Thromboembolic Disease and Antithrombotic Therapy in Newborns

Maureen E. Andrew,* Paul Monagle, Gabrielle deVeber, and Anthony K.C. Chan

This update uses an evidence based approach to analyze and present the epidemiology of neonatal thrombosis, etiologies, currently used techniques for diagnosis with their limitations, and current therapeutic approaches. In addition, the approaches to both prevention and optimal therapies are discussed.

In Section I Dr. Paul Monagle addresses the epidemiology of neonatal thrombosis outside of the central nervous system in both arterial and venous locations, and those that occur in utero. The specific contributions of catheters and congenital prothrombotic disorders are delineated. Dr. Monagle also describes currently used techniques for the diagnosis of thrombotic events as well as their limitations and the current therapeutic approaches.

I. SYSTEMIC THROMBOEMBOLIC DISEASE IN NEWBORNS

Paul Monagle, MBBS, MSc, FRACP, FRCPA**

Systemic Venous Thromboembolic Disease

1. Incidence

Estimates of the incidence of symptomatic venous TE (VTE) support the generally accepted view that the frequency in newborns is significantly less than for adults. An international registry of symptomatic VTE in newborns reported an incidence of 0.24 per 10,000 admissions to neonatal intensive care units. A German prospective nationwide two-year registry reported an incidence of symptomatic neonatal TE (which included CNS

Thromboembolic events (TEs) during childhood are increasing in their frequency and severity, and occur in children surviving previously life-threatening primary diseases. Newborns comprise the largest group of children developing TEs. This paper discusses the epidemiology, diagnostic tests, acquired and congenital prothrombotic risk factors, long-term outcomes, and antithrombotic therapy for the management of TEs in newborns. Due to the unique features and the significance of TEs in the central nervous system (CNS), sinovenous thrombosis (SVT) and arterial ischemic stroke (AIS) will be considered separately; cerebrovascular lesions in premature infants will not be discussed.

In preparation for this manuscript, comprehensive Medline reviews were performed to identify all relevant publications, which were analyzed based upon the study design; results of studies with stronger designs were given more influence in the analysis. The striking features of this review were the deficiencies in our knowledge with respect to appropriate diagnostic strategies, optimal therapy for newborns with TEs, and the contribution of congenital prothrombotic disorders. Well-designed trials are required to improve our ability to care for neonates with TEs.

In Section II, Dr. Gabrielle deVeber reviews the epidemiology of neonatal thrombosis within the central nervous system, in both arterial and venous locations and those that occur in utero. The neurological presentation, risk factors including congenital prothrombotic disorders, anatomical distribution, diagnostic tests, use of antithrombotic therapy and neurologic outcome of neonates with either sinovenous thrombosis or arterial ischemic stroke are discussed.

In Section III, Dr. Anthony Chan reviews the current approaches to the prevention and treatment of neonatal thrombosis. Information on the differences in the response of neonates compared to adults to antithrombotic therapy and new approaches to the prevention and treatment of thrombosis in neonates are emphasized.

* Deceased

** Royal Children’s Hospital, Department of Hematology, Flemington Road, Parkville 3052, Victoria, Australia

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events) to be 0.51 per 10,000 births, with approximately half of the cases being VTE and half arterial. The comparable incidence of VTE in the adult population is estimated at 2.5 to 5.0% of the population.

2. Central Venous Line Related Thrombosis

General information: The literature reports that over 80% of VTE in newborns are secondary to central venous lines (CVLs). Central lines are usually placed either into umbilical veins (UVC) or into the upper venous system through peripheral veins from the arm or through major vessels such as jugular veins (CVLs). UVCs or CVLs are used extensively in premature and full term infants who require supportive care in the form of fluids, drugs or total parenteral nutrition (TPN). There are several possible mechanisms by which CVLs cause TEs including damage to vessel walls, disrupted blood flow, infusion of substances such as parenteral nutrition that damage endothelial cells, and thrombogenic catheter materials.

Umbilical venous catheters: There are several studies assessing the incidence of UVC-related VTE. Autopsy studies estimate the incidence of UVC-related VTE at 20–65% of infants who die with a UVC in place. Clinical studies estimate the incidence of UVC-related VTE to be approximately 13%

Central venous lines: There are numerous studies reporting the risk of CVL-TE based on loss of CVL patency and/or objective tests with or without confirmation by ultrasound or angiography. Although there is no definitive study determining the incidence of CVL-related VTE in newborns, the published studies clearly identify CVLs as the most important risk factor.

Right atrial thrombosis: Right atrial thrombosis frequently occurs in newborns with CVLs. Clinically overt symptoms of right atrial thrombosis include cardiac failure, CVL malfunction, persistent sepsis, and appearance of a new cardiac murmur. Fatal pulmonary embolism (PE) occurs secondary to CVL-related VTE, although possibly less frequently than from VTE in the lower limbs.

3. Diagnosis

The reported incidence of VTE in newborns is dependent on the choice of diagnostic test, varying from 5% by ultrasound to 64% by angiography, and there are no studies comparing currently used diagnostic tests. Little is known about the precision and accuracy of noninvasive imaging techniques that are commonly used to make the diagnosis of VTE in newborns. Studies in older children suggest that ultrasound is poorly sensitive (20%) for upper system CVL-related VTE compared to venography. The low pulse pressure in premature newborns likely makes ultrasound more difficult to interpret. Similarly, the presence of CVLs makes compressibility difficult to assess, which greatly reduces the sensitivity of ultrasound.

4. Clinical Symptoms/Complications

General information: The clinical symptoms and complications of VTE can be classified as acute or long term. The acute clinical symptoms, besides loss of CVL patency, include swelling, pain, and discoloration of the related limb, swelling of the face and head with superior vena cava syndrome, and respiratory compromise with PE. The long-term clinical complications include prominent collateral circulation in the skin over the chest, back, neck and face, repeated loss of CVL patency requiring treatment with local thrombolytic therapy, repeated requirement for CVL replacement, eventual loss of venous access, CVL-related sepsis, chylothorax, chylopericardium, recurrent VTE necessitating long-term anticoagulation therapy with its associated risk of bleeding, and post thrombotic syndrome (PTS). Specific long-term sequelae of UVC-related VTE include portal hypertension, splenomegaly, gastric and esophageal varices, major bleeding related to the varices, and hypertension.

