

Review Article

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## Thrombosis in neonates and children

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**Abstract.** The incidence of thrombosis is lower in children than in adults, however thrombosis related pediatric morbidity and mortality are significant. The incidence of thrombosis is maximum in neonates and during adolescence. The hemostatic system in the newborn differs from children and adults. Children till 6 months of age have lower levels of the vitamin-K-dependent coagulation factors II, IX, and X, compared to adults. Levels of thrombin inhibitors, such as antithrombin and heparin cofactor II, are similarly low at birth. Levels of protein C and S are low at birth. Protein S levels approach adult values by the age of 3-6 months, but protein C levels remain low even into childhood. Furthermore, plasminogen levels are low in newborns and infants. Thrombin generation is decreased (probably because of low prothrombin levels) and delayed in newborns compared with adults. There is a second peak of thrombosis during adolescence with more adult like risk factors

In this article we will review the literature for pertinent clinical and management issues of experts in the field of neonatal and pediatric thrombosis. The material is presented in a manner that is relevant to clinical practice.

Key words: Adolescence thrombophilia, pediatric anticoagulation, newborn hemostatic system

### 1. Introduction

Thromboses, either venous or arterial are uncommon events in pediatrics. This fact poses challenges for management, as expertise in managing multiple cases is infrequent and evidence for recommendation for antithrombotic therapy in pediatrics is largely extrapolated from adult recommendations. The incidence of thrombosis is lower in children than in adults; however thrombosis related pediatric morbidity and mortality are significant. The incidence of thrombosis peaks in the neonatal period and again during adolescence. Pediatric thrombosis is additionally challenging as this is a group that is not physiologically uniform. Newborns are children less than 28 days of age, and children between 28 days to 16 years of age. The age of adolescence is ill defined.

However, the impact of thrombotic events on children is huge; they lead to significant sequelae both physical and developmental. This has led to several important reviews and guidelines on these

issues (1-4). Early diagnosis and optimal treatment strategies for thrombosis in newborns and children are extremely important to avoid such complications.

### 2. Why are newborns and children different from adults?

The hemostatic system is a dynamic, evolving entity. The age based levels of coagulation factors and the age based normal values for coagulation tests, result in a major challenge to pediatricians, surgeons and any one who faces the task of evaluating children. These parameters affect the frequency and natural history of thrombosis. The response to therapeutic agents also differs from adults due to age dependent distribution, binding, and clearance of anti-thrombotic drugs. Frequency and type of inter-current illnesses and concurrent medications also vary with age (1-3).

Even documenting a thrombus is a major problem as many tests need general anesthesia. The inability to perform many diagnostic studies in pediatric patients hinders the ability to investigate and monitor children. Limited vascular access reduces the ability to effectively deliver anti-thrombotic therapy. Specific pediatric formulations of anti-thrombotic drugs are not available (suspension/liquid preparations) and difficulty in dosing vitamin K antagonists

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Table 1. Risk factors for neonatal thrombosis

Maternal risk factors	Acquired neonatal risk factors	Inherited factors
Maternal diabetes,	Intravascular catheters	Protein C,S deficiency
Antiphospholipid,	Sepsis,	Factor V Leiden mutation.
anti-cardiolipin antibodies	Dehydration,	Prothrombin G20210A mutation,
Family history of thrombosis	Asphyxia,	Methyl tetrahydrofolate reductase deficiency,
Intra uterine growth retardation contributing factors	Small for gestational age	LP(a) lipoprotein
	Some Congenital heart diseases	
	Polycythemia	

Table 2. Initial workup for thrombosis to evaluate for hypercoagulable state in newborns and children

1. Hematological tests–Complete hemogram (Hb/TLC/platelet count, DLC),PT/aPTT
2. Radiology as indicated by symptoms.
3. Thrombophilia workup
  - Activated protein C resistance and/or the factor V Leiden mutation
  - Antithrombin
    - Lupus anticoagulant (which may be screened by using the dilute Russell viper venom test)
    - Anticardiolipin antibodies
    - Prothrombin gene 20210A mutation
    - Lipoprotein (a) level
    - Plasma homocysteine values Protein C (Usually decreased in acute thrombosis)
    - Protein C (Usually decreased in acute thrombosis)
    - Free and total protein S (Usually decreased in acute thrombosis)

Heparin therapy affects antithrombin, protein C, protein S and activated protein C resistance.

Warfarin affects protein C, protein S and antithrombin.

