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Evidence based recommendation for anticoagulation in children with congenital heart disease (Primary prophylaxis: cardiac catheterization, mechanical heart valves, cardiac shunts, central lines and Secondary prophylaxis: Systemic thrombosis and stroke)

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Evidence based recommendations for antithrombotic therapy in infants and children have been summarized and published by the American Academy of Chest Physicians (AACP). The guidelines are updated and republished every 4 years by an expert panel in pediatric anticoagulation. The guidelines are graded based on the level of evidence supporting each recommendation thus clarifying for the treating physician how strong the recommendations are. The grading is based on an estimate of risk and benefit and the methodologic strength of the studies supporting the recommendation. Grade 1 and grade 2 recommendations differ in that the estimate of risk and benefit associated with each approach was either clear or unclear, respectively. The methodologic strength of the study(ies) providing support for the recommendation is then graded as wither A, B, or C. Grade A and B represent randomized trials without or with important limitations, respectively. Grade C represents observational studies. The latest summary further clarifies the recommendation by including any underlying values and preferences associated with the recommendation.

Summary of pediatric recommendations for antithrombotic therapy:

1.1. Venous thromboembolism

In neonates with venous thromboembolism (VTE)

1.1.1 We suggest treatment with either unfractionated heparin or LMWH or monitoring radiographically and anticoagulation if extension occurs (Grade 2C).

1.1.2 We suggest that if they elect anticoagulation, clinicians administer unfractionated heparin or LMWH, and subsequently administer LMWH for 10 days to 3 months (Grade 2C).

1.1.3 We suggest that clinicians adjust the dose of unfractionated heparin to prolong the APPT corresponding to an antifactor Xa level of 0.35 to 0.7 units/ml (Grade 2C).

1.1.4 We suggest that clinicians adjust the dose of LMWH to achieve an antifactor Xa level of 0.5 to 1.0 units/ml (Grade 2C).

1.1.5 We suggest, that if the thrombus extends following discontinuation of heparin therapy, clinicians administer vitamin K antagonists or extended LMWH therapy (Grade 2C).

1.1.6 We suggest that clinicians *not* use thrombolytic therapy for VTE in neonates unless there is major vessel occlusion that is causing critical compromise of organs or limbs (Grade 2C). If thrombolytic therapy is used, we suggest supplementation with plasminogen (fresh frozen plasma) immediately prior to thrombolysis (Grade 2C).

1.1.7 We suggest that, in general, clinicians should remove either CVLs or UVCs that are in situ. However if either CVLs or UVCs are still in place at the completion of the above therapy, we suggest prophylactic dosing with LMWH to prevent recurrent VTE until such time as the CVL or UVC is removed (both Grade 2C).

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1.2 Systemic venous thromboembolic disease in children

1.2.1 First thromboembolic event

For children (over 2 months of age) with an initial TE:

1.2.1.1 We recommend treatment with IV heparin sufficient to prolong the APTT to a range that corresponds to an antifactor Xa level of 0.35 to 0.7 units/ml or LMWH sufficient to achieve an antifactor Xa level of 0.5 to 1.0 units/ml 4 h after an injection (Grade 1C+).

1.2.1.2 We recommend initial treatment with heparin or LMWH for 5 to 10 days (Grade 1C+). For patients in whom subsequent vitamin K antagonists will be used, we recommend beginning oral therapy as early as day 1 and discontinuing heparin/LMWH on day 6 if the INR is therapeutic on two consecutive days (Grade 1C+). For massive PE or extensive DVT, we recommend a longer period of heparin or LMWH therapy (Grade 1C+).

1.2.1.3 We suggest continuing anticoagulant therapy for idiopathic TEs for at least 6 months using vitamin K antagonists to achieve a target INR of 2.5, range 2.0 to 3.0 or alternatively LMWH to maintain an antifactor Xa level of 0.5 to 1.0 units/ml (Grade 2C).

Underlying values and preferences: The suggestion to anticoagulate idiopathic DVT in children for at least 6 months rather than lifelong places a relatively high value on avoiding the known risk of bleeding secondary to anticoagulant therapy in young active adults, and less importance on the unknown risk of recurrence in the absence of an ongoing clinical precipitating factor.

