CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy in Neonates and Children

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **Neonates and children differ from adults in physiology, pharmacologic responses to drugs, epidemiology, and long-term consequences of thrombosis. This guideline addresses optimal strategies for the management of thrombosis in neonates and children.**

Methods: **The methods of this guideline follow those described in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.**

Results: **We suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism (Grade 2C). When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist (Grade 2C). We suggest that therapeutic unfractionated heparin in children is titrated to achieve a target anti-Xa range of 0.35 to 0.7 units/mL or an activated partial thromboplastin time range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C). For neonates and children receiving either daily or bid therapeutic low-molecular-weight heparin, we suggest that the drug be monitored to a target range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after subcutaneous injection or, alternatively, 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after subcutaneous injection (Grade 2C).**

Conclusions: **The evidence supporting most recommendations for antithrombotic therapy in neonates and children remains weak. Studies addressing appropriate drug target ranges and monitoring requirements are urgently required in addition to site- and clinical situation-specific thrombosis management strategies.** ***CHEST 2012; 141(2)(Suppl):e737S–e801S***

Abbreviations: ACCP = American College of Chest Physicians; AIS = arterial ischemic stroke; ALL = acute lymphoblastic leukemia; APLA = antiphospholipid antibody; aPTT = activated partial thromboplastin time; ASA = acetylsalicyclic acid; BCPS = bilateral cavopulmonary shunt; CC = cardiac catheterization; CSVT = cerebral sinovenous thrombosis; CVAD = central venous access device; FFP = fresh frozen plasma; HIT = heparin-induced thrombocytopenia; ICH = intracerebral 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; PE = pulmonary embolism; PFA = platelet function analyzer; PFO = patent foramen ovale; PICU = pediatric ICU; PTS = postthrombotic syndrome; RCT = randomized control trial; RR = risk ratio; rUK = recombinant urokinase; RVT = renal vein thrombosis; TCD = transcranial Doppler; TE = thromboembolism; TIA = transient ischemic attack; tPA = tissue plasminogen activator; TPN = total parenteral nutrition; UAC = umbilical arterial catheter; UFH = unfractionated heparin; UVC = umbilical venous catheter; VAD = ventricular assist device; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

1.0. We suggest that where possible, pediatric hematologists with experience in thromboembolism (TE) manage pediatric patients with TE (Grade 2C)**. When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist** (Grade 2C)**.**

1.1. We suggest that therapeutic unfractionated heparin (UFH) in children is titrated to achieve a target range of anti-Xa activity of 0.35 to 0.7 units/mL or an activated partial thromboplastin time (aPTT) range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C)**. We suggest that when initiating UFH therapy, UFH boluses be no greater than 75 to 100 units/kg and that boluses be withheld or reduced if there are significant bleeding risks** (Grade 2C)**. We suggest avoiding long-term use of therapeutic UFH in children** (Grade 2C)**.**

1.2. We suggest, for neonates and children receiving either once- or twice-daily therapeutic low-molecular-weight heparin (LMWH) that the drug be monitored to a target anti-Xa activity range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after subcutaneous injection or 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after subcutaneous injection (Grade 2C)**.**

1.3. We suggest, for children receiving vitamin K antagonists (VKAs), that the drug be monitored to a target international normalized ratio (INR) of 2.5 (range, 2.0-3.0), except in the setting of prosthetic cardiac valves where we suggest adherence to the adult recommendations outlined in the article by Whitlock et al in this supplement (Grade 2C)**. We suggest that INR monitoring with point-of-care monitors be made available where resources make this possible** (Grade 2C)**.**

1.5. We suggest that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day (Grade 2C)**.**

2.1. We suggest that central venous access devices (CVADs) or umbilical venous catheters (UVCs) associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ (Grade 2C)**. We suggest either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis rather than no follow-up** (Grade 2C)**; however, in previously untreated patients, we recommend the start of anticoagulation if extension occurs** (Grade 2C)**. We suggest that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations** (Grade 2C)**. If either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation, we suggest a prophylactic dose of anticoagulation until such time as the CVAD or UVC is removed** (Grade 2C)**. We suggest against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs** (Grade 2C)**. We suggest if thrombolysis is required, tissue plasminogen activator (tPA)**

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is used rather than other lytic agents (Grade 2C), **and we suggest plasminogen (fresh frozen plasma [FFP]) administration prior to commencing therapy** (Grade 2C).

2.2. For unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the inferior vena cava (IVC), we suggest either (1) supportive care with radiologic monitoring for extension of thrombosis (if extension occurs we suggest anticoagulation) or (2) anticoagulation with UFH/LMWH or LMWH in therapeutic doses rather than no therapy. If anticoagulation is used, we suggest a total duration of between 6 weeks and 3 months rather than shorter or longer durations of therapy (Grade 2C). **For unilateral RVT that extends into the IVC, we suggest anticoagulation with UFH/LMWH or LMWH for a total duration of between 6 weeks and 3 months** (Grade 2C).

2.3. For bilateral RVT with evidence of renal impairment, we suggest anticoagulation with UFH/LMWH or initial thrombolytic therapy with tPA followed by anticoagulation with UFH/LMWH (Grade 2C).

2.4. For neonates with CVADs, we recommend to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over no prophylaxis (Grade 1A) **or intermittent local thrombolysis** (Grade 2C). **For neonates with blocked CVADs, we suggest local thrombolysis after appropriate clinical assessment** (Grade 2C).

2.6. For neonates and children having modified Blalock-Taussig shunts (MBTS), we suggest intraoperative UFH therapy (Grade 2C). **For neonates and children after MBTS surgery, we suggest either aspirin or no antithrombotic therapy as compared with prolonged LMWH or VKAs** (Grade 2C).

2.9. For neonates and children with acute femoral artery thrombosis, we recommend therapeutic doses of IV UFH as initial therapy compared with aspirin or no therapy (Grade 1B) **or LMWH** (Grade 2C). **We suggest subsequent conversion to LMWH, or else continuation of UFH, to complete 5 to 7 days of therapeutic anticoagulation as compared with a shorter or longer duration** (Grade 2C).

2.10. For neonates and children with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial UFH therapy and who have no known contraindications, we recommend thrombolysis (Grade 1C). **For neonates and children with femoral artery thrombosis, we recommend surgical intervention compared with UFH therapy alone when there is a contraindication to thrombolytic therapy and organ or limb death is imminent** (Grade 1C).

2.11. For neonates and children with peripheral arterial catheters in situ, we recommend UFH continuous infusion at 0.5 units/mL at 1 mL/h compared with normal saline (Grade 1A).

2.12. For neonates and children with a peripheral arterial catheter-related TE, we suggest immediate removal of the catheter (Grade 2B). **For neonates and children with a symptomatic peripheral arterial catheter-related TE, we suggest UFH anticoagulation with or without thrombolysis or surgical thrombectomy and microvascular repair with subsequent heparin therapy** (Grade 2C).

2.13. For neonates with umbilical arterial catheters (UACs), we suggest UAC placement in a high rather than a low position (Grade 2B).

2.14. For neonates with UAC, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25-1 unit/mL, total heparin dose of 25-200 units/kg per day) to maintain patency (Grade 2A).

2.16. For neonates and children requiring cardiac catheterization (CC) via an artery, we recommend administration of IV UFH as thromboprophylaxis over no prophylaxis (Grade 1A) **or aspirin** (Grade 1B). **For neonates and children requiring CC via an artery, we recommend the use of UFH doses of 100 units/kg as a bolus compared with a 50-unit/kg bolus** (Grade 1B). **In prolonged procedures, we suggest further doses of UFH rather than no further therapy** (Grade 2B).

2.17. For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage, we suggest anticoagulation, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months rather than shorter or longer treatment duration (Grade 2C). **For neonates with CSVT with significant hemorrhage, we suggest either (1) anticoagulation or (2) supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted as compared with no therapy** (Grade 2C).

2.18. For neonates with a first arterial ischemic stroke (AIS), in the absence of a documented,

ongoing cardioembolic source, we suggest supportive care over anticoagulation or aspirin therapy (Grade 2C).

2.19. For neonates with a first AIS and a documented cardioembolic source, we suggest anticoagulation with UFH or LMWH (Grade 2C).

