INTRODUCTION

Thrombotic disease is uncommon in newborns. However, this disorder can cause serious morbidity. The pathogenesis, clinical features, and diagnosis of neonatal thrombosis excluding the central nervous system (CNS) are reviewed here. CNS thromboembolic disease and the management of neonatal thrombosis are discussed separately.

COAGULATION AND FIBRINOLYSIS

The components of the coagulation and fibrinolytic systems in newborns are similar to those in older children and adults (figure 1 and figure 2). However, plasma concentrations of these components in newborns differ markedly from children and adults, and the concentrations change from birth through infancy [1-4].

- Concentrations of the vitamin K-dependent coagulation factors (II, VII, IX, X) and contact factors (XI, XII, prekallikrein, high molecular weight kininogen) are 50 to 70 percent of adult values [5]. These values increase rapidly after birth, reaching adult levels of most components by six months of age [1].
- Concentrations of factors V, VIII, XIII, von Willebrand's factor, and fibrinogen are at least 70 percent of adult values [1].
• Coagulation inhibitors (antithrombin, heparin cofactor II, protein C, protein S) are approximately 50 percent of adult levels [1]. However, the concentration of alpha-2 macroglobulin is greater in newborns than adults.
• The rate of thrombin generation in newborn plasma is 30 to 50 percent of adult values [6].
• Concentrations of the fibrinolytic factors plasminogen and alpha-1-antiplasmin are lower than adult values [1]. However, levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) are higher.

The altered concentrations of procoagulant, anticoagulant, and fibrinolytic factors may put newborns at increased risk of bleeding or thrombotic complications compared to older children, especially in the presence of other hemostatic challenges such as indwelling catheters. Other risk factors including metabolic disease or elevated hematocrit also have been identified [7,8].
EPIDEMIOLOGY:

Information on epidemiology comes predominantly from the Canadian and German registries of thrombosis in newborns and children [9,10].

The Canadian registry included 97 cases of symptomatic thrombosis, excluding stroke, submitted from newborn intensive care units (NICUs) in North America, Europe, and Australia during a 30 month period [9]. The incidence was estimated at 24 per 10,000 NICU admissions. In this series, thrombosis was venous, arterial, and mixed in 62, 34, and 4 percent, respectively.

The German registry reported 79 newborns with thrombosis during a two year period [10]. Of the newborns included, 34 (43 percent) were preterm. The incidence of thrombosis, which included stroke, was estimated at 5.1 per 100,000 births. Venous thrombosis occurred in 76 percent of cases.

The mortality rate associated with neonatal thrombosis is high. In the Canadian registry, for example, mortality rates for both aortic and right atrial or superior vena cava thrombosis were 33 percent [9]. However, in this report the majority of newborns with thrombotic disease had underlying critical illness, which likely contributed to the poor outcome.

CLINICAL FEATURES:

The clinical presentation of thrombosis is variable. Signs and symptoms depend upon the location and size of the thrombus. The most common predisposing factor for thrombosis is the presence of a catheter [9,10]. In thrombosis unrelated to a catheter, renal vein thrombosis is the most common [10].

Thrombocytopenia often accompanies thrombosis in newborns. Patients should be evaluated for a thromboembolic disorder if thrombocytopenia cannot be explained by other conditions.

Venous thrombosis: Many cases of venous thrombosis are asymptomatic and detected incidentally [11,12]. Most are associated with central venous catheters [9,13]. The presenting sign may be loss of patency of the catheter.

Central catheters are usually placed through the umbilical vein, major vessels such as the jugular vein, or peripheral veins in the arms or legs. They are widely used to provide intravenous fluids, parenteral nutrition, and medications to term and preterm infants who require intensive care. In a series of 193 infants with central venous catheters, central venous or intracardiac thrombosis occurred in 13 percent [14]. The location of the tip of the catheters may have an effect on the incidence of thrombosis.

Symptomatic thrombosis in the inferior vena cava (IVC) typically presents as swelling of the lower limbs and lower body. Superior vena cava (SVC) thrombosis typically presents as swelling of the arm, neck, and head. The severity of the swelling depends
upon the size of the thrombus. Chylothorax may be the presenting sign of SVC thrombosis [15-17].

The long-term outcome of venous thromboembolic disease in newborns depends upon the location. Portal vein thrombosis related to umbilical venous catheterization may result in portal hypertension [18,19]. Long-term sequelae of renal vein thrombosis include systemic hypertension, renal insufficiency, and renal tubular dysfunction [20]. (See below).

A potential complication is post-thrombotic syndrome, a disorder characterized by edema and impaired viability of subcutaneous tissue in an extremity [13]. The condition is caused by incompetent perforating valves, resulting in blood flow directed from deep to peripheral veins. This disorder has been recognized in children, although the incidence following venous thrombosis in newborns is not known [21].

Portal vein thrombosis: In the neonate, umbilical vein catheterization is associated with an increased risk of portal vein thrombosis (PVT) [18,19,22,23]. This was illustrated in a large retrospective review that reported an overall estimated incidence of portal vein thrombosis detected by abdominal ultrasonography of 3.6 per 1000 admissions [23]. Of the 133 infants identified with portal vein thrombosis, an umbilical vein catheter was inserted in 97 (73 percent) and in half of these cases, catheter placement was placed in a site with low venous flow rate such as an intrahepatic location. Poor outcome was reported in 36 infants as either hepatic lobar atrophy (30 cases) or portal hypertension (6 cases). In this study, the overall incidence of 3.6 per 1000 admissions may be underestimated because not all admitted infants had abdominal ultrasounds. In another study, the incidence of portal vein thrombosis with appropriate placement of umbilical vein catheter was 1.3 percent [22]. In this study [22], the outcome of portal vein thrombosis was associated with ultrasound grading of PVT; 62 percent of the patients with grade 3 PVT had lobar atrophy or portal hypertension.