Neither drug affects results of anticardiolipin antibodies, factor V Leiden, the prothrombin mutation, or lipoprotein(a) or homocysteine levels.

(VKAs) adds to the problem. Even low molecular-weight heparins (LMWH) are available as pre-dosed syringes based on adult weight. The newborn diet consisting of breast milk and infant formulas contain different levels of vitamin K. Medication compliance issues are a problem mostly in adolescents, additionally many children may be on anticonvulsants, steroids or other medications for their illness and children often need antibiotic therapy for infections.

In this article we will review the literature for pertinent clinical and management experience of experts in neonatal and pediatric thrombosis. The material is presented in a manner that is relevant to clinical practice. We will discuss newborn and other pediatric thrombosis separately.

### 3. Newborn

In most cases of thrombosis in the newborn the child is sick or has an acquired pro-thrombotic factor. While investigating such children it is not infrequent for the inciting factor to unmask a pre existing congenital thrombotic condition.

Congenital thrombophilia needs to be strongly considered in neonates with a clinically significant thrombosis, unprovoked or extensive venous thrombosis, ischemic skin lesions, purpura fulminans or a positive family history of thrombophilia.

### 4. Pathophysiology

The hemostatic system in the newborn differs from both children and adults. The newborn's hemostatic system matures rapidly, the values for coagulation tests depend both on the gestational and postnatal age of the infant. Children till 6 months of age have lower levels of vitamin-K-dependent coagulation factors II, IX, and X, compared to adults. Levels of thrombin inhibitors e.g. anti thrombin and heparin cofactor II are also lower as are important anticoagulant proteins C and S. Protein S levels approach adult values by the age of 3-6 months, but protein C levels remains low throughout childhood. It is important to note that plasminogen levels are low in newborns and infants. Thrombin generation is

delayed and decreased in newborns in comparison to adults (1).

### **5. Risk factors for neonatal thrombosis**

Both maternal and neonatal risk factors have been identified for neonatal thromboses (2,5). Many researchers have shown that along with one or more acquired precipitating factors, the investigation may also reveal an underlying inherited thrombophilic defect. Maternal diabetes, antiphospholipid and anti-cardiolipin antibodies (6,7), and maternal factors resulting in IUGR (8) are important factors, a family history familial thrombophilia. Intensive medical care for premature and ill infants often requires central vascular access devices and they are the commonest inciting factor for thromboembolism. Other important risk factors are sepsis, prematurity, dehydration and congenital thrombophilias (Table 1 and 2).

### **6. Investigation of neonatal thrombosis**

Aside from the routine requirements of standardization of tests and factor assays to prevent inter laboratory variation, the evolving neonatal coagulation system requires sequential reference ranges that reflect gestational and postnatal age. Even sample collection in the newborn can lead to fallacies, hence care is needed while drawing coagulation samples to avoid contamination with intravenous fluids and heparin. Slow passage through plastic tubing may also result in activation of coagulation and a shortening of the PT, aPTT and TT. Spurious thrombocytopenia can occur in these samples and inspection can show fibrin strands and platelet clumps. Neonatal sample tubes should be prepared and used to reduce error due to inadequate sample volume and higher neonatal hematocrit (1). Initial baseline workup is outlined in table 3, the extent of workup is dictated by the presence of inciting factor for thrombosis and probability of underlying thrombophilia based on clinical evidence.

The most clearly defined cause of neonatal thromboses are congenital deficiency states of homozygous/double heterozygous deficiencies of Protein C and Protein S that result in neonatal purpura fulminans. Therapy for these conditions involves replacement of these proteins. Other thrombophilic states have been identified. At the present time extensive thrombophilic screening of the neonate with thrombosis cannot be recommended as part of evidence based guidelines (1,2).

Thrombosis must be confirmed before thrombolytic or anticoagulation treatment due to the risk of intra cranial hemorrhage or other significant bleeding events. Doppler ultra sound is the most frequently used imaging modality and is non-invasive. However doppler can fail to diagnose thrombosis in the aorta, right atrium, veins of upper extremity and inferior vena cava. These sites are better visualized by contrast angiography (9,10). CT and MRI scans are indicated for imaging of thrombosis-related problems of the central nervous system (1).

