Thrombosis in newborn infants

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ABSTRACT
The incidence of thrombosis is higher among newborn infants than in any other stage of pediatric development. This fact is the consequence of labile characteristics of the neonatal hemostatic system, in addition to exposure to multiple risk factors and the wide use of vascular catheters. Venous thromboses, which mainly affect the limbs, the right atrium and renal veins, are more frequently seen than arterial thromboses. A stroke may be caused by the occlusion of the arterial flow entering the brain or by occlusion of its venous drainage system. *Purpura fulminans* is a very severe condition that should be treated as a medical emergency, and is secondary to severe protein C deficiency or, less frequently, protein S or antithrombin deficiency. Most thrombotic events should be managed with antithrombotic therapy, which is done with unfractionated and/or low molecular weight heparins. *Purpura fulminans* requires protein C replacement and/or fresh frozen plasma infusion. Thrombolytic therapy is done using tissue plasminogen activator and should only be used for life-, or limb-, or organ-threatening thrombosis.
Key words: *thrombosis, newborn infant, heparin, anticoagulants, thrombolytic therapy.*

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INTRODUCTION

During the first month of life, the likelihood of thrombotic complications is 40 times higher than at any other pediatric age, especially in critically-ill children or those who have a central catheter in place. Catheterization is undoubtedly the most important risk factor for both arterial and venous thromboembolism. Approximately 90% of thromboembolic events are catheter-related.[1,2] The presence of a catheter favors the occurrence of thrombosis by different mechanisms, either isolated or combined. Catheters may cause mechanical damage to the vascular wall and slowing or interruption of the blood flow, they are manufactured with potentially-thrombogenic material, or they are used to infuse agents that damage the vascular wall.[3] Other predisposing factors include perinatal asphyxia, prematurity, heart conditions, sepsis, hypoxia, and maternal diabetes. Congenital prothrombotic disorders play an irrelevant role in this period.[4]

The overall incidence of thromboembolism in hospitalized newborn infants is approximately 2.4 per 1000 admissions.[2,5] It has been reported that 1% of newborn infants with catheters have symptoms indicative of thrombosis,[6] and it is estimated that the incidence of catheter-associated asymptomatic thrombosis is 20-30%.[7-11]

An adequate management of thrombosis is generally complicated due to the extrapolation of adult management techniques. However, over the past years, major differences related to age have been observed in this condition (epidemiology, diagnostic tests, pharmacokinetics of antithrombotic agents), which have favored the use of diagnostic and therapeutic procedures appropriate for this period in life.

FEATURES OF THE HEMOSTATIC SYSTEM IN NEWBORN INFANTS

The hemostatic system of newborn infants has a series of special characteristics different from that of adults, which make it especially labile.[12] A reduced synthesis of several coagulation proteins (factors II, VII, IX, X, XI and XII, high molecular weight kininogen, antithrombin III, proteins S and C), an altered function of other coagulation proteins (fibrinogen, plasminogen), an accelerated clearance of factors, and differences in platelet functioning are some of the specific differences between the hemostatic system of adults and newborn infants. In addition, both

stimuli occurred during childbirth (acidosis, hypoxia, thermal changes, release of tissue factor) and a frequent exposure to trauma and manipulation result in a coagulation mechanism that is more active than that of adults. Although components of the hemostatic system start synthesizing during the tenth week of gestation and increase gradually, values reached at birth are remarkably different among them (*Table 1*).[9,13-17]

Below we present the most important information regarding coagulation factors in newborn infants:[7,16,18-24]

- Vitamin K-dependent factors (II, VII, IX, X) and contact factors (XII, XI, prekallikrein and high molecular weight kininogen) are reduced to varying degrees.
- Fibrinogen and factors V, VIII and XIII levels are similar to those of adults.
- Von Willebrand factor level is almost twice that of adults.

The time necessary for reduced factors to reach normal values is variable and may range from a few days to several months.[14-16,19,25,26] Most factors reach 80% of the value of adults by six months old.

In addition, fibrinogen is quantitatively normal, but has qualitative differences because it has a higher sialic acid content and a shorter half life.[27-30]

In spite of these alterations, newborn infants maintain a hemostatic balance because natural inhibitors are also different from those of adults:[13-15,19,25,26,31-35]

- Antithrombin is reduced by 50%, and proteins C and S, by 60%.
- Protein S circulates absolutely freely (active form) because newborn infants lack C4b, a binding protein of protein S.
- Alpha-2-macroglobulin is high, approximately twice the level of adults.

Fibrinolytic activity is also altered, with plasminogen levels reduced by 50%.

Many of the above mentioned differences in the hemostatic system are even sharper among preterm infants.