2.20. For neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C).

2.21. For neonates with clinical presentations of homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of FFP every 12 h or protein C concentrate, when available, at 20 to 60 units/kg until the clinical lesions resolve (Grade 1A). **For neonates with homozygous protein C deficiency, after initial stabilization, we recommend long-term treatment with VKA** (Grade 1C), **LMWH** (Grade 1C), **protein C replacement** (Grade 1B), **or liver transplantation** (Grade 1C) **compared with no therapy.**

2.22.1. In children with first VTE (CVAD and non-CVAD related) we recommend acute anticoagulant therapy with either UFH or LMWH (Grade 1B). **We recommend initial treatment with UFH or LMWH for at least 5 days** (Grade 1B). **For ongoing therapy, we recommend LMWH or UFH. 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 INR has not exceeded 2.0 compared with no therapy** (Grade 1B).

2.22.2. We suggest that children with idiopathic VTE receive anticoagulant therapy for 6 to 12 months compared with no therapy (Grade 2C).

Underlying values and preferences: Families who place a high value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor and a lower value on avoiding the inconvenience of therapy or potential impact of therapy on growth and development and bleeding risk associated with antithrombotic therapy are likely to choose to continue anticoagulant therapy beyond 6 to 12 months.

2.22.3. In children with secondary VTE (ie, VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for 3 months (Grade 2C) **as compared with no further therapy. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing asparaginase therapy, we suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved** (Grade 2C).

2.22.4. In children with recurrent idiopathic VTE, we recommend indefinite treatment with VKAs (Grade 1A).

2.22.5. In children with recurrent secondary VTEs with an existing reversible risk factor for thrombosis, we suggest anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy (Grade 2C).

2.22.6. In children with a CVAD in place who have a VTE, if a CVAD 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 rather than no anticoagulation prior to removal** (Grade 2C). **If CVAD access is required and the CVAD is still functioning, we suggest that the CVAD remain in situ and the patient be given anticoagulants** (Grade 2C). **For children with a first CVAD-related VTE, we suggest initial management as for secondary VTE as previously described.**

2.22.7. In children with CVAD in place who have a VTE and in whom the CVAD remains necessary, we suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed (Grade 2C). **If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE** (Grade 2C).

2.23. In children with VTE, we suggest that thrombolysis therapy be used only for life- or limb-threatening thrombosis (Grade 2C). **If thrombolysis is used in the presence of physiologically low levels or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen** (Grade 2C). **In children with VTE in whom thrombolysis is used, we suggest systemic thrombolysis or catheter-directed thrombolysis, depending on institutional experience and, in the latter case, technical feasibility.**

2.24. In children with life-threatening VTE, we suggest thrombectomy (Grade 2C). **In children who have had a thrombectomy, we suggest anticoagulant therapy as per recommendation (Recommendation 2.22)** (Grade 2C). **In children > 10 kg**

body weight with lower-extremity VTE and a contraindication to anticoagulation, we suggest placement of a retrievable IVC filter (Grade 2C). **In children who receive a filter, we suggest that the filter be removed as soon as possible if thrombosis is not present in the basket of the filter and when contraindication to anticoagulation is resolved** (Grade 2C). **In children who receive an IVC filter, we recommend appropriate anticoagulation for VTE (see Recommendation 1.2) as soon as the contraindication to anticoagulation is resolved** (Grade 1C).

2.25. In children with cancer, we suggest that management of VTE follow the general recommendations for management of VTE in children. We suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (eg, use of asparaginase) (Grade 2C).

Remarks: The presence of cancer, the need for surgery, chemotherapy, or other treatments may modify the risk-benefit ratio for treatment of VTE, and clinicians should consider these factors on an individual basis.

2.26. For children with VTE in the setting of antiphospholipid antibodies (APLAs), we suggest management as per general recommendations for VTE management in children.

2.27. For children with VTE, independent of the presence or absence of inherited thrombophilic risk factors, we suggest that the duration and intensity of anticoagulant therapy as per Recommendation 2.22.

2.28. For children with first VTE secondary to structural venous abnormalities, we suggest anticoagulation as per other "spontaneous" VTE (Recommendation 2.22) and consideration of subsequent percutaneous or surgical interventions, depending on patient factors and institutional experience. For children with recurrent VTE secondary to structural venous abnormalities, we suggest indefinite anticoagulation unless successful percutaneous or surgical interventions can be performed (Grade 2C).

2.29. For children with right atrial thrombosis related to CVAD, we suggest removal of the CVAD with or without anticoagulation, depending on the individual risk factors, compared with leaving the CVAD in situ (Grade 2C). **For children with large (> 2 cm) mobile right atrial thrombosis, we suggest anticoagulation, with appropriately timed CVAD removal, and consideration of surgical intervention or thrombolysis based on individualized risk-benefit assessment compared with no anticoagulation therapy** (Grade 2C).

2.30. For CVADs, we suggest flushing with normal saline or heparin or intermittent recombinant urokinase (rUK) to maintain patency as compared with no therapy (Grade 2C). **For blocked CVADs, we suggest tPA or rUK to restore patency** (Grade 2C). **If after at least 30 min following local thrombolytic instillation CVAD patency is not restored, we suggest a second dose be administered. If the CVAD remains blocked following two doses of local thrombolytic agent, we suggest radiologic imaging to rule out a CVAD-related thrombosis** (Grade 2C).

2.31. For children with short- or medium-term CVADs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B).

2.34. For children receiving long-term home total parenteral nutrition (TPN), we suggest thromboprophylaxis with VKAs (Grade 2C).

2.35. For children who have bilateral cavopulmonary shunt (BCPS), we suggest postoperative UFH (Grade 2C).

2.36. For children after Fontan surgery, we recommend aspirin or therapeutic UFH followed by VKAs over no therapy (Grade 1C).

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

2.38. For pediatric patients with cardiomyopathy, we suggest VKAs no later than their activation on a cardiac transplant waiting list (Grade 2C).

Underlying values and preferences: Parents who place a high value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring and a lower value on the uncertain reduction in thrombotic complications are unlikely to choose VKA therapy for their children who are eligible for transplant.

2.39. For children with primary pulmonary hypertension, we suggest starting anticoagulation with VKAs at the same time as other medical therapy (Grade 2C).

2.40-2.42. For children with biologic or mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population.

2.44. For children with ventricular assist devices (VADs), we suggest administration of UFH (Grade 2C)**. We suggest starting UFH between 8 and 48 h following implantation** (Grade 2C)**. In addition, we suggest antiplatelet therapy (either aspirin or asprin and dipyridamole) to commence within 72 h of VAD placement** (Grade 2C)**. For children with VAD, once clinically stable, we suggest switching from UFH to either LMWH or VKA (target INR 3.0 range, 2.5-3.5) until transplanted or weaned from VAD** (Grade 2C)**.**

2.45. For patients undergoing hemodialysis via an arteriovenous fistula, we suggest routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy (Grade 2C)**.**

2.46. For patients undergoing hemodialysis via CVAD, we suggest routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy (Grade 2C)**.**

2.47. For children having hemodialysis, we suggest the use of UFH or LMWH during hemodialysis to maintain circuit patency independent of type of vascular access (Grade 2C)**.**

2.48. For children with Kawasaki disease, we recommend aspirin in high doses (80-100 mg/kg per day during the acute phase for up to 14 days) as an antiinflammatory agent, then in lower doses (1-5 mg/kg per day for 6 to 8 weeks) as an antiplatelet agent (Grade 1B)**. For children with Kawasaki disease, we recommend IV γ-globulin (2 g/kg, single dose) within 10 days of the onset of symptoms** (Grade 1A)**.**

2.49. For children with moderate or giant coronary aneurysms following Kawasaki disease, we suggest that warfarin in addition to low-dose aspirin be given as primary thromboprophylaxis (Grade 2C)**.**

2.50. For children with Kawasaki disease who have giant aneurysms and acute coronary artery thrombosis, we suggest thrombolysis or acute surgical intervention (Grade 2C)**.**