Renal vein thrombosis: Renal vein thrombosis (RVT) accounts for approximately 10 percent of venous thrombosis in newborns and is the most common form of thrombosis not associated with a vascular catheter [9].

The proposed mechanisms resulting in RVT include reduced renal blood flow, hyperosmolality, hypercoagulability, and increased blood viscosity [24,25]. Risk factors associated with RVT include prematurity, perinatal asphyxia, shock, dehydration, sepsis, polycythemia, cyanotic congenital heart disease, and maternal diabetes [24,26,27]. In addition, there is increasing evidence that infants with RVT are more likely to have an inherited prothrombotic conditions compared to the general population [24,27]. These include factor V Leiden mutation, protein C and S deficiency, methylenetetrahydrofolate reductase (MTHFR) mutation, and elevation of lipoprotein (a).

Renal vein thrombosis (RVT), which may occur as an extension of IVC thrombosis, typically presents with one of the following cardinal features of RVT; flank mass, hematuria, or thrombocytopenia. However, in one series of 23 cases of which 83 percent were diagnosed in the first month after birth, the complete triad was seen in only 13 percent [20].
The clinical presentation of neonatal RVT was demonstrated by a systematic review of the literature from 1992 to 2006 that identified 271 patients from 13 case series [28]. The following findings were noted:

- The time of presentation varied and occurred in-utero (7 percent), by three days of life (67 percent), and after three days of life but before one month of age (26 percent). Most of the patients were born fullterm (71 percent) and there was a male predominance (67 percent).
- Patients had one or more of the following findings at presentation; gross hematuria (56 percent), thrombocytopenia (48 percent), and/or a palpable abdominal mass (45 percent).
- Approximately 70 percent of cases were unilateral, which involved the left kidney in two-thirds of these patients.
- In approximately 44 percent of cases, the thrombus extended into the IVC and adrenal hemorrhage occurred in 15 percent of patients.
- Perinatal risk factors including asphyxia were identified in 32 percent of cases. Other reported risk factors included maternal diabetes mellitus (8 percent) and dehydration (2 percent).
- Among the 149 patients in whom prothrombotic factors were investigated, 53 percent had at least one risk factor identified.

Neonates with RVT have significant mortality and morbidity, particularly with chronic kidney damage that can result in hypertension and renal failure [25,27].

In the previously discussed systematic review (although outcome was not reported consistently in the 13 studies), there were nine reported deaths, all of which were related to coexisting medical conditions (eg, respiratory failure, multiorgan failure, and sepsis) [28]. In the studies that reported long-term outcome, 20 percent of infants were hypertensive (27 of 140 patients), and 71 percent had evidence of irreversible renal damage (156 of 221 patients) including eight patients who required chronic renal replacement therapy (eg, dialysis and transplantation).

Right atrial thrombosis: Right atrial thrombosis is associated with central venous catheter placement. In one report, this disorder was detected by prospective echocardiography in the first few days after birth in 4 of 76 (5 percent) very low birth weight infants who had umbilical catheters [29]. Symptomatic intracardiac thrombosis can present as a new murmur, heart failure, or persistent sepsis, as well as malfunction of the catheter [13]. A systematic review suggests that a right atrial thrombosis that is small (<2 cm in every dimension) and is neither mobile nor snake-shaped can be treated with a conservative approach [30].

Arterial thrombosis: Nearly all cases of arterial thrombosis are associated with arterial catheters [13]. Umbilical and peripheral (radial, posterior tibial) artery catheters are typically used for monitoring of blood pressure and blood gases; the femoral artery is often used for cardiac catheterization.

The incidence of arterial thrombosis is variable and depends in part upon the method of detection used. Thrombosis that resulted in occlusion of an umbilical artery catheter (UAC) occurred in 0 to 13 percent of cases when unfractionated heparin was used and 13 to 73 percent without heparin [13].
Umbilical artery catheter: UAC-associated thromboses are usually asymptomatic. However, some present with signs of severe ischemia or organ dysfunction. Depending upon the location of the thrombus, signs can include coolness, poor perfusion, and blanching of a toe, one or both limbs, or the buttocks, or mimic aortic coarctation. Occlusion of the renal, mesenteric, or branches of the spinal arteries can result in hypertension with or without renal failure [31], necrotizing enterocolitis, and spinal cord infarction [32,33].

Peripheral artery occlusion: The incidence of thrombosis associated with peripheral artery catheterization in newborns is not known [13]. Clinical signs include decreased or absent peripheral pulses, diminished perfusion with a prolonged capillary refill time, and a cool, pale extremity. The diagnosis can be confirmed by Doppler ultrasound.

Severe thrombosis in an extremity can result in long-term arterial insufficiency. This may impair growth of the affected limb [34].

Purpura fulminans: Purpura fulminans can result from deficiencies of either protein C, protein S, or both [35]. It can also accompany sepsis or disseminated intravascular coagulation. This disorder is extremely rare.

Purpura fulminans is characterized by microvascular thrombosis in the dermis followed by perivascular hemorrhage, necrosis, and minimal inflammation [35]. The lesions can progress very quickly into full-thickness necrotic injury of the skin that is not reversible.

**DIAGNOSIS:**

The diagnosis of vascular thrombosis is confirmed by imaging. Infants with thrombosis should be evaluated for prothrombotic disorders.

Imaging: Contrast angiography is considered the gold standard. However, it is rarely used because newborns with thrombosis are usually severely ill.

Ultrasound examination is used to confirm thrombosis in most cases. The advantages of this technique are that it is noninvasive, does not require exposure to ionizing radiation, and can be performed at the bedside.

The accuracy of ultrasound may be reduced by the presence of a catheter because reduced compressibility of the vessel lumen by the ultrasound probe (a sign of thrombosis) is difficult to assess [13]. Interpretation may also be limited by the low pulse pressure in preterm and sick newborns.