1.2.1.4 We suggest that for secondary TEs, anticoagulant therapy be continued for at least 3 months using vitamin K antagonists to achieve a target INR of 2.5, range 2.0 to 3.0 or alternatively LMWH to maintain an antifactor Xa level of 0.5 to 1.0 units/ml (Grade 2C).

1.2.1.5 We suggest that in the presence of ongoing risk factors, such as active nephrotic syndrome, ongoing asparaginase therapy, or a lupus anticoagulant, anticoagulant therapy, in either therapeutic or prophylactic doses continue until the risk factor has resolved (Grade 2C).

1.2.1.6 We suggest that clinicians not use thrombolytic therapy routinely for venous TE in children (Grade 2C). Treatment needs to be individualized, based on the size and location of the thrombus and the degree of organ compromise. If thrombolytic therapy is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen (fresh frozen plasma) (Grade 2C).

1.2.2 Recurrent thromboembolic event

1.2.2.1 For children with recurrent idiopathic TEs: we recommend indefinite therapy with either therapeutic or prophylactic doses of vitamin K antagonists (Grade 1C+). We suggest LMWH as an alternative if vitamin K antagonist therapy is too difficult (Grade 2C).

1.2.2.2 For children with recurrent secondary TEs: we suggest following the initial 3 months of therapy, anticoagulation therapy be continued for at least a further 3 months, or until removal of any precipitating factors (Grade 2C).

1.2.3 CVL-related thrombosis:

There are two aspects to the management of CVL-related thrombosis. First, management of the CVL itself and, second, anticoagulation therapy.

1.2.3.1 We suggest that if the CVL is no longer required, or is non-functioning, it be removed (Grade 2C). We suggest at least 3–5 days of anticoagulation prior to removal. If CVL access is required and the CVL involved is still functioning, we suggest the CVL to remain in situ (Grade 2C).

Remark: anticoagulation therapy should be given as described in recommendations 1.2.1.1–1.2.1.6.

1.2.3.2 For children with a first CVL-related DVT after the initial 3 months of therapy, we suggest prophylactic doses of vitamin K antagonists (INR 1.5 to 1.8) or LMWH (antifactor Xa levels of 0.1 to 0.3) be given until the CVL is removed (Grade 2C).

1.2.3.3 For children with recurrent CVL-related TEs after the initial 3 months of therapy, we suggest prophylactic doses of vitamin K antagonists (INR 1.5 to 1.8) or LMWH (antifactor Xa levels of 0.1 to 0.3) be continued until removal of the CVL. If the recurrence

occurs while on prophylactic therapy, we suggest continuing therapeutic doses until the CVL is removed or for a minimum of 3 months (Grade 2C).

1.3 Renal vein thrombosis

1.3.1 For unilateral RVT in the absence of uremia, and in the absence of extension into the IVC, we suggest supportive care with careful monitoring of the RVT for extension (Grade 2C). Alternatively, we suggest anticoagulation with UFH or LMWH (Grade 2C).

1.3.2 For unilateral RVT that does extend into the IVC, we suggest anticoagulation therapy with UFH or LMWH for 6 weeks to 3 months (Grade 2C).
Remark: the therapeutic range is as for venous thrombosis.

1.3.3 For bilateral RVT with various degrees of renal failure, we suggest UFH (and not LMWH) and thrombolytic therapy (Grade 2C).

1.4 Central Venous Line (CVL) Prophylaxis

1.4.1 For children with CVLs, we recommend *against* routine primary prophylaxis (Grade 1B).

1.4.2 For children having long-term home TPN, we suggest antithrombotic prophylaxis therapy. We suggest vitamin K antagonists with a target INR of 2–2.5 continuously, or alternatively for the first 3 months after each CVL is inserted (all Grade 2C).
Remark: the optimal drug and dose are unknown.

1.5 Primary prophylaxis for BT shunts in neonates

1.5.1 For neonates having BT shunts, we suggest intraoperative heparin followed by either aspirin (5 mg/kg/day) or no further anticoagulant therapy (Grade 2C).