2.51. For children with CSVT without significant intracranial hemorrhage, we recommend anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation (Grade 1B)**. In children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms, we suggest administration of a further 3 months of anticoagulation** (Grade 2C)**. For children with CSVT with significant hemorrhage, we suggest initial anticoagulation as for children without hemorrhage or radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted at that time** (Grade 2C)**. In children with CSVT and potentially recurrent risk factors (for example, nephrotic syndrome, asparaginase therapy), we suggest prophylactic anticoagulation at times of risk factor recurrence** (Grade 2C)**. We suggest thrombolysis, thrombectomy, or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy** (Grade 2C)**.**

2.52. For children with acute AIS, with or without thrombophilia, we recommend UFH or LMWH or aspirin as initial therapy until dissection and embolic causes have been excluded (Grade 1C)**. For children with acute AIS, we suggest, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis for a minimum of 2 years as compared with no antithrombotic therapy** (Grade 2C)**. For children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs), we suggest changing to clopidogrel or anticoagulant therapy with LMWH or VKA** (Grade 2C)**. For children with AIS, we recommend against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols** (Grade 1C)**.**

2.53. For AIS secondary to cardioembolic causes, we suggest anticoagulant therapy with LMWH or VKAs for at least 3 months (Grade 2C)**. For AIS secondary to cardioembolic causes in children with demonstrated right-to-left shunts (eg, patent foramen ovale [PFO]), we suggest surgical closure of the shunt** (Grade 2C)**.**

2.54. For AIS secondary to dissection, we suggest anticoagulant therapy with LMWH or VKAs for at least 6 weeks (Grade 2C)**. Ongoing treatment will depend on radiologic assessment of degree and extent of stenosis and evidence of recurrent ischemic events.**

2.55. For children with acute AIS secondary to non-Moyamoya vasculopathy, we recommend UFH or LMWH or aspirin for 3 months as initial therapy compared with no treatment (Grade 1C)**. For children with AIS secondary to non-Moyamoya vasculopathy, we suggest ongoing antithrombotic therapy should be guided by repeat cerebrovascular imaging.**

2.56. For children with acute AIS secondary to Moyamoya, we suggest aspirin over no treatment as initial therapy (Grade 2C)**.**

2.57. For children with Moyamoya, we suggest they be referred to an appropriate center for consideration of revascularization.

Thromboembolism (TE) in pediatric patients is rare and makes management studies a challenge, resulting in limited direct evidence. In children, ~50% of all drugs used are unlicensed or off-label, reflecting the paucity of specific trials in children.[1,2] Thus, most recommendations are based on extrapolation from adults. There is evidence that such extrapolation may, in many circumstances, be inappropriate.[3-5]

Fortunately, recent regulatory initiatives have resulted in the development of specific pediatric investigational plans for select novel anticoagulants.[6] Although these studies will take years to complete, they will provide excellent data on the safety and efficacy of currently used anticoagulants in children as well as an understanding of the newer drugs. At the same time, additional research is required to understand the basic pharmacokinetics and pharmacodynamics of commonly prescribed antithrombotic drugs in children because significant differences exist in antithrombotic activity and impact on monitoring tests in children compared with adults.[4,7]

This article is divided into two sections. The first section details the evidence showing that the interaction of antithrombotic agents with the hemostatic system of the young differs from that of adults. This section describes the pediatric-specific aspects of mechanisms of action; therapeutic ranges; dose regimens; monitoring requirements; factors influencing dose-response relationships; and side effects of antithrombotic, antiplatelet, and thrombolytic agents. The second section provides the evidence and recommendations for antithrombotic therapy in specific clinical situations in neonates and children.

In managing children with antithrombotic therapy, as with any therapy, the values and preferences of the patient and family are crucial to consider in the treatment algorithms. Preliminary studies suggest that these values and preferences can vary widely among families, perhaps related to culture and religion, but certainly reflect the variation in patient and parental personal views and experiences.[8]

Throughout this article, the term "pediatric patients" refers to all neonates and children (birth-18 years). "Neonates" refers to infants from birth to 28 days corrected for gestational age. "Children" refers to patients aged 28 days to 18 years. The age at which adolescents should be considered adults from the perspective of treatment guidelines remains controversial. Young adults (18-25 years) are sparsely represented in most adult data about management of TE. In other areas of medicine, this demographic is being recognized as a separate entity, which requires specific study.[9] In addition to chronologic age, clinicians need to consider factors such as physical development, stage of puberty, and emotional and intellectual development. Adolescents are transitioned to adult services after they leave school or between 16 and 21 years of age, depending on their local jurisdiction. In addition, there is considerable variation based on individual circumstances.

Comprehensive literature searches were performed as per the American College of Chest Physicians (ACCP) guidelines based on the questions presented in Table 1, and recommendations are based on the ACCP grades of recommendation.[10] Where possible, because of the physiologic and pathophysiologic differences as well as the markedly different implications of therapy, recommendations are presented for neonates and children separately. However, in cases where the available data do not adequately differentiate between the two age groups, the combined recommendations are presented.

1.0 Antithrombotic Therapy in Pediatric Patients

The use of antithrombotic drugs in pediatric patients differs from adults.[11] First, the epidemiology of TE in pediatric patients differs from that seen in adults.[12-24] Second, the hemostatic system is a dynamic, evolving entity that likely affects not only the frequency and natural history of TEs in children but also the response to therapeutic agents.[4,25,26] Third, the distribution, binding, and clearance of antithrombotic drugs are age dependent.[27-29] Fourth, the frequency and type of intercurrent illnesses and concurrent medications vary with age. Fifth, the need for general anesthesia to perform many diagnostic studies in pediatric patients has an impact on the ability to investigate and monitor TEs and, hence, the confidence one can have in therapeutic decisions. Sixth, limited vascular access reduces the ability to effectively deliver some antithrombotic therapies and can influence the choice of antithrombotic agent. Often, the only vascular access available is used for drug delivery, so accurate monitoring of blood anticoagulant levels is difficult. Seventh, specific pediatric formulations of antithrombotic drugs are not available, making accurate, reproducible dosing difficult, which is especially the case for vitamin K antagonists (VKAs) (no suspension/liquid preparation) and low-molecular-weight heparin (LMWH) (in many countries, the most readily available