TABLE 1. *Normal average values of procoagulant, inhibitory and fibrinolytic factors at 24 hours of life and approximate time needed to reach normal values*

	Term newborn infant	Preterm newborn infant	Time to achieve a normal value
Procoagulant:			
Fibrinogen#	2.83	2.43	At birth
F. II*	0.48	0.45	2-12 months
F. V	0.72	0.88	At birth
F. VII*	0.66	0.67	2-12 months
F. VIII	1.00	1.11	At birth
F. IX*#	0.53	0.35	3-9 months
F. X*	0.40	0.41	2-12 months
F. XI*#	0.38	0.30	1-2 months
F. XII*#	0.53	0.38	9-14 days
F. XIII*	0.79	0.70	4-5 days
Prekallikrein*	0.37	0.33	More than 6 months
HMWK*	0.54	0.49	2-3 months
Von Willebrand factor*	1.53	1.36	5-6 months
Inhibitory:			
Antithrombin*#	0.63	0.38	3 months
A2M*#	1.39	1.1	Adult
Protein C*#	0.35	0.28	2-9 months
Protein S*#	0.36	0.26	3 months
Fibrinolytic:			
Plasminogen*	1.95	1.70	6-12 months
Alpha-2-AP*	0.85	0.78	3-4 days
PAI*#	6.40	5.40	3-4 days
TPA*	9.60	8.48	3-4 days

Fibrinogen is expressed in g/L; all the other values are expressed in U/mL.
F.: factor; HMWK: high molecular weight kininogen; A2M: alpha-2-macroglobulin; alpha-2-AP: alpha-2-antiplasmin; PAI: plasminogen activator inhibitor; TPA: tissue plasminogen activator.
* Values are different for adults; # values are different between preterm and term newborn infants.

CLINICAL PRESENTATIONS

Venous thrombosis

Deep vein thrombosis

This is a common condition in patients hospitalized in the Critical Care Unit; its incidence has been reported to be 2-22%. Superior vena caval thrombosis may be asymptomatic or accompanied by edema in the neck, face and/or upper chest, collateral circulation and, eventually, acute heart failure.[36] Limb thrombosis may appear as a change in skin color, swelling, edema, pain, elevated temperature and cyanosis. In the case of upper limb involvement, superior vena cava syndrome may also develop.[18,19,26,37,38]

Post-thrombotic syndrome is a long-term complication that may develop as a result of neonatal thrombosis, as of one month after the event and up to 10 years later. It is characterized by chronic edema in the limbs together with skin discoloration, impaired wound healing, skin ulcers and, commonly, functional incapacity. It is the result of extravasation of RBCs and inflammatory mediators following damage to venous valves caused by the thrombus.[39]

Renal vein thrombosis

It accounts for 10% of venous thrombosis cases in the neonatal period.[1,40] It is the most common type of thrombosis not related to a central venous catheter. Its clinical presentation starts as a palpable mass in the flank, hematuria, proteinuria, thrombocytopenia, renal failure and/or arterial hypertension.[1,35] The classical triad of symptoms –palpable mass, hematuria and renal failure– is seen only in 13% of patients.[41] If thrombosis reaches the vena cava (approximately in 50% of cases), it may also be accompanied by edema, hypothermia and lower limb cyanosis.[41-45] Approximately 25% of cases are bilateral.[5,46]

Renal vein thrombosis occurs in the first month of life, generally, in the first three days of life (67% of cases), but it may also develop *in utero*.[1,13,25,32-35,42,43,47,48]

Risk factors associated with this condition include asphyxia, dehydration, acidosis, arterial hypotension, polycythemia, and maternal diabetes.

Diagnosis is made by Doppler ultrasound, which shows a loss of renal corticomedullary differentiation or, preferably, a color Doppler ultrasound, which allows to observe absence of flow in the involved vein.[35,49-51]

Anticoagulant therapy with unfractionated or low molecular weight heparin has improved survival remarkably, which at present is approximately 85%,[1,40] and prevents renal atrophy in two thirds of patients.[41]

Right atrial thrombosis

It accounts for approximately 6% of neonatal thromboses. A central venous catheter is present in almost all cases.[52] Its clinical presentation is variable and includes signs of right-sided heart failure, persistent sepsis, sudden manifestation of murmur, bradycardia, tachyarrhythmia or respiratory distress.[1,20] The diagnostic method of choice is transthoracic echocardiogram.

Its most serious complications are pulmonary thromboembolism, which becomes apparent due to acute respiratory distress, and stroke.

Arterial thromboses

Arterial thromboses are, in general, iatrogenic complications of umbilical, peripheral or femoral artery catheterization. Its actual incidence in newborn infants is unknown and varies depending on the method used for assessment: 1-3% based on clinical signs, 14-35% based on ultrasonography, and 64% based on angiography.[1,53-56]

Symptoms depend on thrombus location and size, and may go from no symptoms at all (malfunctioning catheter) to limb-threatening massive ischemia, arterial hypertension with or without renal failure (renal artery occlusion), necrotizing enterocolitis (mesenteric artery occlusion) or even stroke (due to patent foramen ovale).[1,57,58]