1.6 Primary prophylaxis for Stage 1 Norwoods in neonates

1.6.1 For patients who underwent the Norwood procedure, we suggest heparin immediately after the procedure (Grade 2C).

1.7 Primary prophylaxis for Fontan surgery in children

1.7.1 For children after Fontan surgery, we suggest aspirin (5 mg/kg/day) or therapeutic heparin followed by vitamin K antagonists to achieve a target INR of 2.5 (range 2 to 3) (Grade 2C).
Remark: the optimal duration of therapy is unknown. Whether patients with fenestrations require more intensive therapy until fenestration closure is unknown.

1.8 Primary prophyalxis for endovascular stents in children

1.8.1 For children having endovascular stents inserted, we suggest administration of heparin perioperatively (Grade 2C).

1.9 Primary prophylaxis for dilated cardiomyopathy in neonates and children

1.9.1 We suggest that children with cardiomyopathy receive vitamin K antagonists to achieve a target INR of 2.5 (range 2 to 3), commencing no later than activation on a cardiac transplant waiting list (Grade 2C).
Underlying values and preferences
Our suggestion for administration of vitamin K antagonists places a high value on avoiding thrombotic complications, and a relatively low value on avoiding the inconvenience, discomfort and limitations of anticoagulant monitoring, in children with a potentially curative therapy (for their cardiomyopathy) available.

1.10 Primary prophylaxis for biological prosthetic heart valves in children

1.10.1 For children with biological prosthetic heart valves, we recommend treatment according to the adult guidelines [1] (Grade 1C+).

1.11 Primary prophylaxis for mechanical prosthetic heart valves in children

1.11.1 For children with biological prosthetic heart valves, we recommend following the adult guidelines [1] and according to evidence of valve dysfunction (Grade 1C+).

1.12 Primary prophylaxis for mechanical prosthetic heart valves in children

1.12.1 For children with mechanical prosthetic heart valves, we recommend administration of vitamin K antagonists following adult guidelines [1] for the intensity of therapy (target INRs) (Grade 1C+).

1.12.2 In children where additional antithrombotic therapy is required due to failure of vitamin K antagonists or a contra indication to full dose vitamin K antagonists, we suggest adding aspirin (6–20 mg/kg/day) (Grade 2C).

1.13 Thromboprophylaxis for cardiac catheterization in neonates and children

1.13.1 For neonates and children requiring cardiac catheterization via an artery, we recommend intravenous heparin prophylaxis (Grade 1A).

1.13.2 We suggest use of heparin doses of 100 to 150 units per kg as a bolus. Further doses may be required in prolonged procedures (both Grade 2B).

1.13.3 For prophylaxis for cardiac catheterization, we recommend *against* aspirin therapy (Grade 1B).

1.14 Femoral artery thrombosis following CC

1.14.1 For children or neonates with a femoral artery thrombosis, we recommend therapeutic doses of intravenous heparin (Grade 1C). We suggest treatment for at least 5–7days (Grade 2C).
Remark: the optimal duration of therapy is unknown.

1.14.2 For children or neonates with limb-threatening or organ-threatening(via proximal extension) femoral artery thrombosis who fail to respond to initial heparin therapy, and who have no known contraindications, we recommend administration of thrombolytic therapy (Grade 1C).

1.14.3 For children femoral artery thrombosis in selected cases, we suggest surgical intervention, in particular when there is a contraindication to thrombolytic therapy, or organ or limb death is imminent (Grade 2C).

1.15 Peripheral artery thrombosis

1.15.1. For neonates and children with peripheral arterial catheters in situ, we recommend administration of low dose heparin through the catheter, preferably by continuous infusion, to prolong the catheter patency (Grade 1A).

1.15.2 For children with a peripheral arterial catheter related TE, we suggest immediate removal of the catheter (Grade 2C). We suggest subsequent anticoagulation with or without thrombolysis, depending on the clinical situation (Grade 2C).

1.16 Aortic thrombosis secondary to umbilical artery catheters in neonates

1.16.1 For UAC, we suggest low dose heparin infusion (1–5 units/h) (Grade 2A).

1.16.2 We suggest that aortic thrombosis secondary to UAC is managed by the same principles as femoral artery thrombosis secondary to cardiac catheters. If there is evidence of renal failure, then urgent restoration of renal blood flow is required, and we suggest thrombolysis or thrombectomy (all Grade 2C).

