Updates in thrombosis in pediatrics: where are we after 20 years?

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The incidence of venous thromboembolism (VTE) in the pediatric population is increasing. Technological advances in medicine and imaging techniques, improved awareness of the disease, and longer survival of life-threatening or chronic medical conditions all contribute to the increase in VTE rates. There is a paucity of data on management of VTE based on properly designed clinical trials, but there is significant advancement in the last 2 decades. This review summarizes the progress made in pediatric thrombosis, including epidemiological changes, advances in anticoagulant agents, and outcomes of VTE.

Introduction

Children with venous thromboembolism (VTE) are increasingly diagnosed due in part to increasing survival rates of children with previously fatal diseases. Central venous lines (CVLs) are more commonplace especially in critically ill children, as well as improved imaging modalities which allow for a more accurate diagnosis, all contribute to an increase in the rate of thrombotic events. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin are in widespread use in the pediatric population. However, proper clinical trials addressing the issue of optimal dosing, therapeutic range, efficacy, and duration are lacking. Other anticoagulation agents, such as direct thrombin inhibitors (DTIs) and the anti-FXa inhibitor fondaparinux, have not been properly assessed for safety or efficacy in children.

The true frequency of adverse outcomes, particularly VTE-related mortality, recurrent VTE, and the development of postthrombotic syndrome (PTS) remain poorly understood. Future studies must aim to define a risk-stratified approach to antithrombotic therapy in children to ultimately improve long-term outcomes. This review summarizes the progress of anticoagulation therapy in the pediatric population in the last 2 decades, including epidemiological changes, advances in anticoagulant agents, and our understanding of outcomes for VTE.

Incidence of VTE in children

Almost 20 years ago, Andrew et al[1] published a comprehensive report on pediatric VTE based on a Canadian registry of children with venous thrombotic complications. The incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) was estimated to be 5.3 per 10 000 hospital admissions or 0.07 per 10 000 children.[1] According to the Dutch registry, the annual incidence of VTE was estimated to be 0.14 per 10 000 children.[2] Other national registries have reported similar incidences.[3,4] The Canadian neonatal registry reported an incidence of arterial and venous thromboembolism of 24 per 10 000 admissions to the neonatal intensive care unit.[5] In Germany, a neonatal survey estimated an incidence of symptomatic venous and arterial thromboembolism of 0.51 per 10 000 births.[6] Subsequent single center reports (in Alabama) reported an incidence of thrombosis of 21.9 per 10 000 admissions (2006-2008).[7] Using the Kids' Inpatient Database (KID) 2006, Setty et al reported that VTE was identified in 18.8 per 10 000 discharges.[8] The Pediatric Health Information System (PHIS) estimates the VTE incidence as 58.0 per 10 000 discharges.[9] The KID[8] and PHIS[9] databases report that the majority of VTEs were associated with cardiovascular disease, which is in contrast to the earlier Canadian data[1] showing that cancer was the most commonly associated condition in childhood VTE. Therefore, the data suggest a 3- to 10-fold increase in the frequency of VTE diagnosis in hospitalized children over the past 15 years.

These data are supported by studies that have specifically reported changing rates of VTE with time, for example, from 34-58 cases per 10 000 admissions from 2001-2007[9] or from 0.3-28.8 per 10 000 admissions from 1992-2005.[10] Other studies have also reported increasing trends.[11] Most studies report a bimodal peak distribution in which infants less than 1 year of age and adolescents are at the greatest risk for development of VTE, with overall equal sex distribution between male and female subjects, although this may not be true when considering specific age groups such as neonates or adolescents.