### **7. Management of neonates**

Management of venous thrombo- embolism in the newborn period varies depending on the location and extent of the thrombus as well as the risk for acute embolic complications and risk of vascular compromise. Treatment options include supportive care only, anticoagulant therapy, thrombolytic therapy or surgery. (All Recommendations on the management of neonatal thrombosis are Grade C, based on level IV evidence, unless otherwise stated). The thrombus needs to be closely monitored, and therapy should be altered if there is extension or failure of resolution with the given treatment. In some certain cases only supportive therapy may be given, if the thrombus is small, asymptomatic and catheter related, and the inciting device is removed, further intervention may not be needed. However large randomized controlled studies to give evidence based support are lacking. Anticoagulant therapy is required for extensive, clinically significant thrombosis, clearance of most drugs is increased in the young, but clearance of aspirin is slower in neonates, potentially placing them at risk for bleeding for longer periods of time.

### **8. Unfractionated heparin**

In neonates unfractionated heparin (UH) remains the most frequently used anticoagulant, its' half life is shorter, secondary to increased clearance in newborns and young children. Investigators have shown that neonates receiving continuous UH therapy require higher doses than older pediatric or adult patients to achieve therapeutic adult activated partial thromboplastin time (aPTT) levels (11,12). The efficacy of UH might also be decreased in neonates because of the physiologically low plasma anti-thrombin concentrations (13). Thrombocytopenia is common in the sick neonate and every attempt should be made to maintain a platelet count above  $50 \times 10^9 / l$  during heparin therapy, close

Table 3. Unfractionated heparin use in neonates and children upto 2 months of age

Loading dose of heparin : 75-100 units/kg  
 Continuous infusion : 28 units/kg/hour  
 Monitor with aPTT or heparin assay, first blood sample 4 hours after loading dose.  
 (Use nomogram for dose adjustment.)

Table 4. Recommendations for low molecular weight heparin (LMWH) therapy in neonates and children less than 2 months

Pretreatment laboratory evaluation:

- CBC with platelets, aPTT, PT with international normalized ratio, ALT, AST, bilirubin total and direct, serum creatinine.

Recommended therapeutic target range:

- 0.5 – 1.0 antifactor Xa U/ml.

Initial Therapeutic dosing:

- Enoxaparin 1.5 mg/kg SQ q 12 hours
- Reviparin < 5 kg is 150 U/kg SQ q 12 hours
- >5 kg is 100 U/kg SQ q 12 hours

Prophylactic dose:

- Enoxaparin 0.75 mg/kg SQ q 12 hours
- Reviparin < 5 kg is 50 U/kg SQ q 12 hours  
 <5 kg is 30 U/kg SQ q 12 hours

Anti-Xa U/mL	Percent of prior dose	Repeat anti-Xa
< 0.35	125	4 hours after next dose
0.35-0.49	110	4 hours after next dose
0.5-1.0	Same dose	Next day
1.1-1.5	80	4 hours after dose
1.6-2.0	Hold until anti-Xa < 1.0 U/ml, then 70	4 hours after dose
>2.0	Hold until anti-Xa <0.5 U/mL, then 40	4 hours after dose

Laboratory monitoring:

- Draw anti-Xa level 4 hours after dose given.
- When anti-Xa level is 0.5-1.0 U/mL, repeat next day, then 1 week later and monthly there after.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; CBC, complete blood count; SQ, subcutaneous.

monitoring is required to prevent hemorrhage. The use of heparin in the neonatal period is complicated by the physiological immaturity of the hemostatic system, with reduced levels of antithrombin resulting in relative heparin resistance (14). The advantages of unfractionated

heparin is that it has rapid which include risk of bleeding, need for monitoring, heparin induced thrombocytopenia, osteopenia, and need for designated intravascular access (1-4). A dosage regimen for unfractionated heparin is shown in Table 3 (3).

In the absence of a validated therapeutic range for the use of heparin in neonates, the aPTT should be prolonged to a therapeutic range corresponding to an anti-Xa level of 0.35-0.7 units/ml. The limitations of anti-Xa assay are that it provides only limited information on the anticoagulant and pro-hemorrhagic effects of heparin *in vivo*. Due to neonatal antithrombin deficiency, standard anti Xa assays will tend to underestimate heparin (16). Nomograms are available for dosage adjustment.