Table 1—*[Introduction] PICO Questions for Antithrombotic Therapy in Neonates and Children*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.1	Neonates (premature and term up to 28 d corrected age)	Treatment	DVT (CVL and non-CVL related), PE	Anticoagulation, thrombolysis	No therapy, each other	• Mortality • Pulmonary embolus • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.2-2.3	Neonates (premature and term up to 28 d corrected age)	Treatment	Renal vein thrombosis-unilateral	Anticoagulation	No therapy	• Mortality • Renal failure • Renal atrophy • Hypertension • Extension • Recurrent VTE • Hemorrhage (major and CNS)	RCT, observational studies
2.2-2.3	Neonates (premature and term up to 28 d corrected age)	Treatment	Renal vein thrombosis-bilateral or IVC involvement	Anticoagulation, thrombolysis	No therapy, each other	• Mortality • Renal failure • Renal atrophy • Hypertension • Extension • Recurrent VTE • Hemorrhage (major and CNS)	RCT, observational studies
2.4-2.5	Neonates (premature and term up to 28 d corrected age)	Prophylaxis	CVAD	Local heparin (1-2 units/mL infusion) or heparin lock, intermittent local thrombolysis	No therapy, each other	• Patency • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS)	RCT, observational studies
2.4-2.5	Neonates (premature and term up to 28 d corrected age)	Prophylaxis	CVAD	Systemic heparin or LMWH prophylaxis	No therapy, each other	• Patency • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS	RCT, observational studies
2.6	Neonates (premature and term up to 28 d corrected age) and children	Prophylaxis	Blalock-Taussig shunt	Anticoagulation (heparin or LMWH), aspirin, clopidogrel	No therapy, each other	• Intracardiac thrombosis (includes shunt thrombosis) • Mortality • Tissue loss • Hemorrhage (major and CNS)	RCT, observational studies
2.7	Neonates (premature and term up to 28 d corrected age) and children	Treatment	Blalock-Taussig shunt-blocked	Thrombolysis	Surgical intervention	• Intracardiac thrombosis (includes shunt thrombosis) • Mortality • Tissue loss • Hemorrhage (major and CNS)	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.8	Neonates (premature and term up to 28 d corrected age)	Prophylaxis	Stage 1 Norwood	Anticoagulation	Antiplatelet therapy	• Intracardiac thrombosis • Mortality • Tissue loss • Hemorrhage (major and CNS)	RCT, observational studies
2.9-2.10	Neonates (premature and term up to 28 d corrected age) and children	Treatment	Femoral artery thrombosis	Anticoagulation	No therapy or antiplatelet therapy	• Claudication • Leg shortening • Tissue loss • Hemorrhage (major and CNS)	RCT, observational studies
2.9-2.10	Neonates (premature and term up to 28 d corrected age) and children	Treatment	Femoral artery thrombosis	Thrombolysis (followed by standard anticoagulation or antiplatelet therapy), thrombectomy	Anticoagulation or antiplatelet therapy (without thrombolysis), each other	• Claudication • Leg shortening • Tissue loss • Hemorrhage (major and CNS)	RCT, observational studies
2.11	Neonates (premature and term up to 28 d corrected age) and children	Prophylaxis	Peripheral arterial catheters (excluding femoral artery)	Thrombolysis	No therapy	• Tissue loss • Growth failure • Hemorrhage (major and CNS)	RCT, observational studies
2.12	Neonates (premature and term up to 28 d corrected age) and children	Treatment	Peripheral arterial thrombosis (excluding femoral artery)	Thrombolysis	No therapy, thrombectomy, anticoagulation, antiplatelet therapy	• Tissue loss • Growth failure • Hemorrhage (major and CNS)	RCT, observational studies
2.13-2.14	Neonates (premature and term up to 28 d corrected age)	Prophylaxis	UAC	Exposure (high position [> T10])	Low position (L3-L5)	• Aortic thrombosis • NEC • Hemorrhage (major and CNS)	RCT, observational studies
2.13-2.14	Neonates (premature and term up to 28 d corrected age)	Prophylaxis	UAC	Heparin prophylaxis	No therapy	• Patency • Aortic thrombosis • Hemorrhage (major and CNS) • NEC • Embolization (eg, digital artery) • Tissue loss • Mortality	RCT, observational studies
2.15	Neonates (premature and term up to 28 d corrected age)	Treatment	Aortic thrombosis (UAC related or spontaneous)	Thrombolysis	Anticoagulation	• Mortality • Tissue loss • Renal impairment • Hypertension • NEC • Embolization • Hemorrhage (major and CNS)	RCT, observational studies
2.16	Neonates (premature and term up to 28 d corrected age) and children	Prophylaxis	Cardiac catheter	Heparin prophylaxis, Aspirin prophylaxis	No therapy	• Femoral artery thrombosis • Embolization non-CNS • Cardioembolic stroke • Hemorrhage (major and CNS)	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.17	Neonates (premature and term up to 28 d corrected age)	Treatment	CSVT	Anticoagulation	No therapy	• Mortality • Functional status • Extension • Recurrent CSVT • Hemorrhage (major and CNS) • Visual outcomes/need for surgical management of increased ICP (fenestration shunt)	RCT, observational studies
2.18-2.20	Neonates (premature and term up to 28 d corrected age)	Treatment	AIS (unknown vs embolic vs traumatic/dissection vs thrombophilia) (no documented ongoing cardioembolic source)	Anticoagulation	No therapy	• Mortality • Functional status • Hemorrhage (major and CNS) • Recurrent AIS (rare)	RCT, observational studies
2.18-2.20	Neonates (premature and term up to 28 d corrected age)	Treatment	AIS (documented cardioembolic source)	Anticoagulation	Antiplatelet therapy or no therapy	• Mortality • Functional status • Hemorrhage (major and CNS) • Recurrent AIS (rare)	RCT, observational studies
2.18-2.20	Neonates (premature and term up to 28 d corrected age)	Treatment	AIS (recurrent)	Antiplatelet therapy or anticoagulation	No therapy	• Mortality • Functional status • Hemorrhage (major and CNS) • Recurrent AIS (rare)	RCT, observational studies
2.21	Neonates (premature and term up to 28 d corrected age)	Treatment	Purpura fulminans	Protein C replacement, fresh frozen plasma	Anticoagulation	• Mortality • Vision • Neurologic outcome • Primary thrombosis • Recurrent thrombosis (among those with major vessel thrombosis at presentation)	RCT, observational studies
2.22	Children (day 28 to 16-18 y)	Treatment	DVT (CVAD and non-CVAD related), PE	Anticoagulation	No therapy, each other	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.23	Children (day 28 to 16-18 y)	Treatment	DVT (CVL and non-CVL related), PE	Systemic thrombolysis (in conjunction with anticoagulant therapy), local thrombolysis ± pharmacomechanical thrombolysis (in conjunction with anticoagulant therapy)	Anticoagulation	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS) • Phlegmasia cerulea dolens	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.24	Children (day 28 to 16-18 y)	Treatment	DVT (CVL and non-CVL related), PE	Thrombectomy, IVC filter	Anticoagulation	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Filter migration or filter fracture • Filter nonretrievability (for temporary filters) • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.25	Children (day 28 to 16-18 y) with cancer or leukemia	Treatment duration/ intensity	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/LMWH)	VKAs	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Hemorrhage (major and CNS) • Recurrence (DVT or PE)	RCT, observational studies
2.26	Children (day 28 to 16-18 y) with antiphospholipid antibodies or lupus anticoagulant	Treatment duration/ intensity	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/LMWH)	VKAs	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.27	Children (day 28 to 16-18 yr) with positive thrombophilia	Treatment duration/ intensity	DVT (CVAD and non CVAD related), PE	Anticoagulation, Interventional radiology or surgical stenting, dilatation or bypass	No therapy, Each other	• Mortality • Primary Pulmonary embolus • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.28	Children (day 28 to 16-18 y) with structural venous abnormality	Treatment	DVT (CVL and non-CVL related), PE	Interventional radiology or surgical stenting, dilatation or bypass	Anticoagulation	• Mortality • Extension • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.29	Children (day 28 to 16-18 y)	Treatment	Right atrial thrombosis (± CVAD related)	Thrombolysis, surgical thrombectomy (followed by standard anticoagulation or antiplatelet therapy)	Anticoagulation (without thrombolysis or surgical thrombectomy), each other	• Mortality • PE • Paradoxical stroke • Postthrombotic syndrome • Recurrent VTE • Hemorrhage (major and CNS)	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.30-2.34	Children (day 28 to 16-18 y)	Prophylaxis	CVAD	Local heparin (1-2 units/mL infusion), heparin lock, intermittent local thrombolysis	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS)	RCT, observational studies
2.30-2.34	Children (day 28 to 16-18 y)	Prophylaxis	CVAD (short or medium term, eg, PICU)	Systemic anticoagulation prophylaxis	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS) mortality	RCT, observational studies
2.30-2.34	Children (day 28 to 16-18 y)	Prophylaxis	CVAD (long term, eg, oncology)	Systemic anticoagulation prophylaxis	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Major bleeding • Mortality	RCT, observational studies
2.30-2.34	Children (day 28 to 16-18 y) with positive thrombophilia	Prophylaxis	CVAD (long term, eg, oncology)	Systemic anticoagulation prophylaxis	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS) • Mortality • Postthrombotic syndrome	RCT, observational studies
2.30-2.34	Children (day 28 to 16-18 y)	Prophylaxis	CVAD (long term, eg, home TPN)	Systemic anticoagulation prophylaxis	No therapy	• Patency • CVAD dysfunction • Sepsis/CVAD infection • DVT • PE • Hemorrhage (major and CNS) • Mortality • Postthrombotic syndrome	RCT, observational studies
2.35	Children (day 28 to 16-18 y)	Prophylaxis	Glenn or bilateral cavo pulmonary shunt	Anticoagulation prophylaxis	No therapy	• Intracardiac thrombosis • Mortality • Tissue loss • Hemorrhage (major and CNS) • Ischemic stroke • Fontan surgery	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.36	Children (day 28 to 16-18 y)	Prophylaxis	Fontan surgery	Anticoagulation, antiplatelet therapy	No therapy	• Intracardiac thrombosis • Mortality • Fontan takedown • Ischemic stroke • Hemorrhage (major and CNS)	RCT, observational studies
2.37	Children (day 28 to 16-18 y)	Prophylaxis	Endovascular stents	Heparin or LMWH or aspirin prophylaxis	No therapy	• Patency • Mortality • Pulmonary emboli • Ischemic stroke	RCT, observational studies
2.38	Children (day 28 to 16-18 y)	Prophylaxis	Dilated cardiomyopathy	VKAs or aspirin prophylaxis	No therapy	• Mortality • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)	RCT, observational studies
2.39	Children (day 28 to 16-18 y)	Prophylaxis	Primary pulmonary hypertension	VKAs	No therapy	• Mortality • Thrombosis • Heart/lung transplantation • Hemorrhage (major and CNS)	RCT, observational studies
2.40-2.42	Children (day 28 to 16-18 y)	Prophylaxis	Biologic prosthetic heart valves	VKAs or aspirin	No therapy	• Mortality • Valve replacement • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)	RCT, observational studies
2.40-2.42	Children (day 28 to 16-18 y)	Prophylaxis	Mechanical prosthetic heart valves	Antiplatelet agents, anticoagulation, antiplatelet agents, and VKAs	No therapy	• Mortality • Valve replacement • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)	RCT, observational studies
2.40-2.42	Children (day 28 to 16-18 y)	Prophylaxis	Mechanical prosthetic heart valves with a history of thrombotic events while on antithrombotic therapy	Combination, antiplatelet agents, and VKAs	VKAs alone	• Mortality • Valve replacement • Thrombosis • Ischemic stroke • Hemorrhage (major and CNS)	RCT, observational studies
2.43	Children (day 28 to 16-18 y)	Prophylaxis	Bacterial endocarditis	Anticoagulation	No therapy	• Primary embolic stroke • Mortality • Hemorrhage (major and CNS)	RCT, observational studies
2.44	Children (day 28 to 16-18 y)	Prophylaxis	Ventricular assist devices	Anticoagulation, antiplatelet agents, prophylaxis	No therapy	• Mortality • Thrombosis • Ischemic stroke • Blocked circuit requiring surgery • Hemorrhage (major and CNS)	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.45-2.46	Children (day 28 to 16-18 y)	Prophylaxis	Hemodialysis (arteriovenous fistula)	Continuous anticoagulation, procedural UFH or LMWH	No therapy	• Mortality • Thrombosis • Shunt dysfunction • Shunt infection • Hemorrhage (major and CNS)	RCT, observational studies
2.45-2.46	Children (day 28 to 16-18 y)	Prophylaxis	Hemodialysis (CVAD)	Continuous anticoagulation, procedural UFH or LMWH	No therapy	• Mortality • Thrombosis • CVAD dysfunction • Sepsis/CVAD infection • Hemorrhage (major and CNS)	RCT, observational studies
2.47	Children (day 28 to 16-18 y)	Prophylaxis (during procedure)	Hemodialysis (arteriovenous fistula or CVAD)	Anticoagulation	No therapy	• Thrombosis • CVAD dysfunction • Sepsis/CVAD infection • Dialysis failure • Hemorrhage (major and CNS)	RCT, observational studies
2.48-2.50	Children (day 28 to 16-18 y)	Prophylaxis	Kawasaki disease	Aspirin, IVIG, aspirin and IVIG,	No therapy	• Coronary aneurysms • Myocardial infarction • Mortality • Hemorrhage (major and CNS)	RCT, observational studies
2.48-2.50	Children (day 28 to 16-18 y)	Treatment	Kawasaki disease with coronary aneurysms	Anticoagulation	Antiplatelet therapy	• Myocardial infarction • Mortality • Hemorrhage (major and CNS)	RCT, observational studies
2.48-2.50	Children (day 28 to 16-18 y)	Treatment	Kawasaki disease with coronary aneurysms and acute coronary artery thrombosis	Thrombolysis	Anticoagulation	• Myocardial infarction • Mortality • Hemorrhage (major and CNS)	RCT, observational studies
2.51	Children (day 28 to 16-18 y)	Treatment	CSVT	Anticoagulaton, thrombolysis (followed by standard anticoagulation)	No therapy, each other	• Mortality • Thrombus extension • Functional status • Hemorrhage (major and CNS)	RCT, observational studies
2.52	Children (day 28 to 16-18 y)	Treatment	AIS (undetermined cause, in situ thrombosis, thrombophilia)	Anticoagulation or aspirin, thrombolysis	No therapy, each other	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)	RCT, observational studies
2.53	Children (day 28 to 16-18 y)	Treatment	AIS (cardioembolic)	Anticoagulation	Aspirin	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)	RCT, observational studies