Pulmonary embolism: The frequency of PE during the newborn period is unknown but likely underestimated because the clinical features are often subtle or masked by a primary respiratory illness. Diagnostic strategies are not easily extrapolated from adults for several reasons including the inability to perform ventilation-perfusion scans, the frequent presence of underlying lung disease, and the lack of proven sensitivity of ultrasound to screen for a peripheral source of PE.

Recurrence: There is no information on the incidence of recurrent VTE in newborns. Recurrent VTE occurs in 5–13% of older children depending upon the primary treatment and in 4–10% of adults depending upon whether the VTE is secondary or idiopathic.

Post thrombotic syndrome: PTS, a serious long-term outcome of VTE, is caused by incompetent perfusing valves and blood flow directed from the deep system into the superficial system leading to edema and impaired viability of subcutaneous tissues. Approximately 20% of adults with VTE develop PTS, and symptoms may occur early or be delayed as long as 5–10 years after the initial event. Recently, PTS has been described in its early forms in children, some of whom developed their VTE as newborns. Newborns and young infants are potentially at an increased risk for PTS because the fibrinolytic system is physiologically suppressed. Long-term follow-up of newborns with VTE is critically important to determine the frequency and severity of PTS.
5. Renal Vein Thrombosis

**General information:** Renal vein thrombosis (RVT) is the most common non-catheter related VTE in newborns and is responsible for approximately 10% of all VTE in newborns. Almost 80% of all RVT present within the first month and usually within the first week of life.\(^{2,30-32}\) Some newborns developed RVT in utero.\(^{32}\) The incidence in males and females is similar, both sides are affected equally, and RVT occurs bilaterally in 24% of newborns.\(^{32}\)

**Etiology:** The pathologic conditions associated with RVT include perinatal asphyxia, shock, polycythemia, cyanotic congenital heart disease (CHD), maternal diabetes, dehydration, and septicemia. These disorders result in reduced renal blood flow, increased blood viscosity, hyperosmolality, and hypercoagulability.\(^{32}\)

**Clinical presentation:** Newborns usually present with a flank mass, hematuria, proteinuria, thrombocytopenia and nonfunction of the involved kidney. Clinical findings suggestive of associated acute interior vena cava-related VTE include cold, cyanotic and edematous lower extremities. Chronic obstruction is characterized by dilation of collateral veins over the abdomen and upper thighs as well as bilateral PTS.

**Diagnosis:** Currently ultrasound is the radiographic test of choice because of its practicality, sensitivity to an enlarged kidney and lack of adverse effects.\(^{33,34}\) In the first week, the affected kidney swells and becomes echogenic with prominent echo-poor medullary pyramids. Subsequently, the swelling decreases and the kidney becomes heterogeneous with loss of corticomedullary differentiation. Ultimately, depending on the degree of recovery, ultrasound may demonstrate focal scarring or atrophy.\(^{35}\) Magnetic resonance imaging (MRI) and computerized tomography (CT) have also been used.\(^{36}\)

**Outcome:** The outcome of RVT has changed from a frequently lethal complication to one in which over 85% of newborns survive with current anticoagulation therapy (see below). Unfortunately, there are no recent studies assessing long-term morbidity such as hypertension and loss of renal function. (See Table 1.)

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**Systemic Arterial Thromboembolic Disease**

1. **General Information**

Arterial TEs in newborns are, with few exceptions, iatrogenic complications that occur secondary to indwelling arterial catheters, placed for monitoring, diagnostic, and therapeutic purposes.\(^{37,38}\) Either umbilical arterial catheters (UACs) or peripheral arterial catheters are used for monitoring while the femoral artery is the most common site for cardiac catheterization during early infancy. Arterial TEs may require urgent treatment due to risk of organ or limb loss and present management dilemmas because of the limited information on optimal therapy.

Both the diagnostic and therapeutic approaches to arterial TEs during early infancy differ from those for adults. For example, angiography is rarely used for diagnosis because of the risk of inducing another arterial TE at the site where the catheter is introduced, and embolectomy is in general avoided because of a high failure rate due to re-occlusion in tiny vessels.

2. **Umbilical Arterial Catheters**

**Incidence:** Major clinical symptoms of UAC-related TEs occur in 1–3% of infants.\(^{39}\) Loss of patency due to UAC-related TEs occurs in 13–73% of catheters in the absence of unfractionated heparin (UFH) and 0–13% in the presence of UFH.\(^{40}\) The reported incidence of UAC-related TEs reflects, in large part, the diagnostic test chosen. Studies using ultrasound report an incidence of UAC-related TEs from 14–35%, compared to incidences as high as 64% in studies using angiography. Finally, autopsy studies report an incidence of UAC-related TEs from 9–28%.\(^{40}\)

**Position:** There continues to be debate as to the optimal position for the tips of UACs. Positions are considered as “high” with UAC tips between T6 and T10 and “low” with UAC tips between L3 and L5. High UACs are reported to function better with fewer complications.\(^{41}\) However, the complications may be more serious since a local thrombus may result in occlusion of the celiac, mesenteric, and renal arteries. Major artery TEs also occur with UACs in a low position.\(^{41,42}\) At this time there is no convincing evidence that the location of the tip of UACs influences the incidence of TEs.

**Clinical presentation:** The clinical presentation of UAC-related TEs varies depending upon the extent of the TE and involvement of other arteries. The majority of newborns are clinically asymptomatic or with minor symptoms, while a smaller percentage have major symptoms of severe ischemia to the legs and selected organ dysfunction. UAC-related TEs may present with necrotizing enterocolitis secondary to mesenteric artery occlusion, hypertension with or without renal failure secondary to renal artery thrombosis, and limb compromise secondary to embolic events.\(^{43,44}\) Careful monitoring of temperature, color, capillary refill time and pulses of the legs are important for early detection of arterial catheter related TEs.