In one series of 47 infants with umbilical venous catheters, the accuracy of Doppler echocardiography was poor compared to contrast venography in detecting asymptomatic thrombus [12]. Thrombi were detected by venogram in 14 patients (30 percent). The sensitivity and specificity of echocardiographic diagnosis for the three cardiologists who interpreted the studies ranged from 21 to 43 and 76 to 94 percent, respectively. However, the relative accuracy of these techniques to detect symptomatic thrombosis is not known.
Renal vein thrombosis imaging: Ultrasound is the most commonly used imaging technique to confirm the diagnosis of RVT. The ultrasound features depend upon the timing of the examination [36-38]. During the first few days, echogenic streaks appear in a peripheral focal segment of the affected kidney. During the first week, the kidney appears swollen and echogenic, with prominent and less echogenic medullary pyramids. As the swelling decreases, the kidney appears heterogeneous with loss of corticomedullary differentiation. The kidney may subsequently atrophy with focal scarring or recover. Color Doppler ultrasonography may show absent intrarenal and renal venous flow in the early stages of RVT [36]. Indeed, the sonographic findings can be used to predict outcome [39].

Coagulation studies: Prothrombotic disorders, including deficiencies of antithrombin, protein C, protein S, and plasminogen; factor V Leiden mutation and prothrombin G20210A; methylenetetrahydrofolate reductase C677T (MTHFR667), and elevated fasting homocysteine; and elevated lipoprotein (a) have been associated with thromboembolism in newborns and children [11,13]. However, the incidence of these disorders in newborns with thrombosis is not known and the contribution of the prothrombotic state to the pathogenesis of neonatal thrombosis is uncertain [40].

We perform an evaluation for prothrombotic disorders in all newborns with clinically significant thrombosis. Whether newborns with catheter-related thrombosis require these studies is uncertain. In one study of 53 infants, there was no increased risk of prothrombotic genetic disorders (ie, factor V Leiden mutation, MTHFR 667, and prothrombin G20210A) in the 16 infants with umbilical catheter (UC) thrombosis compared to those without UC thrombosis [41]. However, patients with thrombosis that is not catheter-related and those with recurrence should be evaluated. A meta-analysis concluded that an inherited prothrombotic state increases the risk of thrombosis in neonates [42]. Prothrombotic states are associated with recurrence (except factor V Leiden and lipoprotein (a)). However, for individuals presenting with thrombosis as a neonate, the recurrence is often a distant event, occurring at the earliest in the teenage years.

Neonatal values for coagulation and fibrinolytic factors should be compared to reference ranges for postnatal and gestational age [43]. Abnormal values should be repeated in four to six weeks and parents should be counseled about the results. Consultation with a pediatric hematologist should be obtained for patients with prothrombotic disorders, and family members should be evaluated after appropriate counseling.

The following studies should be obtained at presentation of a thrombotic event:

- Antithrombin, protein S, and protein C concentrations should be measured in the newborn. Tests that are abnormal in the newborn should be repeated in six to eight weeks. Deficiencies of antithrombin, protein S, and protein C are extremely rare.
- The infant should be tested for the factor V Leiden mutation and prothrombin G20210A. These conditions are most frequent in individuals of European white ethnicity and rare in those with Asian and African ancestry [11,44,45]. Testing can be deferred if blood sampling is difficult because the results will not affect
therapy, although they may affect risk of recurrent thrombosis. Alternatively, these conditions can be excluded by testing the parents.

- Prothrombin time (international normalized ratio, INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen concentration should be measured in the newborn for a baseline before initiation of any therapy.
- Maternal blood should be tested for lupus anticoagulant and anticardiolipin antibody.
- Both parents should be tested for the prothrombotic state if the results of the newborn's tests are abnormal. The results of the parents' studies will help to distinguish acquired from congenital deficiencies.

Evaluation for other prothrombotic disorders should be considered in newborns if thrombosis is severe, recurrent, or spontaneous. These disorders include increased lipoprotein (a) concentration, deficiency of methylenetetrahydrofolate reductase or plasminogen, and dysfibrinogenemia. Homocysteine concentration can be measured in maternal serum if homocystinuria is suspected; newborn screening is available for this disorder in many states.

SUMMARY AND RECOMMENDATIONS

- Newborn infants are at risk for thrombosis because plasma concentrations of procoagulant, anticoagulant, and fibrinolytic factors are altered as compared with older children and adults. The risk is dramatically increased by the presence of an indwelling catheter, or by medical conditions predisposing to thrombosis, including prematurity and sepsis.
- Thrombocytopenia often accompanies thrombosis and should prompt an evaluation for thrombosis.
- Most venous thrombi are asymptomatic. Many are associated with an indwelling venous catheter, in which case a common presenting symptom is loss of catheter patency. When symptomatic, thrombosis of the inferior vena cava (IVC) or superior vena cava (SVC) may present with swelling of the affected extremities.
- Portal vein thrombosis is a complication of umbilical vein catheterization and develops in approximately 1 percent of infants with appropriately placed catheters; rates are higher if the catheter is placed in a zone of lower flow such as the liver. Portal vein thrombosis may lead to hepatic lobar atrophy or portal hypertension.
- Renal vein thrombosis (RVT) accounts for approximately 10 percent of venous thrombosis in newborns and is the most common form of thrombosis not associated with a vascular catheter. RVT typically presents with flank mass, hematuria, or thrombocytopenia. Risk factors for RVT include prematurity, perinatal asphyxia, dehydration, sepsis, polycythemia, cyanotic congenital heart disease, maternal diabetes, and inherited prothrombotic conditions.
- Right atrial thrombosis is associated with central venous catheter placement. It can present as a new murmur, heart failure, or persistent sepsis, as well as malfunction of the catheter.
- Arterial thrombosis is almost always associated with arterial catheters, such as umbilical and peripheral artery catheters are typically used for monitoring of
blood pressure and blood gases or femoral artery is often used for cardiac catheterization.