The study of choice for this condition in older children and adults is an angiography, but it is not routinely used in newborn infants due to its risks. For this reason, a Doppler ultrasound is generally used to confirm diagnosis, although its actual specificity has not been validated and, in some cases, it may show false negative results.[1,2,4,28]

Its management is a difficult issue. Catheter removal is mandatory, except in isolated exceptional cases. The risk/benefit ratio of using anticoagulant and thrombolytic agents has not been clearly defined, so every case should be assessed individually.[1] In general, non-occlusive thrombosis may resolve by removing the catheter and with no anticoagulant therapy; however, in the case of significant occlusion, the initial treatment is heparin.[4] In some specific life-, organ, or limb-threatening circumstances, thrombolytic therapy should be attempted.[1]

Stroke

A stroke may be caused by the occlusion of the arterial flow entering the brain or by the occlusion of its venous drainage system –venous sinus thrombosis (VST)–. It typically presents with seizures or lethargy. Focal signs are uncommon, and hemiparesis occurs in less than 25% of children with ischemic stroke and in less than 10% of VST cases.[4,40,59-64] A tense anterior fontanelle, diastasis of the cranial sutures and engorged scalp veins in cases of VST have also been observed.[40,60,62,65]

Ischemic stroke diagnosis is confirmed by angiography or angio-MRI.[40,66] For VST diagnosis, an MRI is the study of choice, but highly satisfactory results have also been observed with transfontanellar Doppler ultrasound and conventional ultrasound.[67-70]

Survival with no neurological sequelae is approximately 33-50%.[40,60,71,72]

Anticoagulant therapy is not recommended for stroke, unless it is a cardioembolic stroke, in which case heparin should be used.[40,73] For VST with no extensive ischemic areas or intracerebral hemorrhage, heparinization is recommended. In the case of extensive ischemic areas or intracerebral hemorrhage, brain monitoring is necessary, together with anticoagulation if the thrombus increases in size.[40,73]

Purpura fulminans

This is a very severe condition that should be managed as a medical emergency. It occurs in children with severe protein C deficiency or, less frequently, protein S or antithrombin deficiency.[74-76] Lesions appear in the capillary vessels of the skin, brain and kidneys because protein C works mainly in microcirculation.

Its clinical presentation is characteristic.[40,74,75,77-81] Children with this condition usually have brain and/or ophthalmic damage secondary to intrauterine thrombosis and, in the first hours of life, evidence the complete clinical picture in a catastrophic manner. Skin lesions start as small ecchymoses that gradually extend following a radial pattern, with reddish/blackish color, that turn into bullae and finally become necrotic and gangrenous. Lesions are mainly located in the limbs, but may appear in any other site. The presence of other hemorrhagic manifestations secondary to disseminated intravascular coagulation is practically continuous. Sometimes, large vessel thrombosis may occur.

A definitive diagnosis is based on low or undetectable levels of protein S or C, a high suspicion when facing this clinical presentation, and recognition of a heterozygote status in both parents.[40,81,82]

This condition improves with the administration of protein C (60 IU/kg every 6-8 hours, with a subsequent customized dose adjustment) or, if this approach fails, fresh frozen plasma (10-20 mL/kg every 8-12 hours). For protein S deficiency, replacement therapy is done using fresh frozen plasma.[79,83] Treatment is administered until lesions resolve completely, which usually occurs in 6-8 weeks.[40] Long-term treatment should include oral anticoagulation (maintaining an international normalized ratio [INR] between 2.5 and 4.5) or with low molecular weight heparin (LMWH), together with protein C (or S) replacement, depending on the patient's symptoms.[40,80] The option for a definitive cure is liver transplant.[40,75]

TREATMENT

General management of thromboses

Asymptomatic thrombosis is managed with supportive care and clot size monitoring. If a central venous catheter is associated with a thrombus, it should be removed. If the thrombus advances, an anticoagulant therapy is required.[73] Symptomatic thrombosis should be managed with anticoagulant therapy and/or, rarely, thrombolytic agents. If central or umbilical venous catheters are associated with the thrombus, they should be removed, if possible, after three to five days of anticoagulant therapy.[73,84] When peripheral arterial catheters are associated with thrombosis, they should be removed immediately.[73] Surgical thrombectomy is rarely indicated in newborn infants because of their small vessels and clinical instability.[85]

Anticoagulant therapy

Not enough randomized controlled trials have been conducted on anticoagulation in children, so therapeutic schemes used in these patients are based on studies conducted in a small number of cases and guidelines that were adapted from adult treatments. At present, the most commonly used recommendations are evidence-based recommendations provided by experts, considering that most pieces of evidence are grade 2C.[26,73,86]

Newborn infants pose two additional hurdles. On one side, it is hard to find an adequate

venous access to collect the samples necessary for treatment monitoring. On the other side, the milk fed to these newborn infants contains different levels of vitamin K, a complication for oral anticoagulant use.

The most commonly used drugs are unfractionated heparin and LMWH. In general, thrombolytic agents are not recommended, except in life-threatening conditions. New anticoagulant agents are under investigation and cannot be recommended for use in newborn infants.