**Diagnosis:** The “gold standard” test for the diagnoses of UAC-related TEs is contrast angiography,\(^{45}\) which is, unfortunately, rarely feasible in critically ill newborns. Noninvasive imaging techniques, while easy to perform at the bedside, have not been validated. The need to critically assess these diagnostic tests was illustrated in a study where ultrasound failed to visualize aortic TEs in 4 patients, 3 of whom had complete aortic obstruction by contrast angiography.\(^{46}\)
Outcome: Symptomatic, acute UAC-related TEs frequently threaten organ or limb viability with a potentially lethal outcome. Long-term morbidity in survivors may manifest as hypertension, abnormal renal function, discrepancies in leg measurements, Claudication and paraplegia. The long-term prognosis of UAC-related TEs remains uncertain and its understanding is important as the outcomes should influence initial management.

3. Peripheral Arterial Catheters

General information: The incidence of TEs secondary to peripheral arterial catheters in the absence of UFH is influenced by catheter material, duration of placement, diameter, length, solutions infused, and arterial site. Acute impairment of arterial blood flow to the hand or foot is characterized by diminished or absent pulses, a prolonged capillary refill time, and a cool, pale hand or foot. Doppler ultrasound is usually used to provide confirmation of the TE. Thrombotic occlusion of the radial artery usually does not result in loss of the entire hand unless the ulnar artery is absent. Several studies, which are discussed below, have shown that UFH prolongs the patency of peripheral arterial catheters.

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Table 1. Incidence, diagnosis, and treatment of non-central nervous system thrombosis.

<table>
<thead>
<tr>
<th>Type of Thrombosis</th>
<th>Incidence</th>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Systemic Venous TE</td>
<td>2.4/1000 admissions to NICU</td>
<td>Upper venous system: Intrathoracic vessels:</td>
<td>Treatment recommendations are not supported by strong evidence</td>
</tr>
<tr>
<td></td>
<td>5.1/100,000 live births</td>
<td>venography sensitive184</td>
<td>LMWH, UFH or observant therapy with close monitoring are options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neck vessels: US sensitive 18</td>
<td>Warfarin is not recommended in children &lt;12 months of age unless induction is a mechanical valve</td>
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<td></td>
<td></td>
<td></td>
<td>Thrombolytic therapy (tPA) is recommended for therapy</td>
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<td></td>
<td></td>
<td></td>
<td>only if potential loss of life, organ or limb due to high</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>incidence of hemorrhage</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>14% in a retrospective</td>
<td>V/Q scan 201</td>
<td>Treatment: as above</td>
</tr>
<tr>
<td></td>
<td>autopsy series</td>
<td></td>
<td>Prophylaxis: UFH flushes or low dose infusions (1 to 3 u/kg/hr)</td>
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<tr>
<td>CVL-related TE</td>
<td>no data for neonates alone</td>
<td></td>
<td>Treatment: as above</td>
</tr>
<tr>
<td></td>
<td>0-30% in infants &lt;1 year</td>
<td>Upper venous system: venography sensitive184</td>
<td>Prophylaxis: UFH flushes or low dose infusions (1 to 3 u/kg/hr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neck vessels: US sensitive 18</td>
<td></td>
</tr>
<tr>
<td>Right Atrial TE</td>
<td>No incidence data</td>
<td>Cardiac catheterization</td>
<td>Treatment: as above</td>
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<tr>
<td></td>
<td></td>
<td>Echocardiography</td>
<td>Prophylaxis: as above</td>
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<tr>
<td></td>
<td></td>
<td>No studies comparing sensitivity and specificity have been completed.</td>
<td></td>
</tr>
<tr>
<td>UVC</td>
<td>20-65% of infants dying</td>
<td>Contrast venography is gold standard US</td>
<td>Treatment: as above</td>
</tr>
<tr>
<td></td>
<td>with a UVC in situ</td>
<td>most commonly used</td>
<td>Prophylaxis: UFH flushes or low dose infusions (1 to 3 u/kg/hr)</td>
</tr>
<tr>
<td></td>
<td>13% in clinical studies</td>
<td>No sensitivity and specificity data</td>
<td></td>
</tr>
<tr>
<td>Non CVL-related TE</td>
<td>2.2/100,000 live births</td>
<td>Contrast venography is gold standard US</td>
<td>Treatment is controversial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US most commonly used</td>
<td>Consider UFH/LMWH if thrombus extends to IVC or involving bilateral renal vein, or renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No studies comparing sensitivity and specificity have been completed.</td>
<td></td>
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<tr>
<td>2. Systemic Arterial TE</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A. UAC</td>
<td>Clinical symptoms 1-5%</td>
<td>Contrast angiography is gold standard16</td>
<td>Prophylaxis:</td>
</tr>
<tr>
<td></td>
<td>Loss of patency:</td>
<td></td>
<td>UFH concentrations as low as 0.25 u/ml can decrease the incidence of catheter occlusion but may not decrease aortic thrombosis</td>
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<tr>
<td></td>
<td>a. absence of heparin 13</td>
<td></td>
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<tr>
<td></td>
<td>to 73%40</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>b. presence of heparin 0</td>
<td></td>
<td></td>
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<td></td>
<td>to 13%40</td>
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<tr>
<td></td>
<td>US 14 to 35%40</td>
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<tr>
<td></td>
<td>Angiography up to 64%40</td>
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<td></td>
<td>Autopsy 9 to 28%40</td>
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<td></td>
</tr>
<tr>
<td>B. Other (femoral or peripheral artery)</td>
<td>No incidence data</td>
<td>Contrast angiography is gold standard</td>
<td>Prophylaxis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UFH 1 u/ml prolongs patency of PACs58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICH not increased in use of low dose UFH185</td>
</tr>
<tr>
<td>Complications of TE</td>
<td>Highest among infants with</td>
<td></td>
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<td></td>
<td>aortic thrombosis or CVL-</td>
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<tr>
<td>Mortality</td>
<td>associated thrombosis</td>
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<td></td>
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<tr>
<td></td>
<td>affecting the right atrium</td>
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<tr>
<td></td>
<td>or the superior vena cava</td>
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<td></td>
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<tr>
<td>Post-phlebitic syndrome</td>
<td>Clinical diagnosis24</td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: TE, thromboembolic event; US, ultrasound; NICU, neonatal intensive care unit; LMWH, low molecular weight heparin; UFH, unfractionated heparin; V/Q, ventilation perfusion scan; UVC, umbilical vein catheter; RVT, renal vein thrombosis; IVC, inferior vena cava; ICH, intracranial hemorrhage
Congenital Prothrombotic Disorders