1.17 Spontaneous aortic thrombosis in neonates

1.17.1 For children suffering spontaneous aortic thrombosis with evidence of renal ischemia, we suggest urgent, aggressive use of thrombolytic or surgical therapy, supported by anticoagulation with heparin or LMWH (Grade2C).

1.18 Kawasaki's disease

In children with Kawasaki's Disease:

1.18.1 We recommend aspirin in high doses (80 to 100 mg/kg/day during the acute phase, up to 14 days) as an anti-inflammatory agent, then in lower doses as an antiplatelet agent (3 to 5 mg/kg/d for 7 weeks or longer) (Grade1C+).

1.18.2 We recommend IV gamma globulin (2 gm/kg single dose) within 10 days of onset of symptoms (Grade 1A).

1.19 Anticoagulation for Kawasaki's disease with giant aneurysms

1.19.1 In children with giant coronary aneurysms following Kawasaki's disease, we suggest warfarin, at a target INR of 2.5 (range 2.0 to 3.0), in addition to low dose aspirin (Grade 2C).

1.20 Sinovenous thrombosis in neonates

1.20.1 For neonates with cerebral venous thrombosis, without large ischemic infarct or intracranial hemorrhage, we suggest initial treatment with either unfractionated heparin or LMWH followed by LMWH for 3 months (Grade 2C).

1.20.2 For neonates with cerebral venous thrombosis, with large ischemic infarct or intracranial hemorrhage, we suggest radiographic monitoring and commencement of anticoagulation if extension occurs (Grade 2C).

1.21 Sinovenous thrombosis in children

1.21.1 For children with cerebral venous thrombosis, we suggest treatment for 5–7 days with either unfractionated heparin or LMWH followed by LMWH or vitamin K antagonists with a target INR of 2.5 (range 2.0 to 3.0) for 3–6 months even in the presence of a localized hemorrhagic infarct (Grade 2C).

1.22 Arterial ischemic stroke in neonates

1.22.1 For neonates with non-cardioembolic AIS, we suggest that clinicians do *not* use anticoagulation or aspirin (Grade 2C).

1.22.2 For neonates with cardioembolic AIS, we suggest anticoagulation with either unfractionated heparin or LMWH for 3 months (Grade 2C).

1.23 Arterial ischemic stroke in children

1.23.1 For children with AIS, we suggest treatment with unfractionated heparin or LMWH for 5–7 days and until cardioembolic stroke or vascular dissection has been excluded (Grade 2C).

1.23.2 For children with AIS and cardioembolic stroke or vascular dissection, we suggest treatment for 5–7 days with unfractionated heparin or LMWH followed by LMWH or vitamin K antagonists for 3–6 months (Grade 2C).

1.23.3 For all children with AIS, we suggest treatment with 2–5 mg/kg/day aspirin after anticoagulation has been discontinued (Grade 2C).

1.23.4 For children with sickle cell disease over 2 years of age, we recommend screening for stroke using transcranial Doppler. If transcranial Doppler is unavailable we recommend intermittent screening with MRI (Grade 1C).

1.23.5 For children with sickle cell disease who have ischemic stroke, we recommend intravenous hydration and exchange transfusion to reduce

hemoglobin S to <30% total hemoglobin (Grade 1C).

1.23.6 For children with sickle cell disease who have ischemic stroke, after initial exchange transfusion, we suggest a chronic transfusion program (Grade 2C).

1.24 Purpura fulminans

1.24.1 For neonates with homozygous protein C deficiency, we recommend administration of either 10 to 20 ml/kg of fresh frozen plasma (FFP) every 12 h or protein C concentrate, when available, at 20 to 60 units/kg until the clinical lesions resolve (Grade 1C+).

1.24.2 We suggest long-term treatment with vitamin K antagonists (Grade 2C), LMWH (Grade 2C), protein C replacement (Grade 1C+), or liver transplantation (Grade 2C).

Reference

[1] Salem D, Stein P, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Theraphy. CHEST 2004;126:457S–82S.