- Arterial thrombosis associated with umbilical artery catheters may be asymptomatic, or may present with ischemia or organ dysfunction, depending on the location of the thrombus.
- Arterial thrombosis associated with peripheral artery catheters may present with decreased or absent peripheral pulses, diminished perfusion with a prolonged capillary refill time, and a cool, pale extremity. If severe, thrombosis in an extremity can result in long-term arterial insufficiency and may impair growth of the affected limb.

- The diagnosis of thrombosis is suspected based on risk factors (eg, the presence of an indwelling catheter) and clinical symptoms, and confirmed by imaging. Ultrasound imaging is used in most cases, although its accuracy may be limited by the presence of an indwelling catheter.
- We perform an evaluation for prothrombotic disorders in all newborns with clinically significant thrombosis, particularly if the thrombosis is not related to an indwelling catheter or is recurrent. Neonatal values for coagulation and fibrinolytic factors should be compared to reference ranges for postnatal and gestational age.

REFERENCES


MANAGEMENT OF THROMBOSIS IN THE NEWBORN

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INTRODUCTION

Thrombotic disease is uncommon in newborns. However, this disorder can cause serious morbidity. The management of neonatal thrombosis excluding the central nervous system (CNS) is reviewed here. The pathogenesis, clinical features, and diagnosis of this disorder and CNS thromboembolic disease are discussed separately.

GENERAL APPROACH

The management of neonatal thrombosis is extrapolated largely from data in adults. Little information is available on management strategies or the efficacy and safety of therapeutic agents.

The approach to an individual infant must balance the risks and benefits.

- For asymptomatic thrombosis, we suggest supportive care and close monitoring of the size of the thrombus [1]. This approach avoids development of bleeding complications that may be associated with anticoagulant or fibrinolytic therapy. If the thrombus extends, we suggest treatment [1]. Alternatively, initial treatment with anticoagulant is a reasonable option. Treatment with anticoagulant at the start is an option.
- For severe symptomatic thromboembolic we suggest treatment with anticoagulation and/or fibrinolytic agents. However, these strategies have not been studied in clinical trials, and data on outcome are sparse [2,3]. The management of less severe events also is uncertain.
Central venous lines or umbilical venous catheters associated with thrombosis should be removed, if possible, after three to five days of anticoagulation [1].

Surgical thrombectomy rarely is performed in newborns [4,5]. In general, this procedure is limited by the small size of blood vessels and the clinical instability of newborns with thrombosis.

Baseline testing: Before antithrombotic therapy is initiated, baseline coagulation testing should be performed. Tests should include:

- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT) and international normalized ratio (INR)
- Plasma fibrinogen concentration
- Platelet count

A cranial ultrasound examination should be done to exclude bleeding. It is especially important for premature infants, who are at increased risk of developing an intracranial hemorrhage. During anticoagulant treatment, the platelet count should be maintained at >50,000/microL, and fibrinogen concentration should be >1 g/L.

**ANTICOAGULANT THERAPY:**

Anticoagulant therapy in the newborn generally consists of administration of standard heparin or low-molecular-weight heparin (LMWH).

Heparin: Standard heparin, also known as unfractionated heparin (UFH) is an indirect thrombin inhibitor that complexes with antithrombin (AT, formerly known as AT III) and converts it from a slow to a rapid inactivator of thrombin, factor Xa, and, to a lesser extent, factors XIIa, XIa, IXa, and VIIa [6,7]. The binding of AT to heparin is mediated by a unique pentasaccharide sequence that is distributed randomly along the heparin chains [8]. The inactivation of thrombin, but not factor Xa, requires the formation of a ternary complex in which heparin binds to both AT and thrombin (figure 1) [9]. This ternary complex (containing heparin, AT, and thrombin) forms only on pentasaccharide-containing chains with at least 18 saccharide units, which is true of most chains of UFH but is less common in LMWH, which therefore have less antithrombin activity [10].

The advantages of UFH are its rapid reversibility and low cost. Disadvantages include its unpredictable pharmacokinetic response and resultant requirement for frequent monitoring.

Infusion of UFH in newborns requires a dedicated intravenous catheter. This avoids interruption of anticoagulation therapy by infusion of other medications and minimizes the risk of inadvertent flushing of the catheter that may lead to excessive anticoagulation.

Dose: The dose of heparin therapy in newborns is based upon a prospective cohort study of UFH treatment in 65 children with thrombosis, of whom 29 were less than one year of age, including 13 newborns [11]. Heparin is administered intravenously in a loading dose of 75 units/kg and an initial maintenance dose of 28 units/kg per hour.
UFH dosing in the neonate should be titrated to both aPTT and anti-factor Xa activity. Significance of the clot and the potential risk of bleeding should also be considered when adjusting the UFH dose [1,12]. We suggest titrating the dose of UFH to achieve an anti-factor Xa level of 0.35 to 0.7 units/mL, and also an activated partial thromboplastin time (aPTT) that is 1.5 to 2 times the upper limit of normal [1]. This contrasts to the approach to dose adjustment in adults, in whom the aPTT range can be used alone because this generally corresponds to an anti-factor Xa activity of 0.35 to 0.7 U/mL [1]. The additional monitoring is necessary for neonates because they have an increased clearance rate of heparin compared with older children or adults [11]. In addition, the efficacy of heparin may be reduced in newborns because the physiologic plasma concentration of antithrombin is low [13,14].

The duration of therapy is uncertain. Our approach is to monitor the thrombus with ultrasound and continue therapy until the thrombus has resolved (with the usual duration of therapy being six weeks to three months) [1]. If the thrombus does not resolve the therapy should be continued for as long as three months, after which we discontinue anticoagulation. If treatment is needed for longer than two weeks, we switch to LMWH.

If the thrombus extends, the heparin therapy may not be optimal. In this case, the dose of UFH can be increased. Alternatively, LMWH, which has a more predictable anticoagulant response, can be used.

Adverse effects:

The major side effects of UFH are bleeding, heparin-induced thrombocytopenia (HIT), and osteoporosis [10]. The risk of bleeding in newborns is uncertain. As in adults, bleeding likely relates to the concentration of heparin as well as underlying disorders that would predispose to bleeding [15]. In one series, no bleeding occurred in 13 newborns given UFH for treatment of thromboembolic disease or prophylaxis [11]. However, aPTT levels were subtherapeutic in most of these patients.