1. General Information

The congenital prothrombotic disorders that have been linked to TEs in newborns include deficiencies of antithrombin (AT), protein C, protein S, and plasminogen; and the presence of prothrombin gene 20210A and Factor V Leiden. In general, the classification of these prothrombotic disorders can be considered as either homozygous or heterozygous. Homozygous prothrombotic disorders usually present in newborns with severe clinical manifestations and require specific urgent therapy. The diagnosis of heterozygous congenital prothrombotic disorders in newborns can be problematic because physiologic values are significantly decreased compared to older children and adults. This issue is further confounded by the presence of acquired disorders, which are present in over 80% of newborns with systemic TEs and frequently have a consumptive component resulting in further decreases in these proteins.

2. Homozygous Prothrombotic Disorders

Protein C: The classical clinical presentation of homozygous protein C deficiency consists of cerebral and or ophthalmal damage that occurs in utero; purpura fulminans within hours or days of birth; and, on rare occasions, large vessel thrombosis. The skin lesions start as small ecchymotic sites that increase in a radial fashion, become purplish black with bullae, and then necrotic and gangrenous. The lesions occur mainly on the extremities but can occur on the buttocks, abdomen, scrotum, and scalp. They also occur at pressure points, at sites of previous punctures, and at previously affected sites. The neurologic complications can result in mental retardation and delayed psychomotor development. The eye involvement consists of vitreous or retinal hemorrhage secondary to thrombosis, which results in partial or complete blindness. These newborns also have severe disseminated intravascular coagulation with secondary hemorrhagic complications, which are frequently in the CNS.

The diagnosis of newborns with homozygous protein C deficiency depends upon the presence of the appropriate clinical features, a protein C level that is not measurable, and, ideally, confirmation of the parents as heterozygotes. The presence of decreased plasma concentrations of protein C in the absence of clinical manifestations and family history cannot be considered diagnostic of homozygous protein C deficiency. For families in whom protein C deficiency has been diagnosed in the parents, genetic testing in utero is an option.

The initial treatment for purpura fulminans is 10 to 20 mL/kg of fresh frozen plasma (FFP) every 12 hours, which will achieve plasma concentrations of protein C of 0.15–0.32 units/mL 30 minutes after infusion, and 0.04–0.10 units/mL at 12 hours. While FFP may restore protein C levels sufficiently to arrest the purpura fulminans, many infants will not tolerate the volume required for ongoing replacement. Also FFP is not virally inactivated. Protein C concentrate, when available, avoids both of these problems. Protein C concentrate is available in all European Union countries and Switzerland; in Canada and the US, it is available on compassionate release only. Protein C concentrate can be administered in doses of 20 to 60 units/kg with the latter achieving peak protein C levels of at least 0.60 units/ml. Replacement of protein C with FFP or concentrate should be continued until the clinical lesions resolve. Long-term treatment options include oral anticoagulant (OA) therapy, protein C replacement, and liver transplantation.

Protein S: Homozygous protein S deficiency also presents at birth with purpura fulminans and with unmeasurable plasma concentrations of protein S. Because there is no protein S concentrate available, FFP is the initial therapy of choice. Further management strategies are similar for homozygous protein C deficiency.

Antithrombin: Homozygous AT deficiency is extremely rare, presents within the first 10 years of life, causes severe TEs, which may be venous or arterial, and is associated with plasma concentrations of AT levels that are less than 10%. From 1966 to 1999 there were 7 children reported in the literature with homozygous AT deficiency who had TEs.

Plasminogen: Homozygous plasminogen deficiency usually presents with ligneous conjunctivitis.

3. Heterozygous Prothrombotic Disorders

Although newborns with heterozygote coagulation inhibitor deficiencies rarely develop TEs, up to 20% of newborns with TEs are heterozygote for a congenital prothrombotic disorder. In addition, heterozygous inhibitor deficiencies have been implicated in other neonatal conditions such as porencephaly, although further studies are required to confirm these associations.

Protein C/Protein S: A number of large studies have confirmed that heterozygous protein C deficiency does not usually present with thrombosis during early infancy. Despite the low absolute risk, numerous case series and cohort studies suggest that there is an increased prevalence of protein C heterozygosity in newborns and infants with TE. The majority of these infants had clinical risk factors that “unmasked” the congenital defect. The diagnosis of heterozygote protein C deficiency in newborns is particularly difficult as physiologic values for protein C at birth may be as low as 17% of adult levels. Occasionally newborns were labelled as protein C defi-
cient when the values were actually normal for age. Similar to protein C deficiency, most individuals with the heterozygous form of protein S deficiency do not suffer TEs until adult life.\textsuperscript{114}

**Antithrombin:** The clinical presentation of the few newborns with heterozygous AT deficiency is diverse, reflecting the site of the thrombus, and have included purpura fulminans.\textsuperscript{60,69} TEs are reported in arterial or venous vessels and in a variety of unusual locations including the CNS and coronary arteries, which results in myocardial infarction. One newborn developed fatal aortic and vena caval thrombosis.

**Other hypercoagulable states:** There are numerous case reports of severe TEs in neonates with factor V Leiden.\textsuperscript{80-82,113} These include arterial and venous TE, including RVT.\textsuperscript{83} In contrast, prothrombin gene mutation has been reported in only one study in any infants with TEs until adult life.\textsuperscript{114} The available information suggests that SVT is under-diagnosed in newborns, in particular in association with asphyxia\textsuperscript{116} or seizures.\textsuperscript{117}

**Neurological presentation:** In the neonatal period, the brain is still relatively immature. As a result, newborns with cerebral damage manifest only a limited number of clinical signs. In newborns, the most frequent neurological signs of SVT are seizures, which are present in over 70\%, and lethargy. Hemiparesis is present in less than 10\%.\textsuperscript{115} In newborns with extensive SVT, external signs may include a tense anterior fontanelle, separation of bony sutures reflecting intracranial hypertension, and dilated scalp veins. Following the initial diagnosis, propagation of the thrombosis may occur in the absence of clinical deterioration.\textsuperscript{109}