Associated conditions

Both adult and pediatric patients who have 2 or more inherited thrombophilia traits have been shown to be at an increased risk of VTE.[12,13] The prevalence of thrombophilic defects in children with VTE varies widely, from 10%-78%.[1,14] Differences in patient cohorts, definition of thrombosis, types of investigations, and study size most likely contribute to the wide variations in the prevalence of VTE. A meta-analysis of observational studies published from 1970-2007 on the impact of thrombophilia traits on VTE development or recurrence in children reported that all investigated traits showed a significant association with first-ever VTE.[12] However, many of the included studies had methodological flaws, so the relative contribution of prothrombotic defects to a child's susceptibility to VTE remains to be elucidated.

Idiopathic VTE in children is rare, and approximately 95% of VTEs in children are usually associated with serious disease. It is

debatable whether children presenting with secondary VTE, such as CVL-related DVT, should be screened for congenital prothrombotic disorders because the results do not generally affect the management of the child. The use of oral contraceptives increases the risk of VTE by 5-fold compared with nonusers (odds ratio = 5.0; 95% confidence interval, 4.2-5.8).[15] Routine screening before the initiation of oral contraceptives is not recommended.[16] Screening for congenital prothrombotic risk factors may be appropriate for children with idiopathic VTE. To date, there is no clinical evidence to support routine screening of asymptomatic children with a positive family history of thrombophilic defect.[17]

Diagnosis and location of peripheral thrombotic events

There is a high incidence of upper extremity thrombosis in children, reflecting a strong association with CVL placement. Modalities used to diagnose VTE in pediatric patients are ultrasound (US), venography, computed tomography (CT), and magnetic resonance imaging (MRI). US is often used because it is readily available, noninvasive, inexpensive, portable, and sensitive to the lower extremities and abdominal viscera, but has poor sensitivity for upper venous system thrombosis.[18] The PARKAA (Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase) study recommended combined venography and US be used in the diagnosis of VTE in the upper venous system of children.[19] Venography alone was unable to detect jugular vein thrombosis and US was not sensitive enough to detect intrathoracic VTE.

CT scan or MRI can be used for the diagnosis of DVT in the subclavian, innominate, or superior vena cava. Magnetic resonance venography (MRV) has been used in adults to diagnose thrombosis, but data in children are lacking. MRV has a high rate of sensitivity and specificity, is noninvasive, and there is no radiation exposure. However, the technique may require sedation in the pediatric population. US is recommended to evaluate VTE in the lower limb venous system in children.[17] MRV may be helpful in evaluating the proximal extent of lower limb thrombosis.[20]

Diagnosis and distribution of PE

There are currently no studies to evaluate the sensitivity and specificity of any diagnostic imaging tests to detect PE in children. Data are extrapolated from adult studies, but isotope lung scanning or CT pulmonary angiography could be considered as the initial imaging modality used for suspected PE.[17]

Treatment

Randomized controlled trials on pediatric anticoagulation are lacking, so physicians rely on consensus evidence-based guidelines.[21] Generally, for the treatment of VTE, most patients receive 3 or 6 months of anticoagulant therapy. Over the last decade, treatment patterns reveal a shift toward the use of LMWH. Other alternatives to traditional anticoagulants are currently being explored for the pediatric population. Patient age, coexisting medical conditions, and compliance issues all factor into the choice of anticoagulants used in children.

Heparin therapy

UFH. UFH has some advantages, primarily a short half-life and the ability to be completely reversed with protamine if necessary. However, difficulties of UFH use include the need for venous access, frequent monitoring, and activated partial thromboplastin time (aPTT) monitoring issues in the laboratory. The correlation between aPTT and heparin effect as measured by anti-FXa ($r^2 = 0.51$) and protamine titration ($r^2 = 0.55$) is relatively weak.[22] aPTT was less predictive of anti-FXa effect in children less than 2 years of age.[23] Therefore, it is suggested that both aPTT and anti-FXa assays be used for the monitoring of UFH therapy in neonates.[24] Coagulation assay results are dependent upon the type of reagent, commercial kits, and analyzers used in the laboratory.[25] Ideally, each laboratory should set up its own pediatric reference ranges for aPTT and anti-FXa assays. Adverse effects of UFH therapy include bleeding, heparin-induced thrombocytopenia (HIT), and heparin-induced osteopenia. HIT is a rare but severe complication of heparin therapy that has been reported in up to 2.3% of children treated in intensive care units.[26]

LMWH. The 3 national registries from Canada, the Netherlands, and the United Kingdom have shown a trend toward the use of LMWH in the clinical management of children with DVT over the last decade. The most commonly reported off-label LMWHs used in the pediatric population are enoxaparin, dalteparin, nadroparin, and tinzaparin, although most studies are case reports, small case series, or observational studies.