### 9. Low molecular weight heparin

Low molecular weight heparins are increasingly used in the treatment of neonatal thrombosis. Dose finding studies have been published, and indicate that as with standard heparin the neonatal dose required, are higher than in older children (17). For example, the recommended dose of enoxaparin is 1.5 mg/kg/dose administered subcutaneously twice per day. This should result in a therapeutic anti-Xa level of between 0.5-1.0 units/ml by chromogenic assay at 4 hours post dose (17,18). LMWH offers several advantages for neonates, 1) the pharmacokinetics are more predictable and require less frequent monitoring, 2) theoretically less risk of bleeding, 3) LMWH is given sub-cutaneously, 4) decreased osteopenia with long term use, 5) Decreased risk of heparin induced Thrombocytopenia (HIT) and 6) less drug interactions. However they cannot be given in renal failure and anti Xa monitoring may not be easily available in all hospitals (17-20). The optimal duration of anticoagulation remains undefined but short term therapy (e.g. 10-14 days) is commonly used, with objective radiological monitoring performed both during and after completion of anticoagulant therapy (19). Table 4 describes commonly used schedules of low molecular weight heparin and parameters for monitoring.

### 10. Thrombolysis

Thrombolytic therapy must be considered only in the scenario of extensive thrombosis with organ/limb damage. As with heparins, the response to thrombolytic agents in the neonate differs from older children. Here it is because of physiologically reduced levels of plasminogen. Successful thrombolysis with Streptokinase has been reported in neonates (48), however the risk of bleeding, antigenicity and availability of more selective agents limit the clinical use of Streptokinase for neonates. *In vitro* studies have demonstrated that t-PA is similar to urokinase and more effective than streptokinase when there

is decreased concentration of plasminogen (1-3,21). The preferred agents for thrombolytic therapy in neonates are t-PA and urokinase (see Table 5). Recommended dosing regimens are shown in Table 4. Failure to achieve lysis of the thrombus may indicate the need for plasminogen supplementation with fresh frozen plasma (1). To reduce the risk of bleeding in the neonate receiving fibrinolytic treatment, keep fibrinogen levels at >100 mg/dl with cryoprecipitate and platelet count > 50 x 10<sup>9</sup>/l by transfusion.

### 11. Oral anticoagulants

Oral therapy with vitamin K antagonist e.g. Warfarin in neonates is difficult because of hepatic dysfunction, drug interactions (anti convulsants etc), Vitamin K supplementation in infant formulas and TPN, and the formulations of the drug that are available. A recent study found that, when compared with older children, infants < 1 year of age required higher Warfarin doses and longer overlap time with Heparin treatment to achieve a therapeutic INR (Table 6) (1,22). Oral anti-coagulant drugs suppress Protein C and S production. The decreased activity of Protein C during the initial 24 to 48 hours of oral anti-coagulation may cause an early pro-thrombotic state, potentiating the syndrome of Warfarin induced skin necrosis, which occurs in Warfarin treated patients with Hereditary Protein C or S.

### 12. Important neonatal clinical scenarios

The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (3) suggests that central venous lines or umbilical venous catheter (UVCs) associated with confirmed thrombosis be removed, if possible, after 3 to 5 days of anticoagulation. They recommend against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs and then thrombolysis should be with tissue plasminogen activator (tPA) with supplement of plasminogen (fresh frozen plasma). For neonates with unilateral renal vein heparin is that it is rapid reversibility and inexpensive. However there are several significant disadvantages which include risk of bleeding, need for monitoring, heparin induced thrombocytopenia, osteopenia, and need for designated intravascular access (1-4). A dosage regimen for unfractionated heparin is shown in Table 3 (3).

Management of congenital homozygous protein C, S in the acute phase requires immediate and

Table 5. Thrombolytic regimes in the neonate.

Drug	Initial bolus dose	Maintenance dose	Duration of treatment
Systemic t-PA	None	0.1-0.6 mg/kg/hr	6 hours
Local t-PA	0.5 mg in Normal Saline, volume required to fill line.	-	
Systemic Urokinase	4400 u/kg	4400 units/kg/hr	6 -12 hours

Table 6. Recommendations for warfarin therapy in neonates

Pretreatment laboratory testing:

- CBC with platelets, aPTT, PT with international normalized ratio (INR).
- ALT, AST, bilirubin total and direct.

Recommended target ranges for INR :

- 2.0-3.0

Loading period:

- For 3-5 days, or until a stable therapeutic INR level is achieved.
- Start after 1-2 days of initiation of heparin therapy.

Dose on day 1 :

- 0.2 mg/kg PO as a single daily dose.

Monitor closely for potential for drug interactions Reduce loading dose if existing hepatic or renal dysfunction or baseline INR > 1.2.

Discontinue heparin 5 days after initiation of Warfarin and when INR > 2.0 daily X 2days.

Consider amount of Vitamin K in diet and supplements.