(Continued)

Table 1—*Continued*

Section		Informal Question	PICO Question				
			Population	Intervention (s)	Comparator	Outcome	Methodology
2.54	Children (day 28 to 16-18 y)	Treatment	AIS (dissection)	Anticoagulation	Aspirin	• Mortality • Recurrent AIS • Functional status • Intracranial hemorrhage	RCT, observational studies
2.55	Children (day 28 to 16-18 y)	Treatment	AIS (vasculopathy other than dissection or moyamoya)	Anticoagulation or aspirin	No therapy	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)	RCT, observational studies
2.56-2.57	Children (day 28 to 16-18 y)	Treatment	AIS (moyamoya, non-sickle cell)	Aspirin (with/without neurosurgical direct/ indirect revascularization), surgical revascularization (direct/indirect)	No antithrombotic therapy (with/without neurosurgical direct/ indirect surgical revascularization), each other	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)	RCT, observational studies
2.56-2.57	Children (day 28 to 16-18 y)	Treatment	AIS (moyamoya, non-sickle cell)	Surgical revascularization (direct/indirect)	Antiplatelet therapy (without direct/ indirect surgical revascularization)	• Mortality • Recurrent AIS • Functional status • Hemorrhage (major and CNS)	RCT, observational studies
2.58-2.59	Children (day 28 to 16-18 y)	Treatment	AIS (sickle cell disease)	Exchange transfusion	No treatment	• Mortality • Recurrent AIS • Functional status • Intracranial hemorrhage	RCT, observational studies
2.58-2.59	Children (day 28 to 16-18 y)	Prophylaxis	Sickle cell disease	Chronic transfusion program	No treatment	• Mortality • Recurrent AIS • Functional status • Intracranial hemorrhage	RCT, observational studies

AIS = arterial ischemic stroke; CSVT = cerebral sinovenous thrombosis; CVAD = central venous assist device; CVL = central venous line; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; NEC = necrotizing enterocolitis; PE = pulmonary embolus(ism); PICO = populations, interventions, comparators, outcomes; PICU = pediatric ICU; RCT = randomized controlled trial; TPN = total parenteral nutrition; UAC = umbilical arterial catheter; UFH = unfractionated heparin; VKA = vitamin K antagonist.

predosed syringes are based on adult weights). Eighth, dietary differences make the use of oral VKAs particularly difficult, which is especially true in neonates because breast milk and infant formulas have very different vitamin K levels. Finally, compliance issues are vastly different, for example, in small infants who cannot understand the need for therapy, adolescents who intellectually comprehend but emotionally are unable to cooperate, and children who experience the effects of inadequate parenting. The social, ethical, and legal implications of these issues frequently interfere with the ability to provide the best treatment for individual neonates and children.

Recommendation

1.0. We suggest that where possible, pediatric hematologists with experience in TE manage pediatric patients with TE (Grade 2C)**. When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist** (Grade 2C)**.**

1.1 Heparin in Neonates and Children

Unfractionated (or standard) heparin (UFH) is commonly used in pediatric patients. In tertiary pediatric hospitals, ~15% of inpatients are exposed to UFH each day.[30]

1.1.1 Mechanism of Action: In this supplement, Garcia et al[31] describe the mechanism of action of UFH. Table 2 lists the specific factors that may alter the activities of UFH in children. The clinical implications of these changes on dosing, monitoring, and effectiveness/safety profile of UFH in children remains to be fully elucidated.