The optimal duration of treatment has not been clearly established but, in general, it should last between six weeks and three months, depending on the clinical condition.[73,87]

Before starting antithrombotic therapy, prothrombin time, activated partial thromboplastin time (aPTT), platelet and fibrinogen levels should be checked. During anticoagulant therapy, platelet count should be maintained above 50 x 10^9/L, while fibrinogen should be over 100 mg/dl. It is also advisable to do a head ultrasound before treatment, especially in preterm infants.

Unfractionated heparin

Unfractionated heparin enhances antithrombin activity, thereby inactivating thrombin and activated factor X (aFX). In order to work, an adequate amount of antithrombin is required. Taking into account that, at birth, the level of antithrombin and the ability to generate thrombin are physiologically reduced (even more in preterm infants), sometimes it is necessary to administer antithrombin to reach an adequate anticoagulant response.[88,89]

The initial bolus dose is 75 IU/kg (10 minutes), followed by a maintenance dose of 28 IU/kg/hour. The objective is to achieve an anti-aFX level of 0.3-0.7 IU/mL four hours after administration, and an aPTT activity of 1.5-2 times the normal value.[88,90] Once an adequate therapeutic range has been achieved, aPTT and platelet count should be controlled every 24 hours.

The most common secondary effects include bleeding due to an excessive dose and heparin-induced thrombocytopenia. If bleeding occurs, discontinue the drug and, if necessary, administer protamine sulfate (1 mg of protamine per 100 IU of heparin, intravenous infusion over 10 minutes).

The main advantages of unfractionated heparin are its low cost and the fast reversibility of its effect, if necessary, because its half life is one hour.

Low molecular weight heparin

The advantages of LMWH over unfractionated heparin include subcutaneous administration, a dose administered every 12-24 hours, minimum monitoring requirements, a more predictable response, and a lower risk of bleeding and heparin-induced thrombocytopenia.[4]

The most commonly LMWH used in newborn infants is enoxaparin. For thrombosis management, a 1.5 mg/kg subcutaneous dose every 12 hours is recommended;[73] however, at present, evidence indicates that the dose required to reach an adequate therapeutic range is approximately 1.7 mg/kg in term infants and 2 mg/kg in preterm infants.[91] The goal is to achieve an anti-aFX level of 0.5-1 IU/ml. For prophylaxis purposes, a half of the therapeutic dose is recommended to reach an anti-aFX level of 0.1-0.3 IU/ml.

Oral anticoagulants

The most commonly used oral anticoagulants are vitamin K antagonists, which act by reducing functional activity of vitamin K-dependent coagulation factors (II, VII, IX and X). Considering that these factors are physiologically reduced in newborn infants, using these drugs in infants is problematic, especially given the great variability of vitamin K in milk, which in turn conditions treatment response: while infant formulas contain vitamin K supplements to prevent vitamin K deficiency bleeding, which renders formula-fed infants to be relatively resistant to this medication, breast milk contains a very low level of vitamin K, making these infants very sensitive to treatment.[1,73,92] In addition, this treatment requires frequent monitoring, making it difficult to find adequate venous accesses for sample collection.[1]

Therefore, based on the available evidence, vitamin K antagonists should be avoided in newborn infants as far as possible.[1] However, in order to make a decision, it should be considered that maintaining anticoagulation with LMWH for several weeks is an invasive procedure, which sometimes leads to an inadequate treatment adherence. Considering every precaution and with controls done as often as necessary based on the patient's characteristics, oral anticoagulation may be indicated for long-term management. During treatment, special attention should be paid to variations in the type or amount of feeding, infectious complications (especially gastrointestinal complications), and antibiotic

therapy.[3] Among exclusively breastfed infants, the low intake of vitamin K provided by breast milk may be compensated by the administration of prophylactic doses of vitamin K or small amounts of formula administered on a daily basis.[1,73]

Warfarin or acenocumarol may be used. The recommended initial dose is 0.2 mg/kg/day to reach an INR between 2 and 3,[40] although it has been observed that the average useful dose for infants is approximately 0.33 mg/kg/day.[93] If bleeding is caused by an excessive dose, vitamin K may be administered to neutralize the effect.[40]

An indication of alternative oral anticoagulants, such as argatroban, bivalirudin or fondaparinux, has not yet been established in newborn infants.[94]

Thrombolytic therapy

Thrombolytic agents generally act by converting plasminogen into plasmin, which acts on fibrin by breaking it down and contributing to thrombus lysis. Since thrombolytic activity may be reduced in these patients due to a decreased plasminogen level, the therapeutic effect of these agents may be limited. Plasminogen supplementation with the administration of fresh frozen plasma may improve fibrinolytic activity.