If bleeding occurs, UFH should be discontinued. For heparin reversal, 1 mg of protamine sulfate can inactivate 100 units heparin. The dose of protamine depends upon the amount of heparin being given, and is calculated by assuming the half-life of heparin to be one hour.

Heparin-induced thrombocytopenia: HIT is a well-recognized complication of heparin therapy in adults [16-19]. Two major mechanisms cause this thrombocytopenia. One mechanism appears to be a direct effect of heparin on platelet activation. In most of these cases, the fall in platelet count occurs within the first two days after heparin initiation, often returns to normal with continued heparin administration, and is of no clinical consequence, at least in adults. The incidence of this type is estimated at 10 to 20 percent of adults receiving UFH. The second type is mediated by antibodies to a heparin-platelet factor 4 complex, which results in platelet activation and aggregation and enhanced generation of thrombin [20,21]. This occurs in 3 percent or less of adults receiving UFH for more than four days [17-19].
HIT has been described in newborns [22,23]. However, it is difficult to evaluate the incidence because critically ill newborns have many reasons to have thrombocytopenia and/or thrombosis.

One report described 34 newborns (mean gestational age 29 weeks) who developed thrombocytopenia (platelet count <70,000/microL, n = 23), a precipitous fall of 30 to 50 percent in the platelet count (n = 5) or thromboses (n = 6) while receiving heparin [22]. Heparin-associated antiplatelet antibodies were found in 14 patients; these patients had clinical characteristics comparable to the 20 infants without antibodies, including the presence of an umbilical artery catheter in all but one patient in each group. Among those who had abdominal ultrasonography, aortic thrombosis occurred in 11 of 13 (84 percent) infants with and 5 of 20 (25 percent) without antibodies. Bleeding was not observed. However, the sensitivity of ultrasound to detect an asymptomatic thrombus in newborns is poor [24]. Thus, the relationship between antibody formation and thrombosis in this population remains uncertain.

HIT should be considered in a newborn with thrombocytopenia of no apparent cause, although HIT is uncommon and other causes of thrombocytopenia occur frequently. In addition, experience with anticoagulants other than heparin is very limited in this age group. Thus, in most cases, heparin therapy should be continued, and the platelet count should be maintained by transfusion.

Osteoporosis: Osteoporosis has been reported in adult patients receiving UFH for more than six months [6]. Bone loss is thought to occur because of decreased bone formation, increased bone resorption, or both. Although cases of osteoporosis associated with heparin have been reported in children, there is no information on this complication in newborns [25].

Low molecular weight heparin: Low molecular weight heparins (LMWHs) have many advantages over UFH [10,26]. These include greater bioavailability when given by subcutaneous injection, longer duration of anticoagulant effect, and clearance that is independent of dose, which results in a more predictable response. They can be administered subcutaneously and require minimal laboratory monitoring and dose adjustment; these are important for newborns with poor venous access. Potential advantages are the reduced risk of immune-mediated thrombocytopenia and osteoporosis.

Because LMWH has a relatively predictable and stable anticoagulation response, we suggest using LMWH over UFH for treatment of neonatal thrombosis, provided that an assay of anti-factor Xa activity (required to monitor the anticoagulation effect of LMWH) is readily available. In clinical settings in which an assay of anti-factor Xa activity cannot be performed with results available within one to two days, UFH should be considered. The physicians' familiarity with the anticoagulant also is an important consideration in choosing LMWH versus UFH.

LMWH is prepared from UFH by chemical or enzymatic methods. Like UFH, LMWH potentiates the inactivation of factor Xa by antithrombin (AT). However, the effect of LMWH on the AT inhibition of thrombin is decreased compared with UFH because most of the molecules in LMWH do not contain enough saccharide units to form the ternary complex in which thrombin and AT are bound simultaneously (figure 1) [10].
As a result, LMWH in the usual therapeutic dose usually does not prolong the aPTT. The aPTT can be prolonged by higher doses of LMWH but not to the same extent as UFH.

Based on limited information, LMWH appears to be safe and effective in newborns. One prospective cohort study included 173 children who were treated with enoxaparin because they had or were at high risk for thromboembolic events [3]. Patients ranged in age from 1 day to 18 years; 21 (14.5 percent) were <36 weeks gestational age and 48 (33.5 percent) were <3 months postnatal age when treatment was initiated. Thrombi resolved clinically in 94 percent of patients who received therapeutic doses. In those receiving prophylaxis, 96 percent had no symptoms of new or recurrent thromboembolic events. Major bleeding occurred in seven (4 percent) patients, of whom four were newborns.

Dose: There are several LMWH preparations and they should not be used interchangeably [27]. In the United States, four preparations (enoxaparin, dalteparin, ardeparin, and tinzaparin) are currently approved by the FDA for different clinical indications. Dosing in pediatric patients has been reported for enoxaparin [28], dalteparin [29], tinzaparin [30] and nadroparin[31].

For treatment: of thrombosis, enoxaparin is initiated in a dose of 1.7 mg/kg per dose subcutaneously twice each day in term infants and 2.0 mg/kg per dose twice each day in preterm neonates [3,28,32]. Doses are adjusted to maintain an anti-factor Xa concentration (measured four hours after the dose) of 0.5 to 1 U/mL, which is also the therapeutic range established in adults [1,33]. We do not recommend the use of dalteparin and tinzaparin in neonates because data on its use are still limited.

For prophylaxis, enoxaparin is initiated at 0.75 mg/kg per dose twice each day. The target concentration of anti-factor Xa for prophylaxis is 0.1 to 0.3 U/mL, which is lower than the target range for treatment [3].