1.1.2 Therapeutic Range: No clinical outcome studies have determined the therapeutic range for UFH in neonates or children. Thus, the therapeutic range for all indications described in this article is extrapolated from the therapeutic range for the treatment of VTE in adults. This equates to an activated partial thromboplastin time (aPTT) that reflects a heparin level by protamine titration of 0.2 to 0.4 units/mL or an anti-Xa level of 0.35 to 0.7 units/mL.[38] The aPTT therapeutic ranges are universally determined using adult plasma.

Extrapolating the aPTT range from adults to pediatric patients is unlikely to be valid. For example, baseline aPTTs in pediatric patients, especially neonates, often are increased compared with adults. Therefore, the therapeutic ranges represent a reduced relative increment in aPTT values.[4,26] Schmidt et al[39] reported that routine assays underestimate UFH concentration, especially in neonates. Recent in vitro and in vivo data also indicate that the aPTT range that correlates to an anti-Xa level of 0.35 to 0.7 units/mL varies significantly with age and heparin dose.[5,27,35-37,40] Further, protamine titration results vary with age,[5] and different commercial anti-Xa kits can give substantially different results for anti-Xa measurements on the same samples probably because of subtle differences in kit formulation. This effect is seen in both adults and children.[35,41,42]

These differences are increased in infants in whom endogenous antithrombin levels are reduced.[43] Thus, the scientific rationale for using a therapeutic range for UFH in children is increasingly questioned. A comparative clinical outcome trial comparing monitored therapy (with a target therapeutic range) to weight-adjusted fixed-dose therapy (unmonitored) is desperately required. However, in the interim, recommendations must be based on the only published data available, despite their limitations.

1.1.3 Doses: One prospective cohort study used a weight-based nomogram to address dosing of UFH in pediatric patients required to achieve adult therapeutic aPTT values.[44] Bolus doses of 75 to 100 units/kg resulted in therapeutic aPTT values in 90% of children

Table 2—*[Section 1.1.1] Factors in Children That Affect the Action of UFH*

UFH Factor	Age-Related Difference	Evidence
UFH acts through antithrombin-mediated catabolism of thrombin and factor Xa	Reduced levels of antithrombin and prothrombin	Strong: multiple studies Andrew et al (1990),[32] Andrew (1992),[33] Andrew et al (1992),[34] Monagle et al (2006)[26]
	Reduced capacity to generate thrombin	Strong: multiple studies Ignjatovic et al (2007),[35] Andrew et al (1990),[32] Andrew (1994)[12]
	Age-related difference in anti-Xa:anti IIa activity	Moderate: Newall et al (2010),[5] Newall et al (2009),[36] Ignjatovic et al (2006)[37]
UFH is bound to plasma proteins, which limits free active UFH	Alterations in plasma binding	Moderate: Ignjatovic et al (2010),[29] Newall et al (2008),[28] Ignjatovic et al (2006),[27] Ignjatovic et al (2006)[37]
Endothelial release of TFPI	Age-related differences in amount of TFPI release for same amount of UFH	Moderate: Ignjatovic et al (2006)[37]

TFPI = tissue factor pathway inhibitor. See Table 1 legend for expansion of other abbreviation.

at 4 to 6 h postbolus. Maintenance UFH doses were age dependent, with infants (up to 2 months old corrected for gestational age) having the highest requirements (average, 28 units/kg per h) and children aged > 1 year having lower requirements (average, 20 units/kg per h). The doses of UFH required for older children are similar to the weight-adjusted requirements in adults (18 units/kg per h).[45] Boluses of 75 to 100 units/kg recently have been shown to result in aPTTs that are unrecordable for > 100 min.[5] This study's implications for the more generalized use of UFH boluses in children are unknown, but the results suggest that the recommendations for initial therapy with a bolus should be reexamined.[5]

There are few data to support the optimal initial doses (bolus or infusions) in neonates, especially premature infants. As with all children, consideration of the individual risk factors for bleeding, and the perceived risk of the thrombosis, will require individualization of the initial dosing strategy until such time as further studies have been completed.

There are few or no data to define optimal prophylactic doses of UFH. Clinicians commonly use a dose of 10 units/kg per h as a continuous infusion, although the efficacy of this has not been proven.[46,47]

1.1.4 Pharmacokinetics: Studies of UFH in newborns are limited but show that the clearance is faster than for older children because of a larger volume of distribution.[48,49] Recent studies demonstrate that following a UFH single bolus in children, the half life, volume of distribution, clearance, and peak serum concentration all vary in children compared with adults. Further, the pharmacokinetics of UFH in children fits a first-order model and is a function of weight rather than of age.[5]

1.1.5 Monitoring: There are now considerable data showing the lack of correlation among the variety of monitoring assays available, especially for UFH. There are no clinical outcome data that recommend one assay over another or even demonstrate the value of monitoring.[5,35,50] However, given the variability of dose requirements for UFH to achieve a target range observed in neonates and children and the increased clinical risk factors for bleeding, monitoring is the current standard of care.[51,52] Although there are no published data to support the practice, many clinicians use anti-Xa assays in preference to the aPTT in children aged < 1 year or for children in pediatric ICUs (PICUs) because there appears to be a lack of correlation between the anti-Xa and the aPTT.[5,35,50] There are standard dosing nomograms for UFH in children (Table 3).[53]

Recommendations for frequency of UFH monitoring are extrapolated from adult practice. The pragmatics of available vascular access, need for painful procedures, and ability of staff to obtain samples actually determine the monitoring schedule.[3]

1.1.6 Adverse Effects: One cohort study reported major bleeding in one in 65 (1.5%, 95% CI, 0.0%-8.3%) children treated with IV UFH for DVT/pulmonary embolism (PE).[44] However, many children in this study were treated with subtherapeutic doses of UFH. A single-center cohort study reported a major bleeding rate of 24% (95% CI, 11%-40%) in 38 children who received UFH therapy while in the PICU.[54]

A common cause of fatal heparin-induced bleeding is accidental overdose, especially in neonates. The most common cause of this is drug error, with 5,000 units/mL or similar concentration vials being erroneously selected instead of 50-units/mL vials. The different uses of heparin in neonatal populations (from line flushes to extracorporeal circuit support) usually mean that vastly different-strength heparin doses are readily available to ward staff. Although rarely reported in the medical literature, the number of cases reported in the popular press appears to be increasing.[4,55-60]

There are only three case reports of pediatric UFH-induced osteoporosis.[61,62] In two of these, the

Table 3—*[Section 1.1.5] Protocol for Systemic Heparin Administration and Adjustment for Pediatric Patients*

I. Loading dose: heparin 75 units/kg IV over 10 min				
II. Initial maintenance dose: 28 units/kg per h for infants aged < 1 y; 20 units/kg per h for children aged > 1 y				
III. Adjust heparin to maintain aPTT of 60-85 s (assuming this reflects an anti-Xa level of 0.35-0.70):				
aPTT, s	Bolus, units/kg	Hold, min	% Rate Change	Repeat aPTT
< 50	50	0	+ 10	4 h
50-59	0	0	+ 10	4 h
60-85	0	0	0	Next day
86-95	0	0	− 10	4 h
96-120	0	30	− 10	4 h
> 120	0	60	− 15	4 h
IV. Obtain blood for aPTT 4 h after administration of the heparin loading dose and 4 h after every change in the infusion rate				
V. When aPTT values are therapeutic, a daily CBC and aPTT				

Adapted with permission.[53] aPTT = activated partial thromboplastin time.

patients had additional risk factors before this complication. These limited data, in conjunction with adult data, would support avoidance of long-term use of UFH in children when alternative anticoagulants are available. This recommendation is strengthened by the physiologic changes in bone seen in childhood, which potentially places children at increased risk of osteoporosis compared with adults.[63,64]

As in adults, the diagnosis of heparin-induced thrombocytopenia (HIT) in children remains problematic.[65] Studies examining the frequency of HIT in children have varied in their reported results, likely because of differences in patient inclusion and laboratory techniques.[30,66-70] Rates vary from almost zero in unselected heparinized children[30] to 2.3% in children in the PICU.[68] UFH exposure in these cases ranged from low-dose exposure during heparin flushes used in maintaining patency of venous access devices (VADs), to supratherapeutic doses given during cardiopulmonary bypass and hemodialysis. Presumed HIT currently is the most common indication for children to receive novel anticoagulant drugs, and the outcome for these children often is poor because of complications of the novel anticoagulants.[71] Danaparoid, hirudin, and argatroban are alternatives to UFH in children with HIT.[65,72-99]

1.1.7 Treatment of Heparin-Induced Bleeding: If UFH needs to be discontinued for clinical reasons, termination of the infusion usually will suffice because of the rapid clearance of UFH. If immediate reversal is required, protamine sulfate rapidly neutralizes UFH activity. The required dose of protamine sulfate is based on the amount of UFH received in the previous 2 h (Table 4).