The REVIVE (Registry of Endovascular Implantation of Valves in Europe) study is the only randomized controlled trial assessing the safety and efficacy of anticoagulant use in children with VTE.[27] Although the study was terminated early and underpowered, the data showed that LMWH was as effective as UFH/oral anticoagulants in children with first episode of VTE. Other observational studies have shown that the majority of neonates and children treated with LMWH have a positive clinical response to treatment with low risk of major bleeding. Bleeding risk for children on LMWH range from 0%-10.8%.[27,28] PROTEKT (Prophylaxis of Thromboembolism in Kids Trial), a multicenter, randomized trial of LMWH for the prevention of CVL-related thrombosis in children, reported no significant difference in the incidence of CVL-related thrombosis between the treatment and control groups.[29] This study was terminated early due to slow recruitment, and therefore the study was underpowered. Routine anticoagulation prophylaxis is not recommended for children with CVL.[21]

For neonates, the recommended starting dose of LMWH is 1.5 mg/kg, but a recent study suggested a higher starting dose of 1.7 mg/kg every 12 hours for term neonates and 2.0 mg/kg every 12 hours for preterm neonates in the absence of considerable bleeding risk.[30] Another retrospective chart review evaluating enoxaparin dosing requirements in infants and children showed that a higher starting dose of enoxaparin (1.7 mg/kg) compared with the starting standard dose (1.5 mg/kg) may result in a faster attainment of therapeutic anti-FXa levels, with significantly fewer venipunctures and dose adjustments and no increase in adverse outcomes.[31] This study suggested that younger children required a higher weight-based dose of enoxaparin (< 3 months: 1.83 mg/kg [SD = 0.31]; 3-12 months: 1.48 mg/kg [SD = 0.36]; 1-5 years: 1.23 mg/kg [SD = 0.21]; and 6-18 years: 1.13 mg/kg [SD = 0.16]) to reach therapeutic anti-FXa levels.[31]

Thrombolytic therapy

There have been reports of successful use of tissue plasminogen activator (tPA) in children, but there is still debate on dosing.[32] The use of thrombolytic therapy is usually reserved for children with extensive thrombosis (eg, massive PE) because there is a significant risk of bleeding: up to 50% of treated children.[33] The role of

monitoring is uncertain, although some studies suggest that fibrinogen levels should be maintained above 100 mg/dL and platelet counts above 100 000 $\times$ 10^9/L.[34,35] Optimal duration of therapy is uncertain, although the risk of bleeding is said to increase with increasing duration of treatment.[35] Other studies have reported that the use of tPA reduces the risk of PTS in children with high-risk lower limb DVT.[36]

Oral anticoagulant therapy

Vitamin K antagonists may be more practical for older children, but the optimal intensity of therapy in childhood VTE management has not been fully elucidated. The target international normalized ratio of 2.5 (range, 2-3) is still based on adult data and is generally accepted as appropriate for the pediatric population with VTE.[17] Warfarin international normalized ratio monitoring can be performed in the outpatient or home setting with formal training on the whole blood capillary monitoring system, thus negating the need for repeated venous access. The bleeding risk in children on warfarin is estimated at 0.5%.[37] Long-term warfarin therapy in children may be associated with the development of osteoporosis.[38]

Other therapy

DTIs. Lepirudin, bivalirudin, and argatroban are 3 DTIs that have been used in children. However, lepirudin appears to cause more bleeding.[39] There are prospective studies on bivalirudin and argatroban. DTIs may be more advantageous because they bind directly to thrombin to form inactive complexes and are therefore not dependent on plasma antithrombin levels. DTIs bind both circulating and bound thrombin, have more predictable pharmacokinetics than heparin, and do not cause HIT. There are no available antidotes for DTIs and they must be used in a hospital setting because they are administered by continuous infusion (except for dabigatran, an oral DTI that is currently in clinical trials in children [www.ClinicalTrials.gov identifier NCT01083732]).

