kg/hr, developed a subdural hematoma, a life-threatening hemorrhage that required surgical drainage.

The results of this study support the efficacy of thrombolysis with low-dose TPA in neonates, but are insufficient to compare the safety or efficacy to standard dose TPA. Although only one of the 8 infants had a bleeding complication, it was life threatening. This negative event highlights the potential risks of thrombolysis in sick premature infants, and for this reason, thrombolysis should be reserved only for limb or life-threatening thrombosis.

Wang M, Hays T, Balasa V, et al. Low-dose tissue plasminogen activator thrombolysis in children. J Pediatr Hematol Oncol 2003;25(5):379-86.

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Accreditation [back to top](#)

Physicians

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Nurses

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Respiratory Therapists

Contact your state licensing board to confirm that AMA PRA category 1 credits are accepted toward fulfillment of RT requirements.

Target Audience [back to top](#)

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Learning Objectives [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Identify common acquired and inherited risk factors for neonatal thrombosis;
- Understand dosing of low molecular heparin in premature and full term infants;
- Understand the sequelae of renal vein thrombosis and stroke in the neonate.

Faculty Disclosure Policy Affecting CE Activities [back to top](#)

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

Unlabelled/Unapproved Uses [back to top](#)

The following faculty members have disclosed that their presentation will reference unlabeled/unapproved use of drugs or products.

John J. Strouse, MD

Has indicated that the presentation includes information on uses of enoxaparin and tissue plasminogen activator that are not approved in children.

Clifford M. Takemoto, MD

Has indicated that the presentation includes information on uses of enoxaparin and tissue plasminogen activator that are not approved in children.

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