Recommendation

1.1. We suggest that therapeutic UFH in children is titrated to achieve a target range of anti-Xa activity of 0.35 to 0.7 units/mL or an aPTT range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C)**. We suggest that when initiating UFH therapy, UFH boluses be no greater than 75 to 100 units/kg and that boluses be withheld or reduced if there are significant bleeding risks** (Grade 2C)**. We suggest avoiding long-term use of therapeutic UFH in children** (Grade 2C)**.**

Table 4—*[Section 1.1.7] Reversal of Heparin Therapy*

Time Since Last Heparin Dose, min	Protamine Dose
< 30	1.0 mg/100 units heparin received
30-60	0.5-0.75 mg/100 units heparin received
60-120	0.375-0.5 mg/100 units heparin received
> 120	0.25-0.375 mg/100 units heparin received

Maximum dose of 50 mg. Infusion rate of a 10 mg/mL solution should not exceed 5 mg/min. Hypersensitivity reactions to protamine sulfate may occur in patients with known hypersensitivity reactions to fish or those previously exposed to protamine therapy or protamine-containing insulin.

1.2 LMWH in Neonates and Children

Despite unproven efficacy, LMWHs have become the anticoagulant of choice in many pediatric patients for primary and secondary prophylaxis of TE.[100] Potential advantages of LMWH include reduced monitoring need, lack of interference by other drugs or diet, reduced HIT, and probable reduced risk of osteoporosis. However, the predictability of the anticoagulant effect with weight-adjusted doses appears to be reduced compared with adults,[101] presumably because of altered plasma binding.[29,102]

Throughout the guidelines in this article, we use the term LMWH and present dosing schedules for a number of different LMWHs. However, most clinical data with respect to LMWH use in pediatric patients are derived from studies that used enoxaparin.[52,100,101,103-111]

1.2.1 Therapeutic Range: Therapeutic ranges for LMWH are extrapolated from adults and based on anti-Xa levels. The guideline for therapeutic LMWHs being given subcutaneously bid is an anti-Xa level of 0.50 to 1.0 units/mL in a sample taken 4 to 6 h following a subcutaneous injection. The majority of clinical studies in children have used this therapeutic range to date, although one study reported using 0.5 to 0.8 units/mL as the target therapeutic range, with good efficacy and safety outcomes.[52] The timing of testing has varied from 2 to 6 h after dosing.[52,108] There are no comparative studies of alternative therapeutic ranges in children. For children receiving a dose once daily, the same target peak level (0.5-0.8 units/mL) or, alternatively, a trough level of < 0.1 units/mL has been used.[52,108] In children treated with continuous IV infusions of LMWH, the same target range of 0.5 to 1.0 units/mL has been used.[112] The Prophylaxis of Thromboembolism in Kids Trial (PROTEKT) prophylaxis trial used a target anti-Xa range of 0.1 to 0.3 units/mL measured 4 to 6 h postdose.[113]

1.2.2 Pharmacokinetics: A two-compartment model describes enoxaparin kinetics. Body weight is the most predictive covariate for clearance and central volume of distribution (clearance, 15 mL/h per kg; central volume of distribution, 169 mL/kg; intercompartmental clearance, 58 mL/h; peripheral volume of distribution, 10 L; absorption rate, 0.414/h). Interindividual variability was found to be 54% for clearance and 42% for volume of distribution.[52]

1.2.3 Doses: The subcutaneous doses of LMWH required in pediatric patients to achieve adult therapeutic peak anti-Xa levels have been assessed for enoxaparin, reviparin, dalteparin, and tinzaparin (Table 5).[114-118] Doses have also been reported for nadroparin.[119] Once-daily dosing for enoxaparin has been described as well.[110] (Schobess et al) Although the initial doses reported in these studies most likely attain the therapeutic range, considerable interpatient dose differences have been reported, suggesting the possible need for routine monitoring of anti-Xa levels in children and neonates.[51] This has been confirmed by recent pharmacokinetic studies of enoxaparin.[52] Initial reports suggested that neonates require higher-per-kilogram doses than older children, and biologic explanations were proposed.[120,121] However, recent studies of nadroparin[122] and enoxaparin[102] demonstrated a difference in dose requirements across a number of different age groups in clinical cohort studies, suggesting that some of these variables may continue to affect drug metabolism well outside the newborn period. Whether clinical effectiveness will be altered by having multiple age-related initial and maintenance dose recommendations is unclear.

Reviews of clinical reports of final dose requirements for neonates have suggested that an even higher initial dose schedule is more appropriate,[123] especially in preterm infants.[111,124,125] However, clinical trials have not been performed to confirm the safety and efficacy of this approach, and it is difficult to recommend the optimal initial dosing strategy for term and premature neonates at this time.

IV dosing for enoxaparin has been reported in one neonate: enoxaparin at 1 mg/kg every 8 h was required to maintain therapeutic levels.[106] Continuous infusion of LMWH (predominantly dalteparin and nadroparin) has also been described in children.[112] Table 5 presents the doses required for prophylactic LMWH for enoxaparin, reviparin, and dalteparin.[114,115,117]

1.2.4 Adverse Events: A recent review of enoxaparin in neonates (n = 240 derived from eight articles, four abstracts, and one review from 1996-2007) reported that minor side effects were common; major bleeding was recorded in 13 of 240 (5%) neonates.[123] Whether premature infants are at increased risk is unclear. No major bleeds were reported in a series of 10 premature neonates.[125]

A review reported that in 308 children treated with therapeutic LMWH for venous thrombosis (from six studies), nine (2.9%) had major bleeding, and 72 (23.4%) had minor bleeding.[108] However, at least one of these studies included neonates.[100] The same review reported that of 133 children treated with prophylactic doses of LMWH for primary prevention of venous thrombosis, one (0.8%) had major bleeding, and four (3.0%) had minor bleeding.[108] There are no data addressing the frequency of osteoporosis, HIT, or other hypersensitivity reactions in children exposed to LMWH.

Treatment of LMWH-Induced Bleeding—Equimolar concentrations of protamine sulfate neutralize anti-IIa activity of LMWH but result in only partial neutralization of its anti-Xa activity.[126] However, in animal models, LMWH-associated bleeding is completely reversed by protamine sulfate.[127-130] The dose of protamine sulfate required depends on the dose and type of LMWH used. Repeat doses of protamine may be required after subcutaneous LMWH. Protocols for reversal have been published.[128]

Table 5—*[Section 1.2.3] Doses of LMWH Used in Pediatric Patients*

Drug	Weight	Age	Initial Treatment Dose	Initial Prophylactic Dose
Weight-dependent dose of reviparin	< 5 kg	na	150 u/kg/dose q12h	50 u/kg/dose q12h
	> 5 kg	na	100 u/kg/dose q12h	30 u/kg/dose q12h
Age-dependent dose of enoxaparin[a]	na	< 2 mo	1.5 mg/kg/dose q12h	0.75 mg//kg/dose q12h
	na	> 2 mo	1.0 mg/kg/dose q12h	0.5 mg/kg/dose q12h
Pediatric (all ages) dose of dalteparin[b]	na	all	129 ± 43 u/kg/dose q24h	92 ± 52 u/kg/dose q24h
Age-dependent dose of tinzaparin	na	0-2 mo	275 u/kg	…
	na	2-12 mo	250 u/kg	…
	na	1-5 y	240 u/kg	…
	na	5-10 y	200 u/kg	…
	na	10-16 y	175 u/kg	…

na = not applicable.

[a] Enoxaparin has 110 anti-factor Xa units/mg.[115]

[b] Dalteparin has 100 anti-factor Xa units/mg.