Considering the high risk of bleeding associated with this treatment, it should be reserved only to infants whose thrombosis is life-, organ-, or limb-threatening.[1,95,96] It is contraindicated in the following situations: active bleeding, major surgery or bleeding in the previous 10 days, neurosurgery in the previous 3 weeks, severe asphyxia in the previous 7 days, invasive procedure in the previous 3 days, seizures in the past 48 hours, gestational age younger than 32 weeks.[97]

The drug of choice is tissue plasminogen activator (TPA). It is administered in a continuous infusion at a dose of 0.1-0.6 mg/kg/hour over 6 hours using a central or peripheral line.[73] No specific lab tests are available to define its therapeutic range or monitoring. A strict clinical, lab and radiological supervision is required. An increase in prothrombin time, aPTT, fibrin degradation products (FDPs) or D-dimer, and a reduction in fibrinogen evidence a response to thrombolytic therapy. It is recommended to maintain fibrinogen values above 100 mg/dL. If bleeding occurs, it is recommended to administer cryoprecipitates (5-10 mL/kg) or fibrinogen and, in life-threatening situations, intravenous antifibrinolytics should be added.

Mortality is not clearly defined and varies between 1.2% and 13% of patients receiving TPA.[98,99] Treatment effectiveness with complete clot resolution ranges between 65% and 94%.[100-102] ■

REFERENCES

1. Greenway A, Massicotte MP, Monagle P. Neonatal thrombosis and its treatment. *Blood Rev* 2004;18(2):75-84.
2. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics* 1995;96(5 Pt 1):939-43.
3. Donato H. Trastornos trombóticos. In: Donato H, Rapetti MC, eds. *Hematología Neonatal*. Buenos Aires: Fundasap; 2007.Pages 255-77.
4. Albisetti M, Andrew M, Monagle P. Hemostatic abnormalities. In: De Alarcón P, Werner E, eds. *Neonatal hematology*. New York: Cambridge University Press; 2005. Pages 310-48.
5. Hilario Barrio A, Gallego Herrero C, Miralles Molina M, Medina López C, et al. Trombosis venosa renal neonatal: diagnóstico precoz con ecografía Doppler y secuelas a largo plazo. *Radiología* 2009;51(6):583-90.
6. O'Neill JA Jr, Neblett WW 3rd, Born ML. Management of major thromboembolic complications of umbilical artery catheters. *J Pediatr Surg* 1981;16(6):972-8.
7. Olinsky A, Aitken FG, Isdale JM. Thrombus formation after umbilical arterial catheterisation. An angiographic study. *S Afr Med J* 1975;49(36):1467-70.
8. Oppenheimer DA, Carroll BA, Garth KE. Ultrasonic detection of complications following umbilical arterial catheterization in the neonate. *Radiology* 1982;145(3): 667-72.
9. Horgan MJ, Bartoletti A, Polansky S, Peters JC, et al. Effect of heparin infusates in umbilical arterial catheters on frequency of thrombotic complications. *J Pediatr* 1987;111(5):774-8.
10. Seibert JJ, Taylor BJ, Williamson SL, Williams BJ, et al. Sonographic detection of neonatal umbilical-artery thrombosis: clinical correlation. *AJR Am J Roentgenol* 1987;148(5):965-8.
11. Andrew M. Developmental hemostasis: relevance to newborns and infants. In: Nathan DG, Orkin SH, Oski FA, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 5th ed. Philadelphia: WB Saunders; 1998. Pages 114-58.
12. Donato H. Hemostasia normal en el feto y el recién nacido. In: Donato H, Rapetti MC, eds. *Hematología Neonatal*. Buenos Aires: Fundasap; 2007. Pages 195-205.
13. Nowak-Göttl U, Von Kries R, Göbel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal* Ed 1997;76(3):F163-7.
14. Schmidt B, Zipursky A. Thrombotic disease in newborn infants. *Clin Perinatol* 1984;11(2):461-88.
15. Khilnani P, Goldstein B, Todres ID. Double lumen umbilical venous catheters in critically ill neonates: a randomized prospective study. *Crit Care Med* 1991;19(11):1348-51.
16. Andrew M, David M, Adams M, Ali K, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood* 1994;83(5):1251-7.
17. Monagle P, Adams M, Mahoney M, Ali K, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Trombophilia Registry. *Pediatr Res* 2000;47(6):763-6.
18. Ament J, Newth CJ. Deep venous lines and thromboembolism. *Pediatr Pulmonol* 1995;20(6):347-8.
19. Marie I, Lévesque H, Cailleux N, Primard E, et al. Les thromboses veineuses profondes des membres supérieurs. À propos de 49 cas. *Rev Med Interne* 1998;19(6):399-408.
21. Kramer SS, Taylor GA, Garfinkel DJ, Simmons MA. Lethal