**Risk factors:** The predisposition for neonatal SVT may relate to 1) physiological factors that may promote SVT, 2) pathological factors associated with the birth process, or 3) postnatal diseases. During birth, the normal molding and overlapping of the cranial sutures can damage the cerebral sinus structures that immediately underlie the sagittal and lateral sinuses, provoking thrombosis.\textsuperscript{118} In the post-natal period, venous flow within sinuses is altered by head positioning.\textsuperscript{119} Perinatal complications including asphyxia are present in 24\% of neonates with SVT. Asphyxia can itself produce seizures and lethargy creating diagnostic confusion between SVT and asphyxia. However, SVT has been frequently identified on cerebral angiography performed in severely asphyxiated neonates.\textsuperscript{120} Coagulation laboratory testing shows prothrombotic abnormalities in 20\% of newborns with SVT, although the contribution of these abnormalities to the causation of SVT has not been defined.\textsuperscript{109,115,121} Newborn illnesses that increase the risk for SVT include dehydration, sepsis, and head and neck disorders including meningitis and others.

**Radiographic features:** The most frequently involved sinuses in neonatal SVT are the superior sagittal and lateral sinuses, the major components of the ‘superficial’ sinus system. Cortical vein thromboses are rare. The ‘deep’ sinovenous system, including the Vein of Galen, straight sinus and internal cerebral veins, is much less frequently involved.\textsuperscript{115} Cerebral parenchymal lesions are associated with SVT in nearly half of newborns and include venous infarcts, which are frequently hemorrhagic and, in some newborns, transient focal edema. When
SVT is extensive, diffuse cerebral swelling with ‘slit-like’ ventricles can result from venous outflow obstruction. Sagittal sinus thrombosis can cause a communicating hydrocephalus resulting from impaired absorption of cerebrospinal fluid into the arachnoid granulations that line the sagittal sinus leading to increased intracranial pressure.

**Diagnostic tests:** The diagnosis of SVT is dependent on imaging either the thrombus within the sinovenous channels or a reduction or obliteration of venous flow within the affected venous sinus. A non-contrast enhanced CT can demonstrate large occlusive thrombi within venous channels as areas of increased density. For the same defect, a contrast-enhanced CT shows areas of low density due to lack of contrast filling. However, since the sinuses are adjacent to the bony skull, and CT scanning is subject to significant interference by ‘bone artefact,’ the CT scan can miss the diagnosis in at least 10% of newborns with SVT. The non-contrast CT scan can also be falsely positive for SVT since the higher hematocrit, slower blood flow and low density of adjacent non-myelinated brain tissue in the infant can combine to produce an apparent ‘dense triangle’ sign of SVT. MRI scanning with venography (MRV) is the most sensitive and specific test, and Doppler flow ultrasound through the anterior fontanelle may demonstrate absent or decreased flow within the sinovenous channels.

**Neurological outcome:** The neurological outcome of neonatal SVT is unclear in the literature even though over 90% of newborns with SVT survive. The best available estimate is that after a mean of 2.1 years, 77% of newborns surviving SVT are neurologically normal. However, given the delayed onset of signs of neurological injury in newborns, long-term follow-up is critically important. In the Canadian Registry, outcomes from July 1992 through June 2000 included death in 7%, neurological deficit in 61%, seizures in 21%, and recurrent cerebral or systemic thrombosis in 9%. The presence of infarcts is associated with a poor outcome. (See **Table 2**.)

### Arterial Ischemic Stroke

**Incidence:** Newborns comprise 25% of children with arterial ischemic stroke (AIS). Previous estimates of the incidence of neonatal AIS have been 28.6 per 100,000 live births. In the Canadian Registry, the incidence of AIS in newborns is 93 per 100,000 live births.

**Clinical features:** Newborns with AIS typically present with seizures or lethargy during the first few days of life. In systematic studies of newborns with seizures, 12–14% have been found to have cerebral infarctions. Focal signs are rare, with hemiparesis present.

### Table 2. Incidence, diagnosis, and treatment of central nervous system thrombosis.

<table>
<thead>
<tr>
<th>Type of Thrombosis</th>
<th>Incidence</th>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Venous TE SVT</td>
<td>41/100,000</td>
<td>Angiogram is the gold standard</td>
<td>Four adult trials support anticoagulation therapy</td>
</tr>
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<td>MRI scanning with venography</td>
<td>Use of anticoagulants in neonates is controversial, probably not indicated in the presence of a large infarct or significant CNS hemorrhage</td>
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<td>Doppler flow US may be sensitive</td>
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<td>CT without contrast has decreased sensitivity and specificity</td>
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<td></td>
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<td>CT with contrast has decreased sensitivity</td>
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<tr>
<td>Cerebral Arterial TE AIS</td>
<td>28.6 to 93 / 100,000 live births</td>
<td>Diffusion weighted MRI diagnoses the early stages of infarct</td>
<td>Use of anticoagulants is controversial, and rarely indicated given negligible risk of recurrence</td>
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<tr>
<td></td>
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<td>CT is not sensitive to diagnose the early stages of infarction</td>
<td>Thrombolytic therapy is rarely, if ever, an option</td>
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<tr>
<td></td>
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<td>MRI/MRA is more sensitive to small or early infarcts</td>
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<td>US has a limited role</td>
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### Complications of SVT

- Mortality: 12%<sup>115</sup>
- Recurrence: <5%<sup>115</sup>
- Seizures: 20%<sup>115</sup>
- Neurological deficit: 38%<sup>115</sup>

### Complications of AIS

- Mortality: <10%<sup>125</sup>
- Recurrence: <1%<sup>125</sup>
- Seizures: 15%<sup>125</sup>

Abbreviations: TE, thromboembolic event; SVT, sinovenous thrombosis; MRI, magnetic resonance imaging; CT, computerized tomography; US, ultrasound; CNS, central nervous system; AIS, arterial ischemic stroke; MRA, magnetic resonance angiogram
in less than 25% of newborns. In some newborns with a normal neonatal course, hemiparesis is first detected during later infancy (typically 4–8 months of age), leading to a CT scan that demonstrates the findings of a remote (presumed pre- or peri-natal) cerebral infarct. In such infants the AIS is presumed to have occurred in utero or in the perinatal period, with no or only subtle signs at birth. The important implication is that infants with presumed pre- or perinatal stroke but having only mild or no neurological sequelae are never diagnosed. The number of children comprising the latter group is unknown.