A prospective study on the use of bivalirudin in neonates[40] and a retrospective study in children[41] showed early clot resolution with low bleeding risk. A phase 1 trial, UNBLOCK (Utilization of Bivalirudin On Clots in Kids; www.ClinicalTrials.gov identifier NCT00812370), investigating the effect of bivalirudin on clot dissolution in children (6 months to 18 years) is ongoing.

Argatroban is used mainly in children with suspected HIT, especially in patients dependent on anticoagulation (eg, during extracorporeal circulation) or in need of a cardiac assist device.[42,43] Argatroban is the only anticoagulant with dosing guidelines for pediatric patients included in the prescribing information in the United States (http://www.argatroban.com).

Other anticoagulants. Fondaparinux is a long-acting, synthetic, antithrombin-dependent inhibitor of FXa. There is only one prospective study on fondaparinux in children,[44] which showed an excellent safety profile, with nearly all patients at therapeutic levels after the initial dose; once-daily dosing kept patients at therapeutic levels. This study did not assess efficacy. The disadvantage of fondaparinux is that it cannot be reversed with protamine. There is an ongoing prospective dose-finding and safety study on fondaparinux in children (www.ClinicalTrials.gov identifier NCT00412464).

Rivaroxaban and dabigatran, both approved for clinical use in adults, are in clinical development for the pediatric population. All new anticoagulants need a pediatric investigation strategy. Many of these anticoagulation agents are in the planning phase or have started recruitment for studies in the pediatric population (eg, apixaban, semuloparin sodium, edoxaban, and vorapaxar). Danaparoid sodium is most commonly used in children with HIT as an alternative anticoagulation therapy for those who are intolerant of heparin.[45,46] A review of novel anticoagulants has been published previously.[47]

Outcomes

Mortality

The Canadian registry reported a mortality rate of 2.2% directly attributable to VTEs.[48]

Recurrent thromboembolic disease

Estimates of VTE recurrence in childhood vary from 4%-21.3%, depending on duration of follow-up, and were highest for children with idiopathic thrombosis.[49] The recurrence risk did not decrease with increased duration of anticoagulation.[50] In neonates, VTE recurrence is approximately 3%.[12] Risk factors reported to be predictive of VTE recurrence include intrinsic coagulation deficiencies,[51] homozygous factor V Leiden,[51] prothrombin gene mutation,[52] antiphospholipid Abs,[53] multitrait thrombophilia,[51] and elevated D-dimer and factor VIII at diagnosis and after standard-duration anticoagulant therapy.[54]

PTS

PTS is a chronic complication of VTE and varies in severity. It remains a concern for long-term morbidity in children who survive decades after a thrombotic event. A meta-analysis reported an overall rate of 26%,[55] with individual studies varying between 10% and 70%.[48,49,54] Kids-DOTT (Prospective Multi-Center Evaluation of the Duration of Therapy for Thrombosis in Children) is a multicenter trial investigating the duration of anticoagulation in children with no known risk factors for recurrence or poor outcomes, which will also likely include PTS incidence rates as part of their long-term outcome study.

There is an urgent need for a validated tool for assessing pediatric PTS in both the upper and lower venous systems, especially with regard to subjective (ie, symptoms) evaluations.[56] The modified Villalta scale[56,57] and the Manco-Johnson instrument[55] have been used to evaluate pediatric PTS. Treatment of PTS is supportive in nature, with the use of compression stockings, limb elevation and avoidance of prolonged standing, and analgesics for pain control.