chylothoraces due to superior vena caval thrombosis in infants. *AJR Am J Roentgenol* 1981;137(3):559-63.
22. Le Coultre C, Oberhänsli I, Mossaz A, Bugmann P, et al. Postoperative chylothorax in children: differences between vascular and traumatic origin. *J Pediatr Surg* 1991;26(5): 519-23.
23. Andrew M, Paes B, Milner R, Johnston M, et al. Development of the human coagulation system in the full-term infant. *Blood* 1987;70(1):165-72.
24. Andrew M, Paes B, Milner R, Johnston M, et al. Development of the human coagulation system in the healthy premature infant. *Blood* 1988;72(5):1651-7.
25. Tinaztepe K, Buyan N, Tinaztepe B, Akkök N. The association of nephrotic syndrome and renal vein thrombosis: a clinic pathological analysis of eight pediatric patients. *Turk J Pediatr* 1989;31(1):1-18.
26. Mulvihill SJ, Fonkalsrud EW. Complications of superior versus inferior vena cava occlusion in infants receiving central total parenteral nutrition. *J Pediatr Surg* 1984;19(6):752-7.
27. Mitchell L, Chait P, Ginsberg J. Comparison of venography with ultrasound for the detection of venous thrombosis in the upper body in children: results of the PARKAA study. *Blood* 1999;94(Suppl 1):588a.
28. Edstrom CS, Christensen RD, Andrew M. Developmental aspects of blood hemostasis and disorders of coagulation and fibrinolysis in the neonatal period. In Christensen RD, ed. *Hematologic problems of the Neonate*. Philadelphia: Saunders; 2000. Pages 239-72.
29. Kurekci E, Kaye R, Koehler M. Chylothorax and chylopericardium: a complication of a central venous catheter. *J Pediatr* 1998;132(6):1064-6.
30. Barnes C, Newall F, Monagle P. Post-thrombotic syndrome. *Arch Dis Child* 2002;86(3):212-4.
31. Andrew M, Brooker LA. Hemostatic disorders in newborns. In: Polin R, Fox W, Abman S, eds. *Fetal and neonatal physiology*. 2nd ed. Philadelphia: WB Saunders; 1998. Pages 1803-33.
32. Reverdiau-Moalic P, Delahousse B, Body G, Bardos P, et al. Evolution of blood coagulation activators and inhibitors in the healthy fetus. *Blood* 1996;88(3):900-6.
33. Nuss R, Hays T, Manco-Johnson M. Efficacy and safety of heparin anticoagulation for neonatal renal vein thrombosis. *Am J Pediatr Hematol Oncol* 1994;16(2):127-31.
34. Wright NB, Blanch G, Walkinshaw S, Pilling DW. Antenatal and neonatal renal vein thrombosis: new ultrasonic features with high frequency transducers. *Pediatr Radiol* 1996;26(9):686-9.
35. Andrew M, Monagle P, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton BC: Decker Inc; 2000. Chapter 8, Thromboembolic complications in specific organ sites and pediatric diseases; Pages 231-76.
36. Ladino M, Ruiz-Esquide F, Guardia S. Trombosis venosa profunda en relación a un catéter central: edema neonatal en esclavina, un caso clínico. *Rev Chil Pediatr* 2001;72(4): 340-4.
37. Rockoff MA, Gang DL, Vacanti JP. Fatal pulmonary embolism following removal of a central venous catheter. *J Pediatr Surg* 1984;19(3):307-9.
38. Derish MT, Smith DW, Frankel LR. Venous catheter thrombus formation and pulmonary embolism in children. *Pediatr Pulmonol* 1995;20(6):349-54.
39. Sharathkumar AA, Pipe SW. Post-thrombotic syndrome in children: a single center experience. *J Pediatric Hemat Oncol* 2008;30(4):261-6.
40. Monagle P, Chan A, Massicotte P, Chalmers E, et al. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl):645S-87S.
41. Zigman A, Yazbeck S, Emil S, Nguyen L. Renal vein thrombosis: a 10-year review. *J Pediatr Surg* 2000;35(11): 1540-2.
42. Lalmand B, Avni EF, Nasr A, Ketelbant P, et al. Perinatal renal vein thrombosis: Sonographic demonstration. *J Ultrasound Med* 1990;9(8):437-42.