The duration of therapy is uncertain, although the usual duration is six weeks to three months. One approach is to monitor the thrombus with ultrasound and continue therapy until the thrombus has resolved and the patient is entirely asymptomatic; if the thrombus was related to a CVL the CVL should also have been removed before stopping therapy [1]. If the thrombus does not resolve the therapy should be continued up to three months.

If bleeding occurs, LMWH should be discontinued. The dose of protamine sulfate depends upon the dose of LMWH and the time since LMWH was administered last. If LMWH was given within four hours, the maximum dose of protamine is 1 mg per 100 units LMWH, given by slow IV push. If LMWH was given more than four hours previously, a lower dose of protamine should be used. However, protamine only partially neutralizes the effects of LMWH [34].

Warfarin: Warfarin is an oral anticoagulant that should not be used in newborns because of the potential risk of bleeding [25]. The effect of warfarin is caused by reduction of the functional plasma concentration of the vitamin-K dependent coagulation factors (factors II, VII, IX, and X). However, the concentration of these factors is physiologically reduced in newborns and often is similar to those of adults receiving
warfarin therapy. Newborns also may have borderline levels of vitamin K, increasing the risk of warfarin-induced bleeding. Because human milk has low concentrations of vitamin K, breastfed newborns are especially sensitive to the effect of warfarin. On the other hand, infant formulas are supplemented with vitamin K, rendering formula fed newborns relatively resistant to treatment.

Another problem with warfarin administration in newborns is its availability only in tablet form. Splitting or crushing the tablet into powder form may cause variability in the dose. In addition, treatment with warfarin requires frequent monitoring of INR.

Other agents: Novel anticoagulants, including direct thrombin inhibitors, are under investigation in children [35]. Optimal properties of these drugs include administration by multiple routes, minimal need for monitoring, and few side effects. None have been tested in newborns.

THROMBOLYTIC AGENTS:

Thrombolytic drugs currently used are intravenously infused plasminogen activators, which promote the conversion of plasminogen to plasmin, with subsequent cleavage of fibrin, fibrinogen, and factors V and VIII, resulting in clot breakdown (figure 2) [2,25]. The thrombolytic activity of these agents may be reduced in newborns because their decreased plasminogen concentration compared with adults leads to decreased generation of plasmin [36,37]. Supplementation with plasminogen by administration of fresh frozen plasma may improve fibrinolytic activity [2].

Fibrinolytic therapy is considered if thrombi are thought to be life-threatening or severely compromising to organs or limbs. Thrombocytopenia (platelet count <100,000/microL), low fibrinogen concentration (<1 g/dL), and severe deficiency of coagulation factors should be corrected before initiating treatment. Contraindications to treatment include major surgery or hemorrhage within the previous 10 days,
neurosurgery within three weeks, a severe asphyxial event within seven days, an
invasive procedure within the previous three days, seizures within 48 hours, prematurity
<32 weeks gestation, systemic septicemia, active bleeding, or the inability to maintain
platelets >100,000/microL or fibrinogen >1 g/dL [38].

Recombinant tissue-type plasminogen activator: Recombinant tissue-type plasminogen
activator (tPA) is the thrombolytic agent of choice. Streptokinase and urokinase also
have been used in newborns. Compared to the others, tPA has improved clot lysis in
vitro [36] and a lower risk of hypersensitivity [39]. Urokinase is not labeled for this
indication in the United States, nor is it approved for use in children.

No clinical trials have evaluated thrombolytic agents in newborns. Treatment of
neonatal thrombosis with tPA is described in case reports and case series using a variety
of doses and treatment regimens [40-45]. As an example, one report described the
authors' experience with treatment of catheter-related thrombus in 14 patients and
reviewed the literature [40]. Treatment with tPA resulted in complete dissolution of the
clot in 11 of the 14 patients and partial lysis in two cases. No severe complications,
including intracranial hemorrhage, occurred. Comparable results were found in a
summary of 80 newborns treated with tPA for spontaneous and catheter-related
thrombosis described in 29 reports [40]. Clot dissolution occurred completely or
partially in 68 and 26 percent of cases, respectively.

Bleeding complications varied widely among reports, with a range of major bleeding
episodes of 0 to 57 percent [40-45]. Because critically ill and preterm newborns are at
risk for hemorrhage in the absence of thrombolytic therapy, information about the risk
of bleeding complications with tPA awaits controlled trials.

Dose: The dose of tPA in newborns is extrapolated from doses in older children and
adults. For systemic therapy, tPA is given in a continuous infusion at a rate of 0.1 to 0.6
mg/kg per hour for six hours, without a loading dose [1]. The drug can be given through
a central or peripheral venous catheter.

Fibrinogen concentration should be measured before and two hours after initiating
therapy, and if bleeding occurs. Fresh frozen plasma and/or cryoprecipitate should be
given if the fibrinogen concentration is <1 g/L or if there is bleeding [1].

Aside from resolution of the thrombus, there is no easy way to measure the
effectiveness of the tPA infusion. The presence of d-dimers or fibrin/fibrinogen
degradation products indicates a fibrinolytic state. Measurement of aPTT may not be
useful if fibrin/fibrinogen degradation products are present, fibrinogen levels are low, or
concurrent heparin therapy is given.

Treatment of bleeding after use of tPA includes use of cryoprecipitate to increase the
fibrinogen concentration, stopping the tPA infusion if possible, and administration of
platelets if needed. Administration of epsilon aminocaproic acid (which inhibits
activation of plasminogen to plasmin) is not needed because tPA has a very short half-
life, and bleeding usually responds to these measures.

Other fibrinolytic agents have been used in adults [46]. Data on their use are not
available for children.
TREATMENT FOR THROMBOSIS IN DIFFERENT LOCATIONS:

As discussed above, data are limited on the outcome of antithrombotic therapy in newborns. An approach is provided below for treatment of thromboembolic conditions.

Before initiating treatment, consultation should be obtained from a pediatric hematologist experienced in the management of these disorders. For additional consultation, a free service is provided by a group of physicians who have extensive experience in neonatal thrombosis (1-800-NOCLOTS) [47].