Discussion

The increase in incidence of VTE among children may be attributable to increased awareness of the condition, medical and technological advances, and longer survival of life-threatening or chronic medical conditions. Identifying patients at risk for thrombosis is the first step toward preventing VTE in children. Evidence-based recommendations are lacking, so management decisions must be made by carefully balancing the risk and benefit in each individual case.

Alternative approaches to currently available anticoagulants are needed, however, data obtained on new agents in adults cannot be directly extrapolated for use in the pediatric population. There is still a widespread tendency to use novel anticoagulants in the pediatric population, in whom proper safety and efficacy data are lacking. Controlled clinical studies need to be performed in children

before any recommendations can be made. To facilitate comparisons across studies, an international concerted effort led to a position paper published by the International Society on Thrombosis and Haemostasis (ISTH) subcommittee outlining definitions and safety outcomes for clinical trials in VTE in children.[58]

When the American College of Chest Physicians (ACCP) pediatric guidelines were first published in 1995,[59] there were less than 25 recommendations for anticoagulation therapy in children. The 2012 ACCP *Chest* guidelines[21] have over 100 recommendations, but, unfortunately, the majority are still at the grade 2C level of evidence and are not uniformly used. A multicenter prospective study on current treatment practices for VTE in pediatric intensive care units revealed that there was incomplete compliance with ACCP guidelines for VTE prophylaxis.[60] More uniform use of such guidelines would at least allow better cohort and follow-up data to be gathered and analyzed appropriately.

After 20 years, there is still an urgent need for clinical trials to determine the optimal preventative and treatment strategies for children affected with thrombotic complications.

Disclosures

Conflict-of-interest disclosure: A.K.C.C. is on the board of directors or an advisory committee for Boehringer Ingelheim, Aventis, and BMS and has consulted for Bayer. P.M. has consulted for Bayer. Off-label drug use: All anticoagulant drugs remain off-label in children.