Warfarin dose adjustments to documented INR during loading period

INR	Percent (%) of Loading Dose to be Given
1.1 – 1.3	100
1.4 – 3.0	50
3.1 – 3.5	25
> 3.5	Hold until INR < 3.5, then restart at 50

Warfarin dose adjustments to documented INR during Maintenance period

INR	Percent(%) of Previous Dose to be Given
1.1 – 1.4	120
1.5 – 1.9	110
2.0 – 3.0	100
3.1 – 4.0	90
>3.5	Hold until INR < 3.5 and restart at 80

Laboratory monitoring:

- Daily INR until therapeutic level reached for 2 consecutive days.
- INR weekly if stable; may require more frequent testing if child ill, on drugs which may lead to interactions.

adequate replacement of the deficient factor. Protein C deficient neonates should receive Protein C concentrate at a starting dose of 40 IU/kg, if concentrate is not immediately available, then FFP 10-20ml/kg can be used as a

temporary measure. During the early stages of replacement therapy as there is ongoing disseminated intravascular coagulation (DIC) the protein C half life is only 2 - 3 hours, necessitating frequent dosing. As DIC is

controlled, the need for replacement decreases to a once a day replacement. (23). Replacement therapy is required for at least 6-8 weeks to facilitate resolution of clinical lesions. Protein C levels should remain in excess of 0.25U/ml to prevent thrombosis. There is currently no available protein S concentrate and FFP is used for replacement therapy at a dose of 10-20 ml/kg every 8 to 12 hours. Long term management remains controversial but current regimens utilize oral anticoagulants with or without concomitant replacement therapy. It is difficult to use vitamin K antagonists in babies they should receive replacement therapy. Older children on warfarin need a higher therapeutic INR range (3.0-4.5) to prevent recurrent skin necrosis (Grade C recommendation based on level IV evidence) and need careful monitoring. Low molecular weight heparin can be used in homozygous protein C deficient patients who have detectable plasma levels of protein. (24).

The management of arterial and venous thromboembolic events in the neonatal period remains controversial and it is generally acknowledged that there is an urgent need for large multicenter studies on which to base recommendations.

### **13. Children**

There is a second peak of thrombosis during adolescence with more adult like risk factors, e.g. systemic lupus erythematosus, antiphospholipid antibodies, smoking, oral contraceptives which can cause thrombosis due to undiagnosed, underlying thrombophilias and sickle cell disease (Table 7). As in newborns the thrombotic events in children have long lasting sequelae (1,3,4,25).

### **14. Diagnosis in children**

The investigation of thrombosis depends on the site of thrombus and the age of child. Though the gold standard diagnostic test for documentation of thrombosis is contrast angiography, in young and unco-operative children ultrasound is a valid surrogate imaging modality. The limitation of ultrasound is that it results in false negative results in upper extremity imaging due to the clavicles and thoracic cage. So, for upper extremity imaging it is insufficient and venography with ultrasound is required (26). Magnetic resonance venography imaging can be used to demonstrate congenital vascular malformations and central venous device thrombus in children (27).

### **15. Management of children**

Out side the neonatal period, dosing and monitoring of anticoagulant therapy is closer to adults. Though issues of formula fed children less than one year of age, difficulty with non pediatric formulations, compliance and drug interactions need to be carefully considered. Regular visits to the consulting physician with close monitoring of coagulation parameters and imaging of the thrombus can result in a satisfactory outcome.

Antithrombotic therapy is required for the resolution and prevention of extension of the thrombus. It can prevent recurrence, embolization and may reduce long-term complications such as post phlebotic syndrome (28).

### **16. Unfractionated heparin**

In children the recommended unfractionated (UF) heparin schedule is a loading dose of 75 to 100 U/kg of UH intravenously over 10 minutes, followed by maintenance in children over one year of age of 20 U/kg per hour, and adolescents (18 U/kg per hour) (29). The increased requirement for UH in the young reflects a faster clearance of UH, due to a larger volume of distribution. Studies have shown that with a therapeutic range of APTT children may have a sub-therapeutic level of heparin, which may result in treatment failure. (13,14), hence monitoring should include APTT, heparin levels and imaging studies for response.

Complications of bleeding can be managed by stopping infusion or reversal with protamine sulphate. Heparin-induced thrombocytopenia (HIT) is rare in children.

### **17. Low molecular weight heparin (LMWH)**

Dosing guidelines in children have been established for many LMWH for age > 2months, enoxaparin, 1mg/kg q12 hours initial dose and 0.5 mg/kg q12 hourly maintenance dose see table 4 (17,18). Monitoring of LMWH therapy with anti-Factor Xa assay is required in young children.