**Radiographic features:** In newborns, arterial infarcts occur only slightly more often in the left than in the right hemisphere. Over two-thirds of newborns have large vessel infarcts with the remainder having small vessel infarcts. In contrast, nearly half of older infants and children have small vessel infarcts. The carotid (‘anterior’) circulation is five times more likely to be involved in neonatal stroke than the ‘posterior’ circulation. Neonatal AIS are hemorrhagic in 20%, and multiple infarcts at diagnosis are present in 15–20%.

**Diagnostic tests:** Radiographic studies in neonatal AIS include CT, MRI, magnetic resonance angiography (MRA) and, less frequently, conventional angiogram. Cranial ultrasound plays only a limited role in AIS in term newborns due to the peripheral location within the brain of most infarcts. This is in contrast to the proven value of cranial ultrasound in defining the centrally located vascular lesions of periventricular leukomalacia in premature infants. Both CT and MRI confirm and characterize infarcts in terms of number, size, vascular territory, and the presence or absence of hemorrhagic conversion. MRI is more sensitive to small or early infarcts that are frequently missed by CT. The radiographic technique that detects infarction in its earliest stages is the diffusion weighted MRI scan. In the latter technique, abnormal focal findings indicating cytotoxic edema precede abnormalities on a regular MRI sequence in newborns. Vascular imaging modalities including MRA and angiography can define the presence or absence of arterial stenosis or occlusion; angiography can further define the underlying stroke mechanism as dissection, embolism, vasculitis, or other processes. However, either technique may fail to show thrombotic occlusion of large cerebral arteries even within several hours or days of the AIS, presumably due to the thrombus having moved distally into the arterial tree, as occurs in adults. Angiography may also fail to show small vessel arterial occlusion. Therefore, in many newborns with AIS, the size and location of the occluded artery is only definable by the size and location of the infarct. Occlusion of major cerebral arteries results in large wedge-shaped infarcts in characteristic vascular distributions involving the cortex. Occlusion of small lenticulostriate arteries, which arise from the stem of the major cerebral arteries, produces small sub-cortical infarcts located in the white matter, basal ganglia, thalamus, and brain stem, which vary from several millimeters to several centimeters in diameter. Multiple infarcts within the same vascular territory can result from a single thrombotic occlusion, for example, simultaneous occlusion in the stem of the middle cerebral artery and the lenticulostriate ‘small’ arteries at their origin.

**Risk factors:** A primary risk factor for AIS is definable in approximately two thirds of affected newborns. Systemic risk factors are present in over half of newborns and include cardiac disease (10%), perinatal complications (50%), and other acute illnesses including dehydration and prothrombotic disorders (25–68%). Congenital protein C deficiency, protein S deficiency, factor V Leiden mutation, and increased lipoprotein (a) have all been reported in newborns and children with perinatal infarction. Acquired conditions are more frequent and include the presence of transplacentally derived maternal antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant) and acquired deficiencies of protein C, protein S, AT, and activated protein C resistance.

**Outcome:** The mortality rate following AIS in newborns is less than 10%. Neurological deficits are detected in two thirds of survivors by several years of age. Lesions that involve the motor cortex, internal capsule, and basal ganglia together are associated with more increased motor disability than lesions limited to the cortex or basal ganglia alone. Other predictors of outcome remain to be defined. In one third of newborns the outcome is normal. However, seizure disorders are present long-term in up to 15% of children. In contrast to older infants and children, fewer than 5% of newborns with AIS have recurrent systemic or cerebral thrombosis. Long-term follow-up studies are needed to elucidate the extent of more subtle adverse outcomes including learning disorders that cannot be detected at young ages.

**III. Antithrombotic Therapy**

**Anthony K.C. Chan, MD, FRCP(C)***

Antithrombotic therapy of TEs in newborns is fraught with difficulty. 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 withhold antithrombotic

* Children’s Hospital, Chedoke McMaster, 1200 Main St. West, Hamilton ONT L8N 3Z5, Canada
Commonly Used Anticoagulants

Unfractionated heparin: UFH is a polydisperse polyanion that mediates its activities through catalysis of AT through a specific pentasaccharide sequence. For UFH to have antithrombin activity, UFH has to have at least 18 saccharide units, which is not required for its antithrombin Xa activity. The antithrombin to anti-factor Xa activity of UFH is 1:1. The activities of UFH can be considered as “anticoagulant,” which refers to UFH’s activities in vitro, and “antithrombotic,” which refers to UFH’s activities in vivo.

Both an increased sensitivity and resistance to UFH’s anticoagulant activities in vitro in plasma from newborns have been reported. Increased sensitivity to UFH is observed in systems based on assays dependent on thrombin generation (e.g. activated partial thromboplastin time [APTT]) and resistance to UFH is observed in systems based on assays that measure the inhibition of exogenously added factor Xa or thrombin and that are dependent on plasma concentrations of AT. The paradox of UFH sensitivity and resistance in plasma from newborns reflects the ratio of AT to prothrombin in the assay system. The in vivo anti-thrombotic effects of UFH in newborn piglets show that decreased concentrations of UFH limit the antithrombotic effects of UFH. Resistance to UFH resistance can be overcome by either increasing the dose of UFH or the AT concentration. Pharmacokinetic studies also show that clearance of UFH is faster in piglets than in older pigs due to a larger volume of distribution.

The studies of UFH in newborns are limited but also show that the clearance of UFH is faster than for older children due to a larger volume of distribution, and that the dose of UFH required achieve a therapeutic APTT is also increased compared to older children. 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 remains unknown.