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References

1. Andrew M, David M, Adams M et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood.* 1994;83(5):1251-1257.
2. van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr*. 2001;139(5):676-681.
3. Gibson BE, Chalmers EA, Bolton-Maggs P, Henderson DJ, Lynn R. Thromboembolism in childhood: a prospective two-year BPSU study in the United Kingdom. *Br J Haematol*. 2004;125(suppl 1):1.
4. Newall F, Wallace T, Crock C et al. Venous thromboembolic disease: a single-centre case series study. *J Paediatr Child Health*. 2006;42(12):803-807.
5. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics.* 1995;96(5 pt 1):939-943.
6. Nowak-Göttl U, von Kries R, Gobel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal Ed*. 1997;76(3):F163-F167.
7. Wright JM, Watts RG. Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. *J Pediatr Hematol Oncol.* 2011;33(4):261-264.
8. Setty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: A tertiary care complication of chronic diseases. *Pediatr Blood Cancer*. 2012;59(2):258-264.
9. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics.* 2009;124(4):1001-1008.
10. Sandoval JA, Sheehan MP, Stonerock CE, Shafique S, Rescorla FJ, Dalsing MC. Incidence, risk factors, and treatment patterns for deep venous thrombosis in hospitalized children: an increasing population at risk. *J Vasc Surg*. 2008;47(4):837-843.
11. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study. *J Pediatr*. 2011;159(4):663-669.
12. Young G, Albisetti M, Bonduel M et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. *Circulation.* 2008;118(13):1373-1382.
13. Almawi WY, Tamim H, Kreidy R et al. A case control study on the contribution of factor V-Leiden, prothrombin G20210A, and MTHFR C677T mutations to the genetic susceptibility of deep venous thrombosis. *J Thromb Thrombolysis*. 2005;19(3):189-196.
14. Ehrenforth S, Junker R, Koch HG et al. Multicentre evaluation of combined prothrombotic defects associated with thrombophilia in childhood. Childhood Thrombophilia Study Group. *Eur J Pediatr*. 1999;158 (Suppl 3):S97-104.:S97-104.
15. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ*. 2009;339:b2921.
16. Dietrich JE, Hertweck SP. Thrombophilias in adolescents: the past, present and future. *Curr Opin Obstet Gynecol*. 2008;20(5):470-474.
17. Chalmers E, Ganesen V, Liesner R et al. Guideline on the investigation, management and prevention of venous thrombosis in children. *Br J Haematol*. 2011;154(2):196-207.
18. Chan AK, deVeber G, Monagle P, Brooker LA, Massicotte PM. Venous thrombosis in children. *J Thromb Haemost*. 2003;1(7):1443-1455.
19. Male C, Chait P, Ginsberg JS et al. Comparison of venography and ultrasound for the diagnosis of asymptomatic deep vein thrombosis in the upper body in children: results of the PARKAA study. Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase. *Thromb Haemost*. 2002;87(4):593-598.
20. Fraser DG, Moody AR, Davidson IR, Martel AL, Morgan PS. Deep venous thrombosis: diagnosis by using venous enhanced subtracted peak arterial MR venography versus conventional venography. *Radiology.* 2003;226(3):812-820.
21. Monagle P, Chan AK, Goldenberg NA 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.
22. Andrew M, Marzinotto V, Massicotte P et al. Heparin therapy in pediatric patients: a prospective cohort study. *Pediatr Res*. 1994;35(1):78-83.
23. Chan AK, Black L, Ing C, Brandao LR, Williams S. Utility of aPTT in monitoring unfractionated heparin in children. *Thromb Res*. 2008;122(1):135-136.
24. Yang JY, Chan AK. Neonatal systemic venous thrombosis. *Thromb Res*. 2010;126(6):471-476.
25. Monagle P, Barnes C, Ignjatovic V et al. Developmental

haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost*. 2006;95(2):362-372.
26. Schmugge M, Risch L, Huber AR, Benn A, Fischer JE. Heparin-induced thrombocytopenia-associated thrombosis in pediatric intensive care patients. *Pediatrics.* 2002;109(1):E10.
27. Massicotte P, Julian JA, Gent M et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res*. 2003;109(2-3):85-92.
28. Massicotte P, Adams M, Marzinotto V, Brooker LA, Andrew M. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr*. 1996;128(3): 313-318.
29. Massicotte P, Julian JA, Gent M et al. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. *Thromb Res*. 2003;109(2-3):101-108.
30. Malowany JI, Monagle P, Knoppert DC et al. Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thromb Res*. 2008;122(6):826-830.
31. Bauman ME, Belletrutti MJ, Bajzar L et al. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeutic levels. *Thromb Haemost*. 2009; 101(1):86-92.
32. Yee DL, Chan AK, Williams S, Goldenberg NA, Massicotte MP, Raffini LJ. Varied opinions on thrombolysis for venous thromboembolism in infants and children: findings from a survey of pediatric hematology-oncology specialists. *Pediatr Blood Cancer*. 2009;53(6):960-966.
33. Biss TT, Brandao LR, Kahr WH, Chan AK, Williams S. Clinical features and outcome of pulmonary embolism in children. *Br J Haematol*. 2008;142(5):808-818.
34. Macartney CA, Chan AK. Thrombosis in children. *Semin Thromb Hemost*. 2011;37(7):763-761.
35. Albisetti M. Thrombolytic therapy in children. *Thromb Res*. 2006;118(1):95-105.
36. Goldenberg NA, Durham JD, Knapp-Clevenger R, Manco-Johnson MJ. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. *Blood.* 2007;110(1):45-53.
37. Streif W, Andrew M, Marzinotto V et al. Analysis of warfarin therapy in pediatric patients: A prospective cohort study of 319 patients. *Blood.* 1999;94(9):3007-3014.
38. Barnes C, Newall F, Ignjatovic V et al. Reduced bone density in children on long-term warfarin. *Pediatr Res*. 2005;57(4):578-581.
39. Shantsila E, Lip GY, Chong BH. Heparin-induced thrombocytopenia. A contemporary clinical approach to diagnosis and management. *Chest.* 2009;135(6):1651-1664.
40. Young G, Tarantino MD, Wohrley J, Weber LC, Belvedere M, Nugent DJ. Pilot dose-finding and safety study of bivalirudin in infants <6 months of age with thrombosis. *J Thromb Haemost*. 2007;5(8):1654-1659.
41. Rayapudi S, Torres A, Jr., Deshpande GG, Ross MP, Wohrley JD, Young G et al. Bivalirudin for anticoagulation in children. *Pediatr Blood Cancer*. 2008;51(6):798-801.
42. Hursting MJ, Dubb J, Verme-Gibboney CN. Argatroban anticoagulation in pediatric patients: a literature analysis. *J Pediatr Hematol Oncol*. 2006;28(1):4-10.
43. Young G, Boshkov LK, Sullivan JE et al. Argatroban therapy in pediatric patients requiring nonheparin anticoagulation: an open-label, safety, efficacy, and pharmacokinetic study. *Pediatr Blood Cancer*. 2011;56(7):1103-1109.
44. Young G, Yee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: a prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. *Pediatr Blood Cancer*. 2011;57(6):1049-1054.
45. Bidlingmaier C, Magnani HN, Girisch M, Kurnik K. Safety and efficacy of danaparoid (Orgaran) use in children. *Acta Haematol*. 2006;115(3-4):237-247.
46. Risch L, Fischer JE, Herklotz R, Huber AR. Heparin-induced thrombocytopenia in paediatrics: clinical characteristics, therapy and outcomes. *Intensive Care Med*. 2004;30(8):1615-1624.
47. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. *Blood.* 2010;115(1):15-20.
48. Monagle P, Adams M, Mahoney M et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. *Pediatr Res*. 2000;47(6):763-766.
49. van Ommen CH, Heijboer H, van den Dool EJ, Hutten BA, Peters M. Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome. *J Thromb Haemost*. 2003;1(12):2516-2522.
50. Estepp JH, Smeltzer M, Reiss UM. The impact of quality and duration of enoxaparin therapy on recurrent venous thrombosis in children. *Pediatr Blood Cancer*. 2012;59(1):105-109.
51. Nowak-Göttl U, Junker R, Kreuz W et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood.* 2001;97(4):858-862.
52. Kenet G, Kirkham F, Niederstadt T et al. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. *Lancet Neurol*. 2007;6(7):595-603.
53. Berkun Y, Padeh S, Barash J et al. Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum*. 2006; 55(6):850-855.
54. Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *N Engl J Med*. 2004;351(11):1081-1088.
55. Goldenberg NA, Donadini MP, Kahn SR et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. *Haematologica*. 2010;95(11):1952-1959.
56. Goldenberg NA, Brandao L, Journeycake J et al. Definition of post-thrombotic syndrome following lower extremity deep venous thrombosis and standardization of outcome measurement in pediatric clinical investigations. *J Thromb Haemost*. 2012;10(3):477-480.
57. Kuhle S, Koloshuk B, Marzinotto V et al. A cross-sectional study evaluating post-thrombotic syndrome in children. *Thromb Res*. 2003;111(4-5):227-233.
58. Mitchell LG, Goldenberg NA, Male C, Kenet G, Monagle P, Nowak-Gottl U. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. *J Thromb Haemost*. 2011;9(9): 1856-1858.
59. Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest.* 1995;108(4 Suppl):506S-522S.
60. Hanson SJ, Lawson KA, Brown AM et al. Current treatment practices of venous thromboembolism in children admitted to pediatric intensive care units. *Paediatr Anaesth*. 2011;21(10): 1052-1057.