Renal vein thrombosis: There are no randomized trials in the treatment of neonatal renal vein thrombosis (RVT), and reported data are based upon retrospective case series. In a systematic review of the literature from 1992 to 2006 that identified 271 patients from 13 case series, the following treatment modalities were used in the 232 patients with available data on management [48]. The frequency of use is also included.

- Supportive care alone — 40 percent
- Unfractionated heparin (UFH) — 22 percent
- Low molecular weight heparin (LMWH) — 21 percent
- Fibrinolytic therapy — 11 percent
- Anti-thrombin therapy — 2 percent
- Warfarin — 1 percent
- Surgical intervention — <1 percent
- Combination of treatment — 4 percent

The renal outcome of the affected kidney did not differ in patients who were treated with supportive care or with heparin therapy (ie, UFH and LMWH) with atrophy of the affected kidney in 76 versus 73 percent of cases at last follow-up, respectively.

Unilateral RVT without compromised renal function or extension into the inferior vena cava (IVC) is managed initially with close observation and supportive care. This approach is supported by a comprehensive review of the literature [48] and by a small observational study that demonstrated anticoagulant treatment of unilateral renal thrombosis did not improve outcome of the affected kidney [49]. A central catheter in the IVC should be removed if present. Alternatively, the neonate can be started on anticoagulation therapy, which is advocated by some experts because renal vein thrombosis occasionally leads to serious complications including death [50]. Supportive care with close monitoring or anticoagulation therapy is both acceptable alternatives. If thrombosis progresses or there is extension into the IVC, UFH or LMWH is recommended [1].

If RVT is bilateral, with or without compromised renal function, we begin heparinization, unless there are contraindications to its use. In this case, UFH should be used because LMWH accumulates with renal insufficiency [1,51]. Concomitant use of fibrinolytic therapy should also be considered [49].

If LMWH is used in patients with renal insufficiency, the dose should be reduced. There are no data regarding dose adjustment of LMWH in neonatal renal failure. This author's approach is to decrease the dose in proportion to the degree of renal insufficiency (eg, 25 percent of the dose is used for infants estimated to have 25 percent of renal function).
and make further adjustments according to the antifactor Xa level. Thrombolytic therapy should be considered for bilateral RVT and renal failure.

Right atrial thrombosis: Right atrial thrombosis usually is associated with the use of central venous catheters and may compromise cardiac function or lead to pulmonary embolism. If possible, the catheter should be removed. We usually begin anticoagulation therapy with UFH or LMWH. If anticoagulation therapy is not begun, the thrombus should be monitored closely. UFH or LMWH should be started if the thrombus increases in size [52]. We begin thrombolytic therapy with tPA if cardiac function is compromised.

Arterial thrombosis: Treatment should be initiated for arterial thrombosis that causes significant impairment of blood flow to an extremity or vital organ. An associated arterial catheter should be removed. If viability of the organ or limb is not immediately threatened, we usually begin anticoagulation therapy with LMWH or UFH [1].

Thrombolytic therapy with tPA should be given in conditions that are life-threatening or if the viability of a limb or organ is jeopardized [1]. Anticoagulant treatment with UFH should be started (without a bolus) during the tPA infusion. The thrombus should be monitored by clinical examination and ultrasonography.

The duration of anticoagulation therapy depends upon the clinical course. If the thrombus resolves, we use a short course (10 to 14 days). If the thrombus persists, we continue LMWH for three months.

NEONATAL PURPURA FULMINANS:

Purpura fulminans in newborns is a rare life-threatening condition characterized by disseminated intravascular coagulation and hemorrhagic skin necrosis [53]. It usually is caused by homozygous or compound heterozygous deficiency in protein C or S, a mechanism that is consistent with the observation of consanguinity in some affected families [53-59]. The heterozygous parents of these infants have type 1 protein C deficiency but infrequently have a history of thrombosis. A similar consumptive coagulopathy occurs in mice in which inactivation of the protein C gene led to total protein C deficiency [60]. Purpura fulminans also can result from acquired protein C deficiency due to consumptive coagulopathy, as in meningococcemia [53].

Clinical presentation: Neonatal purpura fulminans usually occurs on the first day of life. Affected infants present with ecchymoses, extensive venous and arterial thromboses (initially at sites of trauma), laboratory evidence of disseminated intravascular coagulation (thrombocytopenia, hypofibrinogenemia, and increased PT and aPTT times), and extremely low levels of protein C antigen (less than 1 percent of normal) [54-56,61-65]. Delayed presentation of the disorder (after six months of age) has been reported [66].

Diagnosis: The diagnosis of protein C or S deficiency is made by testing a citrated plasma sample for protein C and S activity [53]. The sample must be collected prior to initiation of treatment, but treatment should not be delayed while awaiting the results. Results should be compared to age-specific reference ranges because protein C and S activity in healthy neonates is substantially lower than in older children or adults.
Ideally, the diagnosis is confirmed with genetic testing; a list of clinical laboratories that perform genetic testing for this disorder is available at the GeneTests website.

Initial treatment: Neonatal purpura fulminans is initially treated with a source of exogenous protein C; heparin and antiplatelet agents are ineffective [55,61-65]. Either fresh frozen plasma or protein C concentrate has been used with success:

- Fresh frozen plasma (FFP) is given at a dose of 10 to 20 mL/kg every 12 hours [1,67]. Frequent dosing is necessary because the half-life of protein C in the circulation is only about 6 to 16 hours. However, administration of FFP on a frequent basis is limited by the development of hyperproteinemia, hypertension, loss of venous access, and the potential for exposure to infectious viral agents [68,69].
- A highly purified concentrate of protein C (Ceprotin, Baxter [70]) is given at a starting dose of 100 units/kg IV, followed by 50 units/kg IV every six hours [53,71,72]. Protein C concentrate is available in the United States and Canada for compassionate use in this condition.

