Antithrombotic Therapy in Neonates and Children*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This chapter about antithrombotic therapy in neonates and children is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs, and Grade 2 suggests that individual patient values may lead to different choices (for a full understanding of the grading, see Guyatt et al in this supplement, pages 123S–131S). In this chapter, many recommendations are based on extrapolation of adult data, and the reader is referred to the appropriate chapters relating to guidelines for adult populations. Within this chapter, the majority of recommendations are separate for neonates and children, reflecting the significant differences in epidemiology of thrombosis and safety and efficacy of therapy in these two populations. Among the key recommendations in this chapter are the following: In children with first episode of venous thromboembolism (VTE), we recommend anticoagulant therapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) [Grade 1B]. Dosing of IV UFH should prolong the activated partial thromboplastin time (aPTT) to a range that corresponds to an anti-factor Xa assay (anti-FXa) level of 0.35 to 0.7 U/mL, whereas LMWH should achieve an anti-FXa level of 0.5 to 1.0 U/mL 4 h after an injection for twice-daily dosing. In neonates with first VTE, we suggest either anticoagulation or supportive care with radiologic monitoring and subsequent anticoagulation if extension of the thrombosis occurs during supportive care (Grade 2C). We recommend against the use of routine systemic thromboprophylaxis for children with central venous lines (Grade 1B). For children with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage (ICH), we recommend anticoagulation initially with UFH, or LMWH and subsequently with LMWH or vitamin K antagonists (VKAs) for a minimum of 3 months (Grade 1B). For children with non–sickle-cell disease-related acute arterial ischemic stroke (AIS), we recommend UFH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes have been excluded (Grade 1B). For neonates with a first AIS, in the absence of a documented ongoing cardioembolic source, we recommend against anticoagulation or aspirin therapy (Grade 1B). ***(CHEST 2008; 133:887S–968S)***

Key words: anticoagulation therapy; antithrombotic therapy; children; evidence based; neonates; pediatric; thrombosis

Abbreviations: ACCP = American College of Chest Physicians; AIS = arterial ischemic stroke; anti-FXa = anti-factor Xa assay; APLA = antiphospholipid antibodies; APTT = activated partial thromboplastin time; BCPS = bilateral cavopulmonary shunts; CC = cardiac catheterization; CI = confidence interval; CVL = central venous line; CSVT = cerebral sinovenous thrombosis; DVT = deep venous thrombosis; FFP = fresh frozen plasma; HIT = heparin-induced thrombocytopenia; ICH = intracranial hemorrhage; INR = international normalized ratio; IVC = inferior vena cava; IVH = intraventricular hemorrhage; LMWH = low-molecular-weight heparin; MBTS = modified Blalock-Taussig shunt; NEC = necrotizing enterocolitis; OR = odds ratio; PE = pulmonary embolus; PTS = postthrombotic syndrome; RCT = randomized controlled trial; REVIVE = Reviparin in Venous Thromboembolism; RR = relative risk; rtPA = recombinant tissue plasminogen activator; RVT = renal vein thrombosis; SK = streptokinase; TCD = transcranial Doppler; TE = thromboembolism; TIA = transient ischemic attack; tPA = tissue plasminogen activator; UAC = umbilical artery catheter; UFH = unfractionated heparin; UK = urokinase; UVC = umbilical venous catheter; VAD = ventricular assist device; VKA = vitamin K antagonist; VTE = venous thromboembolism

In neonates with VTE (central venous line [CVL] and non-CVL related):

1.1.1. We suggest that CVLs or umbilical venous catheter (UVCs) associated with confirmed thrombosis be removed, if possible, after 3 to 5 days of anticoagulation (Grade 2C).

1.1.2. We suggest either initial anticoagulation, or supportive care with radiologic monitoring (Grade 2C); **however, we recommend subsequent anticoagulation if extension of the thrombosis occurs during supportive care** (Grade 1B).

1.1.3. We suggest anticoagulation should be with either: (1) LMWH given twice daily and adjusted to achieve an anti-FXa level of 0.5 to 1.0 U/mL; or (2) UFH for 3 to 5 days adjusted to achieve an anti-FXa of 0.35 to 0.7 U/mL or a corresponding aPTT range, followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months (Grade 2C).

1.1.4. We suggest that if either a CVL or a UVC is still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH be given to prevent recurrent VTE until such time as the CVL or UVC is removed (Grade 2C).

1.1.5. We recommend against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 1B).

1.1.6. We suggest that if thrombolysis is required, the clinician use tissue plasminogen activator (tPA) and supplement with plasminogen (fresh frozen plasma) prior to commencing therapy (Grade 2C).

In children with deep vein thrombosis (DVT):

1.2.1. We recommend anticoagulant therapy with either UFH or LMWH (for additional information, see Section 1.2, DVT in Children) [Grade 1B].

1.2.2. We recommend initial treatment with UFH or LMWH for at least 5 to 10 days (Grade 1B). **For patients in whom clinicians will subsequently prescribe VKAs, we recommend beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the international normalized ratio (INR) has not exceeded 2.0** (Grade 1B). **After the initial 5- to 10-day treatment period, we suggest LMWH rather than VKA therapy if therapeutic levels are difficult to maintain on VKA therapy or if VKA therapy is challenging for the child and family** (Grade 2C).

1.2.3. We suggest children with idiopathic thromboembolism (TE) receive anticoagulant therapy for at least 6 months, using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0), or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C). *Underlying values and preferences:* The suggestion to use anticoagulation therapy to treat idiopathic DVTs in children for at least 6 months rather than on a lifelong basis places a relatively high value on avoiding the inconvenience and bleeding risk associated with antithrombotic therapy, and a relative low value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor.

1.2.4. In children with secondary thrombosis in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for at least 3 months using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C).

1.2.5. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing l-asparaginase therapy, we suggest continuing anticoagulant therapy in either therapeutic or prophylactic doses until the risk factor has resolved (Grade 2C).

1.2.6. For children with recurrent idiopathic thrombosis, we recommend indefinite treatment with VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) [Grade 1A].

Remark: For some patients, long-term LMWH may be preferable; however, there are little or no data about the safety of long-term LMWH in children.

1.2.7. For children with recurrent secondary TE with an existing reversible risk factor for thrombosis, we suggest anticoagulation until the removal of the precipitating factor but for a minimum of 3 months (Grade 2C).

1.2.8. If a CVL is no longer required, or is nonfunctioning, we recommend it be removed (Grade 1B). **We suggest at least 3 to 5 days of anticoagulation therapy prior to its removal** (Grade 2C). **If**

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