Advantages of the LMWHs, are that they can be administered subcutaneously, require less frequent monitoring and have fewer interactions. However they are contraindicated in renal failure and if a lumbar puncture is to be performed, at least two scheduled doses of LMWH should be omitted prior to the procedure (1997 the FDA Public Health Advisory)

Table 7. Risk factors for thrombosis in children

Time-limited risk factors:

- Central venous lines
- Infection
- Post infectious transient antiphospholipid antibodies
- Surgery
- Surgically correctable congenital heart disease

Ongoing risk factors:

Thrombophilia

Genetic thrombophilia

- Factor V Leiden, prothrombin 20210 mutation
- Deficient/dysfunctional antithrombin, protein C, protein S, AT III
- Elevations in lipoprotein (a), homocysteine
- Other less common genetic disorders of coagulation regulation or fibrinolysis

Acquired thrombophilia

- Markers of inflammation (elevations in factor VIII, D-dimer, C-reactive protein)
- Primary antiphospholipid antibody syndromes (lupus anticoagulant, anti-2 GPI antibody, anticardiolipin antibody)
- Acquired decrease in coagulation regulatory proteins (nephrotic syndrome, protein-losing enteropathy)

Leukemia, cancer and chemotherapy (e.g., *L. asparaginase*)

Inflammatory diseases (e.g systemic lupus erythematosus, inflammatory bowel disease etc)

Prosthetic cardiac valves, congenital heart disease

Diabetes mellitus

Sickle cell anemia

## 18. Oral anticoagulants

The therapeutic ranges for oral anticoagulant therapy in children are extrapolated from recommendations for adults and consist of an INR between 2.0 and 3.0 for the treatment of venous thrombo-embolism. An initial oral dose of 0.2 mg/kg is recommended with a normal baseline INR and normal liver function studies.

Monitoring oral anticoagulant therapy in children requires more frequent INR measurements and dose adjustments compared to adults. Diets with poor sources of vitamin K (e.g. breast milk) or those with supplemented vitamin K (e.g. total parenteral nutrition and infant formula) induce sensitivity or resistance, to oral anticoagulants (22,30). Children who suffer from medical problems may also be taking concomitant medications that result in drug interactions.

## 19. Thrombolytic agents

As in newborns the thrombolytic agents

commonly used in children are urokinase and recombinant tissue plasminogen activator (r-tPA). Doses for systemic thrombolysis are taken from several studies, recombinant tPA doses vary between 0.1 and 0.6 mg/kg per hour for a duration of six hours (31), though lower doses have been used to reduce risk of bleeding. Catheter-directed thrombolysis through a catheter device with the tip situated within the thrombus offers several advantages over systemic thrombolysis, including higher response rate and decreased rate of major bleeding complications. Recommended doses for catheter-directed thrombolysis with recombinant tPA are 0.01 and 0.2 mg/kg per hour for 24 hours. Catheter-directed thrombolysis can be considered if the catheter is already close to the thrombus. For treating a blocked catheter recombinant tPA in a solution containing 0.5 mg/mL can be instilled, 1 mL/lumen of central line in children under 10 kg, and a solution containing 1.0 mg/mL with 2 mL/lumen in children over 10 kg for two to four hours, this can be repeated (4,31-33).



## 20. Important pediatric clinical scenarios

Monagle P, Chalmers E, Chan A, et al. Antithrombotic Therapy in Neonates and Children: Evidence-Based Clinical Practice Guidelines (3), suggests the use of anticoagulation therapy to treat idiopathic deep vein thrombosis in children for only 6 months rather than lifelong, to avoid the bleeding risk associated with antithrombotic therapy, and relatively low of recurrence in the absence of ongoing risk factors. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing L-asparaginase therapy, they have suggested continuing anticoagulant therapy in either therapeutic or prophylactic doses until the risk factor has resolved. They have recommended that children > 10 kg body weight with lower-extremity DVT and a contraindication to anticoagulation, have a temporary inferior vena cava (IVC) filter placed. In children with non-sickle-cell disease-related arterial ischemic stroke (AIS) the group recommends UH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes has been excluded and then subsequently aspirin prophylaxis (1 to 5 mg/kg/d) for a minimum of 2 years. If AIS secondary to dissection or cardioembolic causes, anticoagulant therapy with LMWH or VKAs for at least 6 weeks, is needed with further treatment dependent on radiologic assessment (3).

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