Subsequent dosing of FFP or protein C concentrate depends upon the patient's response because the half-life of protein C may be shortened considerably during acute thrombosis. The dose is titrated to achieve a trough level of protein C activity of 50 int. units/dL [53]. Treatment is continued until the lesions resolve (typically within six to eight weeks) and the infant is transitioned onto other anticoagulants.

Long-term management: Infants with purpura fulminans must be treated indefinitely with an anticoagulation regimen to prevent thrombosis [56,61,73-75].

Options for long-term management include LMWH (target anti-factor Xa concentration 0.5 to 1 U/mL), protein C supplementation (given subcutaneously), or oral warfarin therapy, or a combination of these drugs. If warfarin therapy is used, the INR usually should be maintained between 2.5 to 3.5. A lower INR of 1.5 to 2.5 is appropriate if the patient is also treated with protein C concentrate; a higher INR of 3 to 4.5 is appropriate if the patient has warfarin-induced skin necrosis [76]. Because LMWH has a predictable and stable anticoagulation response, we generally prefer it over warfarin for use in this age group, as discussed above. A subcutaneous preparation of protein C has been developed which requires administration every third day; this preparation avoids the potential hazards of long-term central venous access [77-80].

Liver transplantation can correct homozygous protein C deficiency and has been used for a patient for whom protein C replacement therapy was not available [81]. A combined liver and renal transplant was successfully used for a patient who developed renal failure due to renal vein thrombosis [82].

**PREVENTION OF THROMBOSIS**

Arterial catheters: To prevent thrombosis, fluid infused through an umbilical artery catheter should contain UFH in a concentration of 0.5 to 1.0 units/mL [1]. In a systematic review of five trials by the Cochrane database, heparinization decreased the risk of catheter occlusion (relative risk 0.20, 95% CI: 0.11-0.35) [83]. The risk of aortic thrombosis, intraventricular hemorrhage, death, or clinical ischemic events did not
appear to be affected, although the small sample size resulted in wide confidence intervals.

Fluid infused through a peripheral artery catheter also should be heparinized, using a similar concentration. Use of UFH prolongs the patency of peripheral catheters, although data are limited in newborns [84-86].

Central venous catheters — Fluid infused through a central venous catheter should contain heparin in a concentration of 0.5 units/mL to prevent thrombosis and catheter occlusion. However, heparinization of central venous catheters (umbilical or peripherally placed percutaneous) has not been studied in well designed trials [87].

Obstructed central venous catheters can be cleared with local instillation of tPA (0.25 to 0.50 mg) [38]. It is important to limit the volume infused to the dead space of the catheter to avoid systemic administration of tPA.

SUMMARY AND RECOMMENDATIONS

- The management of neonatal thrombosis is extrapolated largely from data in adults. Little information is available on management strategies or the efficacy and safety of therapeutic agents. In general, asymptomatic thrombosis is managed by close monitoring of the size of the thrombus and by providing supportive care. Severe symptomatic thromboembolic events typically are treated with anticoagulation and/or fibrinolytic agents. Surgical thrombectomy rarely is performed in newborns.
- Before antithrombotic therapy is initiated, baseline coagulation testing should be performed, including activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR), plasma fibrinogen concentration, platelet count, and cranial ultrasound examination.
- Standard heparin, also known as unfractionated heparin (UFH), may be used in newborns. The advantages of UFH are its rapid reversibility and low cost. Disadvantages include its unpredictable pharmacokinetic response and resultant requirement for frequent monitoring and the need for a dedicated intravenous catheter to avoid interruption of anticoagulation therapy. The major side effects of UFH are bleeding, heparin-induced thrombocytopenia (HIT), and osteoporosis. UFH dosing in the neonate should be titrated to both aPTT and anti-factor Xa activity.
- We suggest that low molecular weight heparin (LMWH) be used rather than UFH for treatment of neonatal thrombosis, provided that an assay of anti-factor Xa activity (required to monitor the anticoagulation effect of LMWH) is readily available (Grade 2C). LMWH is administered subcutaneously, requires less laboratory monitoring and dose adjustment, and probably has reduced risk of immune-mediated thrombocytopenia and osteoporosis as compared with UFH. There are several LMWH preparations and they should not be used interchangeably. By contrast, UFH is preferred over LMWH in patients with renal insufficiency.
- We recommend AGAINST thrombolytic therapy for neonatal thrombosis unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 1B). Contraindications to fibrinolytic therapy include recent or expected surgery, or by a variety of other conditions. This intervention should be undertaken with
caution because of significant risks of major bleeding. Recombinant tissue-type plasminogen activator (tPA) is the thrombolytic agent of choice.

- For neonates with unilateral renal vein thrombosis (RVT) without compromised renal function or extension into the inferior vena cava (IVC), either supportive care with close monitoring or anticoagulation therapy are acceptable alternatives. If thrombosis progresses or there is extension into the IVC, we suggest treatment with UFH or LMWH (Grade 2C). We also suggest heparinization if RVT is bilateral and renal function is compromised (Grade 2C), unless there are contraindications to its use. In this case, UFH should be used because LMWH accumulates with renal insufficiency.

- Right atrial thrombosis usually is associated with the use of central venous catheters and may compromise cardiac function or lead to pulmonary embolism. If possible, the catheter should be removed. We usually begin anticoagulation therapy with UFH or LMWH. We begin thrombolytic therapy with tPA if cardiac function is compromised.

- Arterial thrombosis that causes significant impairment of blood flow to an extremity or vital organ should be treated with anticoagulation therapy with LMWH or UFH, and any associated arterial catheter should be removed. In conditions that are life-threatening or if the viability of a limb or organ is jeopardized, thrombolytic therapy with tPA should be given.

- Neonatal purpura fulminans is a rare life-threatening condition characterized by disseminated intravascular coagulation and hemorrhagic skin necrosis. It usually is caused by homozygous or compound heterozygous deficiency in protein C or S. Early identification of the disorder and treatment with protein C replacement is essential to prevent serious morbidity and death.

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