43. Duncan BW, Adzick NS, Longaker MT, Edwards JR, et al. In utero arterial embolism from renal vein thrombosis with successful postnatal thrombolytic therapy. *J Pediatr Surg* 1991;26(6):741-3.
44. Brill PW, Jagannath A, Winchester P, Markisz JA, et al. Adrenal hemorrhage and renal vein thrombosis in the newborn: MR imaging. *Radiology* 1989;170(1 Pt 1):95-8.
45. Laplante S, Patriquin HB, Robitaille P, Filiatrault D, et al. Renal vein thrombosis in children: evidence of early flow recovery with Doppler US. *Radiology* 1993;189(1):37-42.
46. Marks SD, Massicotte MP, Steele BT, Matsell DG, et al. Neonatal renal venous thrombosis: clinical outcomes and prevalence of prothrombotic disorders. *J Pediatr* 2005;146(6):811-6.
47. Sanders LD, Jequier S. Ultrasound demonstration of prenatal renal vein thrombosis. *Pediatr Radiol* 1989;19(2):133-5.
48. Cozzolino DJ, Cendron M. Bilateral renal vein thrombosis in a newborn: a case of prenatal renal vein thrombosis. *Urology* 1997;50(1):128-31.
49. Greene A, Cromie WJ, Goldman M. Computerized body tomography in neonatal renal vein thrombosis. *Urology* 1982;20(2):213-5.
50. Cremin BJ, Davey H, Oleszczuk-Raszke K. Neonatal renal venous thrombosis: sequential ultrasonic appearances. *Clin Radiol* 1991;44(1):52-5.
51. Hibbert J, Howlett DC, Greenwood KL, MacDonald LM, et al. The ultrasound appearances of neonatal renal vein thrombosis. *Br J Radiol* 1997;70(839):1191-4.
52. Avila ML, Solana CL, Laura JP, Suárez J, et al. Trombectomía auricular derecha en un recién nacido prematuro de muy bajo peso. *Arch Arg Pediatr* 2006;104(3):272-4.
53. Downs JB, Chapman RL Jr, Hawkins IF Jr. Prolonged radial artery catheterization. An evaluation of heparinized catheters and continuous irrigation. *Arch Surg* 1974;108(5):671-3.
54. Hoar PF, Wilson RM, Mangano DT, Avery GJ 2nd, et al. Heparin bonding reduces thrombogenicity of pulmonary-artery catheters. *N C Med J* 1981;305(17):993-5.
55. American Association of Critical-Care Nurses. Evaluation of the effects of heparinized and nonheparinized flush solutions on the patency of arterial pressure monitoring lines: the AACN Thunder Project. *Am J Crit Care* 1993;2(1): 3-15.
56. Cohen RS, Ramachandran P, Kim EH, Glasscock GF. Retrospective analysis of risks associated with an umbilical artery catheter system for continuous monitoring of arterial oxygen tension. *J Perinatol* 1995;15(3):195-8.
57. Bryant BG. Drug, fluid, and blood products administered through the umbilical artery catheter: complication experiences from one NICU. *Neonatal Netw* 1990;9(1):27-32.
58. Glickstein JS, Rutkowski M, Schacht R, Friedman D. Renal blood flow velocity in neonates with and without umbilical artery catheters. *J Clin Ultrasound* 1994;22(9):543-50.
59. De Veber G. Canadian paediatric ischemic stroke registry: analysis of children with arterial ischemic stroke. *Ann Neurol* 2000;48(3):526a.
60. Barron TF, Gusnard DA, Zimmerman RA, Clancy RR. Cerebral venous thrombosis in neonates and children. *Pediatr Neurol* 1992;8(2):112-6.
61. Shevell MI, Silver K, O'Gorman AM, Watters GV, et al. Neonatal dural sinus thrombosis. *Pediatr Neurol* 1989;5(3):161-5.
62. Rivkin MJ, Anderson ML, Kaye EM. Neonatal idiopathic cerebral venous thrombosis: an unrecognized cause of transient seizures or lethargy. *Ann Neurol* 1992;32(1):51-6.
63. De Veber G, Adams M, Andrew M. Neonatal cerebral thromboembolism: clinical and radiographic features. *Thromb Haemostas* 1997;78(Suppl):725.
64. De Veber G, Andrew M, Adams C, Bjornson B, et al. Cerebral sinovenous thrombosis in children. *N C Med J* 2001;345(6):417-23.