The clinically important side effects of UFH include major bleeding, heparin induced thrombocytopenia (HIT) and osteoporosis. In one prospective pediatric study of which 13 were newborns, none had significant bleeding (95% CI: 0-25%), although many patients in this series had sub-therapeutic APTT values. Thus the bleeding rate in newborns with APTT values in the therapeutic range is unknown. In the presence of significant bleeding, the infusion of UFH should be stopped and, if required, the activities of UFH can be immediately reversed using protamine sulphate. Although HIT has been reported in newborns, the exact incidence remains unclear but appears to be low. If anticoagulation is needed when HIT is diagnosed, either danaparoid or lepirudin can be used. 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 monitoring.

Oral anticoagulation: Warfarin is a vitamin K antagonist and functions as an anticoagulant by reducing the functional plasma concentration of vitamin-K dependent factors (factors II, VII, IX, X). 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 normalized ratios (INRs) of 2 to 3. Warfarin is problematic in newborns for several other reasons. First, infant formula is supplemented with vitamin K to prevent hemorrhagic disease of the newborn and makes formula-fed newborns resistant to warfarin. In contrast, breast milk has low concentrations of vitamin K, making breast fed newborns very sensitive to warfarin. The latter can be compensated for by feeding breast-fed newborns 1 to 2 ounces of formula 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 and frequent changes in medications and in diet. Poor venous access becomes an issue for these newborns. Fourth, although these is substantial information on the use of warfarin in children over 3 months of age, there is essentially no information on its efficacy and safety in newborns. Another potential complication of prolonged use includes a negative impact of warfarin on bone density in growing children. In summary, the use of warfarin is problematic and should be avoided 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.
Low Molecular Weight Heparin: Low molecular weight heparin (LMWH) is derived from UFH by using either chemical or enzymatic methods. 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. Due to the decreased molecular weight of LMWH compared to UFH, the antithrombin to anti-factor Xa ratio is about 1:3-5 depending on the particular type of LMWH. The test dependent sensitivity and resistance described for UFH also applies to LMWH when tested in vitro in plasma from newborns. In addition, the clearance of LMWH is also increased in a newborn animal model compared to adults.

The studies of 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 and that the dose of enoxaparin (the most commonly used LMWH in newborns) required to achieve anti-Xa levels in the adult therapeutic range of 0.5–1.0 units/mL is increased compared to older children. One limitation of these studies is that they included infants up to 3 month of age. Similar to UFH, the optimal dose of LMWH in newborns remains unknown.

The clinically important side effect of LMWH is bleeding. In adults, recent meta-analyses have shown that the risk of bleeding appears to be less with LMWH compared to UFH. Although the risk of major bleeding is not precisely known in newborns, there are studies reporting the risk of bleeding in newborns as part of larger patient populations. One pilot study reported no bleeding documented in 7 infants less than 2 months of age (0%, 95% CI 0–47%). In a larger series, 4 of 37 infants had major bleeding (10.8%, 95% CI 3–25.4%). The locations were local at the site of subcutaneous catheters in 2 newborns with little subcutaneous tissue and into pre-existing abnormalities in the CNS in 2 other newborns. Subcutaneous catheters should be used with caution in newborns with little subcutaneous tissue. If the anticoagulant effect of LMWH needs to be terminated immediately, protamine sulphate will reverse the anti-thrombin activity but only partially affect the anti-factor Xa activity.

New anticoagulants: The ideal anticoagulant to be used in newborns or any patient is one that can be administered orally, subcutaneously, and intravenously, requires minimal monitoring and has few side effects. Numerous new anticoagulants are being tested in adults but none has been tested in newborns. Of particular interest is a direct oral thrombin inhibitor (melagatran) that appears to fulfil many of the above requirements. Another area of ongoing research is improving the compatibility of vascular access devices. No trial has demonstrated efficacy of anticoagulant bonded catheters in the neonatal population. New catheter materials in the clinical and preclinical stage of development, such as Hyaluronic Acid coated catheters and AT-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.

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 (FDPs). 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), and may limit their efficacy in newborns. Supplementation of plasminogen may be preferable to increasing the dose of thrombolytic agents in order to optimize thrombolytic therapy in newborns.

There is minimal information on the clinical use of thrombolytic therapy in newborns, and most of it is confined to UK. However, at this time, tPA is the agent of choice because tPA has increased fibrin specificity, improved in vitro clot lysis in plasma from newborns compared to either UK or SK, and the availability of UK is limited since the US Food and Drug Administration issued a warning about potential production problems for UK. There is no therapeutic range and no good correlation between hemostatic parameters and efficacy for thrombolytic therapy. However, the fibrinogen concentration, FDPs, or thrombin clotting time can be used as indicators of significant fibrinogenolysis.

The incidence of bleeding secondary to thrombolytic agents, based upon red cell transfusions requirements, is 20% in the pediatric population. In another review, Zenz et al reported that 1 of 83 term newborns (1.2%, 95% CI 0.3-6.5%) and 11 of 86 premature newborns (13.8%, 95% CI 6.6-21.7%) had intracranial hemorrhage (ICH). However, premature newborns in a randomized control trial 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 newborns who received tPA reported 1 death from bleeding. Based upon the reported literature, the bleeding risk associated with the use of thrombolytic agents in newborns remains unclear but certainly may be major. If bleeding occurs during thrombolytic therapy, factor replacement using FFP or cryoprecipitate as well as other supportive care is recommended. Anti-fibrinolytic agents are rarely indicated. Because of the potential for major bleeding risk and the general lack of information, thrombolytic therapy should be reserved for newborns with
life-, organ- or limb-threatening situations. Prior to thrombolytic therapy, both an ultrasound of the brain to determine if there is a pre-existing hemorrhage and coagulation screening tests to detect a concurrent coagulopathy are recommended. New thrombolytic agents are in various stages of evolution with the goal being more fibrin specificity with less bleeding.

**Guidelines for Antithrombotic Agents**

**Prophylaxis**

**Central venous lines:** Currently, UFH is used to prolong CVL patency in most newborns either in the form of flushes with UFH-containing solutions, or low dose infusions (1 to 3 units/mL/hr). The available information supports this practice.

**Umbilical arterial lines:** The current practice of using low dose UFH infusions was evaluated in a meta-analysis in newborns. Patency, which is likely linked to the presence of local TE, was prolonged by the use of low doses of UFH. However, the presence of local TE detected by ultrasound was not decreased in 2 studies that assessed this outcome. A randomized controlled trial (RCT) of UFH bonded UACs as compared to polyvinyl chloride catheters in 125 neonates did not show a significant reduction in the incidence of clinical complications or prolongation of patency.

**Peripheral lines:** Three studies show that UFH prolongs the patency of peripheral lines. Sellden et al assessed intermittent vs continuous flushing with UFH containing solutions in 338 infants less than 1 year of age with radial arterial catheters. Catheters were removed due to malfunction in 76% of patients receiving intermittent flushes compared to 52% of patients receiving continuous infusions of UFH. In a randomized controlled trial, Rais-Bahrami et al evaluated premature catheter removal in 60 newborns with peripheral arterial catheters. Patency of peripheral arterial catheters was prolonged in infants receiving UFH normal saline flushes compared to UFH dextrose flushes. Butt et al assessed a flow rate of 2 mL/hour and 1 mL/hour in 319 newborns and children and reported that there was no significant difference for duration of catheter patency. However, increasing the concentration of UFH from 1 to 5 units/mL (n = 154) significantly prolonged catheter patency.

**Relationship to ICH:** Three studies assessed the relationship between low dose UFH infusions and ICH. In the first study, a retrospective case control study, UFH was implicated as a risk factor for ICH in low birth weight newborns. However, this study was retrospective, the 95% confidence interval around the odds ratio of 3.9 was large (1.4 to 11.0), and the magnitude of the risk uncertain. 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. The authors reported that newborns with ICH received increased concentrations of UFH compared to those without ICH (59.4 units/kg/day). An odds ratio of 1.96 with a 95% confidence interval of 1.32 and 2.91 was reported. A recent randomized controlled 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. In the same study, the influence of UFH on the coagulation system was also assessed and no differences were detected due to UFH.

**Treatment**

**Venous thromboembolic events:** The optimal treatment of VTE in newborns is uncertain since current guidelines are extrapolated from studies in adults and older children, which is not optimal. Options include thrombolytic therapy; conventional anticoagulation with age-appropriate doses for either a short course (10-14 days) or for approximately 3 months; or close monitoring of the thrombus with objective tests and treating with anti-coagulants if extension occurs. Thrombolytic therapy is rarely indicated in newborns for VTE. When used, tPA is the agent of choice at doses ranging from 0.1-0.5 mg/kg/hour, with the lower doses used when a catheter tip is adjacent to the thrombus. Anticoagulant therapy is usually indicated. If UFH is used the average dose is 28 units/kg/hr and the target APTT range corresponds to an anti-factor Xa level of 0.3-0.7 u/mL. In general UFH should not be used for prolonged periods to avoid osteopenia, and warfarin should be avoided altogether whenever possible. If LMWH is used, the doses are specific to the agent, the target anti-factor Xa level is 0.5-1.0 u/mL and LMWHs can be used for 3 months. For enoxaparin, the most commonly used LMWH in newborns, the dose is 1.5 mg/kg subcutaneously twice daily. If either CVLs or UVCs are in place, they are usually, but not always, removed. If still present at the completion of therapy, prophylactic dosing with LMWH should be considered to prevent recurrent VTE. Monitoring the size of the thrombi during the initial stage of the treatment is important.

**Renal vein thrombosis:** Both anticoagulant and thrombolytic therapy are controversial for RVT. One approach is to use supportive care for unilateral RVT in the absence of uremia, and no extension into the IVC with careful monitoring of the RVT for extension. For unilateral RVT that extends into the IVC anticoagula-
tion therapy with UFH or LMWH is likely indicated. For bilateral RVT with various degrees of renal failure UFH should be used (and usually not LMWH due to its dependence on renal clearance) and thrombolytic therapy seriously considered given the poor prognosis of renal failure in newborns.\textsuperscript{187,188}

**Sinovenous thrombosis:** Four trials in adults together form the basis for the recommended use of anticoagulants.\textsuperscript{189-192} Anticoagulant therapy for neonatal SVT is controversial and is probably not indicated in the presence of a large infarct or significant CNS hemorrhage. In the Canadian Registry of SVT, over one third of newborns with SVT received anticoagulant medications without major bleeding or extension of the SVT.\textsuperscript{115} If anticoagulants are not used, radiographic follow-up for subclinical progression is important and, if it occurs, would usually result in the need for anticoagulants.\textsuperscript{115,130,193}

**Arterial thrombosis:** Similar to treatment for VTE, current guidelines are extrapolated from studies in adults. The options include thrombolytic therapy, a short or longer course of anticoagulation, and, less commonly, close observation. When an arterial catheter related TE occurs, the catheter needs to be removed immediately in most circumstances. If the arterial thrombosis causes significant circulation impairment to the extremities or vital organs, thrombolytic therapy should be considered. Anticoagulant therapy with UFH should be initiated during, or immediately following, thrombolytic therapy for a minimum of a few days. The guidelines for the use of these agents are similar to VTE except that a shorter course of anticoagulation is usually sufficient. Monitoring the course of the thrombus at the initial stage of treatment and prior to discontinuing anticoagulant therapy is important.

**Arterial ischemic stroke:** Numerous trials in adults with AIS show the benefit of therapy with aspirin and, in specific subpopulations, tPA, UFH or LMWH and warfarin.\textsuperscript{194-196} In newborns with AIS, thrombolytic therapy is rarely, if ever, an option, and anticoagulant therapy is controversial. Similar to SVT, anticoagulant therapy is likely not indicated in the presence of a large infarct or significant CNS hemorrhage. In the Canadian Registry of AIS, less than 10% of newborns received anticoagulant medication.\textsuperscript{125} When the etiology of the AIS is clearly embolic, anticoagulant therapy should be seriously considered, even if delayed in institution.

**Summary**

In conclusion, newborns are the group of children in whom TEs most frequently occur, in all locations. Despite this, newborns remain the group of children in whom there is the least information based upon well-designed clinical trials that define the optimal diagnostic methods, optimal treatment and outcome. This article has summarized current information and provided guidelines for treatment. Hopefully, in the future, firm recommendations based on well-designed clinical trials will be available for this important patient population. Development of international cooperative clinical trial groups is required to appropriately determine optimal management pathways to try to reduce the burden of disease caused by TE in newborns.

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