65. De Veber G, Andrew M. Canadian Pediatric Ischemic Stroke Registry: analysis I. *Pediatr Res* 1994;35:379a.
66. Lynch JK, Hirtz DG, De Veber G, Nelson KB. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. *Pediatrics* 2002;109(1):116-23.
67. Macchi PJ, Grossman RI, Gomori JM, Goldberg HI, et al. High field MR imaging of cerebral venous thrombosis. *J Comput Assist Tomogr* 1986;10(1):10-5.
68. Zimmerman RA, Bogdan AR, Gusnard DA. Pediatric magnetic resonance angiography: assessment of stroke. *Cardiovasc Intervent Radiol* 1992;15(1):60-4.
69. Medlock MD, Olivero WC, Hanigan WC, Wright RM, et al. Children with cerebral venous thrombosis diagnosed with magnetic resonance imaging and magnetic resonance angiography. *Neurosurgery* 1992;31(5):870-6.
70. Bezinque SL, Slovis TL, Touchette AS, Schave DM, et al. Characterization of superior sagittal sinus blood flow velocity using color flow Doppler in neonates and infants. *Pediatr Radiol* 1995;25(3):175-9.
71. De Veber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol* 2000;15(5):316-24.
72. De Veber G, Adams M, Andrew M. Canadian Pediatric Ischemic Stroke Registry (analysis III). *Can J Neurol Sci* 1995;22(Suppl):S24a.
73. Monagle P, Chan AK, Goldenberg NA, Ichord RN, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl): e737S- e801S.
74. Adcock DM, Brozna J, Marlar RA. Proposed classification and pathologic mechanisms of purpurafulminans and skin necrosis. *Semin Thromb Hemost* 1990;16(4):333-40.
75. Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. *J Pediatr* 1989;114(4 Pt 1):528-34.
76. Mahasandana C, Suvatte V, Chuansumrit A, Marlar RA, et al. Homozygous protein S deficiency in an infant with purpurafulminans. *J Pediatr* 1990;117(5):750-3.
77. Auletta MJ, Headington JT. Purpurafulminans. A cutaneous manifestation of severe protein C deficiency. *Arch Dermatol* 1988;124(9):1387-91.
78. Adcock DM, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. *Semin Thromb Hemost* 1990;16(4):283-92.
79. Marlar RA, Neumann A. Neonatal purpura fulminans due to homozygous protein C or protein S deficiencies. *Semin Thromb Hemost* 1990;16(4):299-309.
80. Andrew M, Monagle P, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton BC: Decker Inc; 2000. Chapter 3, Congenital prothrombotic disorders: presentation during infancy and childhood; Pages 47-110.
81. Williams MD, Chalmers EA, Gibson BE. The investigation and management of neonatal haemostasis and thrombosis. *Br J Haematol* 2002;119(2):295-309.
82. Dreyfus M, Magny JF, Bridey F, Schwarz HP, et al. Treatment of homozygous protein C deficiency and neonatal purpura fulminans with a purified protein C concentrate. *N C Med J* 1991;325(22):1565-8.
83. Chalmers EA. Neonatal thrombosis. *J Clin Pathol* 2000;53(6):419-23.
84. Edstrom CS, Christensen RD. Evaluation and treatment of thrombosis in the neonatal intensive care unit. *Clin Perinatol* 2000;27(3):623-41.
85. Lin PH, Dodson TF, Bush RL, Weiss VJ, et al. Surgical intervention for complications caused by femoral artery catheterization in pediatric patients. *J Vasc Surg* 2001;34(6):1071-8.
86. Altuna D. Trombosis en pediatría. *Hematología (B Aires)* 2013;17:38-43.
87. Dix D, Andrew M, Marzinotto V, Charpentier K, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatric* 2000;136(4):439-45.
88. Andrew M, Marzinotto V, Massicotte P, Blanchette V, et al. Heparin therapy in pediatric patients: a prospective cohort study. *Pediatric Res* 1994;35(1):78-83.
89. Andrew M, Ofosu F, Schmidt B, Brooker L, et al. Heparin clearance and ex vivo recovery in newborn piglets and adult pigs. *Thromb Res* 1988;52(6):517-27.
90. Schmidt B, Buchanan MR, Ofosu F, Brooker L, et al. Antithrombotic properties of heparin in a neonatal piglet model of thrombin-induced thrombosis. *Thromb Haemost* 1988;60(2):289-92.
91. Streif W, Goebel G, Chan AK, Massicotte MP. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003;88(5):F365-70.
92. Andrew M, Monagle P, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton BC: Decker Inc; 2000. Chapter 9, Oral anticoagulation therapy in pediatric patients; Págs.278-356.
93. Streif W, Andrew M, Marzinotto V, Massicotte P, et al. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999;94(9):3007-14.
94. Young G. Old and new antithrombotic drugs in neonates and neonates and infants. *Semin Fetal Neonatal Med* 2011;16(6):349-54.
95. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest* 2001;119(1 Suppl):344S-370S.
96. Ries M, Easton RL, Longstaff C, Zenker M, et al. Differences between neonates and adults in tissue-type-plasminogen activator (t-PA) catalyzed plasminogen activation with various effectors in carbohydrate sequences of fibrinogen chains. *Thromb Res* 2001;103(3):173-84.
97. Manco-Johnson MJ, Grabowski EF, Hellgreen M, Khemali AS, et al. Recommendations for tPA thrombolysis in children. On behalf of the Scientific Subcommittee on Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. *Thromb Haemost* 2002;88(1):157-8.
98. Zenz W, Arlt F, Sodia S, Beghold A. Intracerebral hemorrhage during fibrinolytic therapy in children: a review of the literature of the last thirty years. *Semin Thromb Hemost* 1997;23(3):321-32.
99. Farnoux C, Camard O, Pinquier D, Hurtaud-Roux MF, et al. Recombinant tissue-type plasminogen activator therapy of thrombosis in 16 neonates. *J Pediatr* 1998;133(1):137-40.
100. Zenz W, Muntean W, Beitzke A, Zobel G, et al. Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. *Br Heart J* 1993;70(4):382-5.
101. Andrew M, Monagle P, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton BC: Decker Inc; 2000. Chapter 10, Thrombolytic therapy; p. 357-84.
102. Browne M, Newall F, Campbell J, Savoia HF, et al. Thrombolytic therapy with tissue plasminogen activator (tPA), analysis of safety and outcome in children. *J Thromb Haemost* 2003;1(Suppl 1):P1488.