Recommendation

1.2. We suggest, for neonates and children receiving either once- or twice-daily therapeutic LMWH, that the drug be monitored to a target anti-Xa activity range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after subcutaneous injection or 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after subcutaneous injection (Grade 2C)**.**

1.3 VKAs in Neonates and Children

VKAs are problematic in newborns for several reasons. First, the plasma levels of the vitamin K-dependent coagulation factors are physiologically decreased in newborns to levels that are comparable to those achieved in adults receiving therapeutic amounts of VKAs with target international normalized ratios (INRs) of 2.0 to 3.0. Second, infant formula is supplemented with vitamin K to prevent hemorrhagic disease of the newborn. In contrast, breast milk has low concentrations of vitamin K, making breast-fed infants very sensitive to VKAs.[131,132] The latter can be compensated for by feeding breast-fed neonates 30 to 60 mL of formula each day. Third, VKAs are only available in tablet form in most countries. Although the tablets can be dissolved in water for administration to newborns, neither stability data nor critical assessment of this practice are available. Fourth, VKAs require frequent monitoring in newborns because of the rapidly changing physiologic values of the vitamin K-dependent coagulation proteins and frequent changes in medications and diet.[133] Finally, although there is substantial information on the use of VKAs in children aged >3 months, there is little efficacy or safety information specific to their use in neonates. Problems of vascular access, frequent intercurrent infections, concurrent medications, lack of liquid preparation, and poor compliance continue to make VKAs difficult to manage in older children as well.[133]

Warfarin is the most commonly used VKA in children.[134-138] Acenocoumarol is used in some European and South American countries.[139,140] Phenprocoumon is the preferred VKA in some parts of Europe. No data about doses of these other agents have been reported. At present, the choice of VKA often is influenced by previous experience and familiarity within a country or region. The remainder of this section will refer to warfarin unless stated otherwise.

The current therapeutic INR ranges for children are directly extrapolated from recommendations for adult patients because there are no clinical trials that have assessed the optimal INR range for children. Thus, for most indications, the therapeutic target INR is 2.5 (range, 2.0-3.0), and the low-dose prophylactic target INR is 1.7 (range, 1.5-1.9). Therapeutic ranges for prosthetic valves are also directly extrapolated from adult data.

The capacity of plasma from children receiving VKAs to generate thrombin is delayed and decreased by 25% compared with plasma from adults with similar INRs,[15] suggesting that the INR therapeutic range for children may be lower than for adults. This hypothesis is further supported by the observation that plasma concentrations of a marker of endogenous thrombin generation, prothrombin fragment 1.2, is significantly lower in children than in adults at similar INR values.[15]

1.3.2 Dose Response: An initial dose of 0.2 mg/kg, with subsequent dose adjustments made according to an INR nomogram, was evaluated in a prospective cohort study of children aged <1 year to 18 years (Table 6).[134] The largest cohort study (n = 319) found that infants required an average of 0.33 mg/kg and teenagers 0.09 mg/kg warfarin to maintain an INR of 2.0 to 3.0.[138]

1.3.3 Monitoring: Monitoring oral anticoagulant therapy in children is difficult and requires close supervision with frequent dose adjustments.[134,138,141]

Point-of-Care Monitoring in Neonates and Children—Studies in children comparing point-of-care monitors to venipuncture INRs, including comparison with World Health Organization reference thromboplastins in the laboratory method, have confirmed their accuracy and reliability.[142,143] Although not assessed in a formalized way, the major advantages identified by families included reduced trauma of venipunctures, minimal interruption of school and work, ease of operation, and portability.[143-149]

Table 6—*[Section 1.3.2] Protocol for Oral Anticoagulation Therapy To Maintain an INR Between 2 and 3 for Pediatric Patients*

I	Day 1: if the baseline INR is 1.0 to 1.3: Dose = 0.2 mg/kg orally	
II	Loading days 2-4: if the INR is:	
	INR	Action
	1.1-1.3	Repeat initial loading dose
	1.4-1.9	50% of initial loading dose
	2.0-3.0	50% of initial loading dose
	3.1-3.5	25% of loading dose
	>3.5	Hold until INR < 3.5 then restart at 50% decreased dose
III	Maintenance oral anticoagulation dose guidelines:	
	1.1-1.4	Increase by 20% of dose
	1.15-1.9	Increase by 10% of dose
	2.0-3.0	No change
	3.1-3.5	Decrease by 10% of dose
	>3.5	Hold until INR < 3.5, then restart at 20% decreased dose

Adapted with permission.[53] INR = international normalized ratio.

1.3.4 Adverse Effects of VKAs: Bleeding is the main complication of VKA therapy. The risk of serious bleeding in children receiving VKAs for mechanical prosthetic valves, as calculated across 13 case series, is <3.2% per patient-year.[150] In one large cohort (comprising 391 patient-years with variable target INR ranges), the major bleeding rate was 0.5% per patient-year.[144] In a randomized trial (n = 41; target INR range, 2.0-3.0 for 3 months), major bleeding occurred in 12.2% (95% CI, 4.1%-26.2%).[151] A single-center study with a nurse-coordinated anticoagulant service reported major bleeding rates of 0.05% per patient-year.[152] Adequate patient and family education protocols have been reported to be a major factor in reducing adverse bleeding events in children on warfarin therapy.[153,154] Nonhemorrhagic complications of VKAs, such as tracheal calcification or hair loss, have been described on rare occasions in young children.[155,156] Two cohort studies described reduced bone density in children receiving warfarin for > 1 year. However, these were uncontrolled studies, and the role of the underlying disorders in reducing bone density remains unclear.[157,158]

1.3.5 Treatment of VKA-Induced Bleeding: In the presence of an excessively prolonged INR (usually >8) and no significant bleeding, vitamin K may be used to reverse the effects of excess anticoagulation. Only limited data are available in children, but IV vitamin K in doses of 30 μg/kg have been used.[159] Algorithms for cessation and reversal of warfarin vs cessation of warfarin alone have not been specifically tested in children and are extrapolated from adult studies. In the presence of significant bleeding, immediate reversal using fresh frozen plasma (FFP) or prothrombin complex concentrates or recombinant factor VIIa may be required.

1.3.6 Alternative Thrombin Inhibitors: A number of reports have documented pediatric use of argatroban,[79,81,84,86,160,161] bivalirudin,[78,162] lepirudin,[82,83,87,89,93,163-165] dabigatran,[166,167] danaparoid,[75,77,92,96,168-175] and fondaparinux.[161,176-180] Most commonly, these agents have been used in children with HIT. Two reviews summarized the clinical indications, doses used, monitoring schedules, and clinical outcomes.[71,181]

Recommendation

1.3. We suggest, for children receiving VKAs, that the drug be monitored to a target INR of 2.5 (range, 2.0-3.0), except in the setting of prosthetic cardiac valves where we suggest adherence to the adult recommendations outlined in the article by Whitlock et al in this supplement (Grade 2C)**. We suggest that INR monitoring with point-of-care monitors be made available where resources make this possible** (Grade 2C)**.**

1.4 Antiplatelet Drugs in Neonates and Children

1.4.1 Background: Compared with adult controls, neonatal platelets are hyporeactive to thrombin, adenosine diphosphate/epinephrine, and thromboxane A_2.[182,183] This hyporeactivity of neonatal platelets is the result of a defect intrinsic to neonatal platelets.[182,183] Paradoxically, the bleeding time is short in newborns because of increased RBC size, high hematocrit levels, and increased levels of multimeric forms of von Willebrand factor.[184-186] The bleeding time was prolonged, relative to adults, throughout childhood in two of three studies.[34,187,188]

Using the platelet function analyzer (PFA)-100 (Dade International, Inc), cord blood samples from term neonates were found to have shorter closure times than samples from older children or adults.[189-191] The shorter closure time correlates with the higher hematocrit levels and increased von Willebrand factor activity (measured by ristocetin cofactor assay) in cord blood.[190] The multiplate whole-blood aggregometry analyzer also demonstrates age-related differences in platelet reactivity.[192] A review has summarized antiplatelet therapy in children.[193]

1.5 Aspirin

1.5.1 Therapeutic Range, Dose Response, and Monitoring: Aspirin remains the most common antiplatelet agent used in pediatrics. The dose of aspirin for optimal inhibition of platelet aggregation is not known. Empirical doses of 1 to 5 mg/kg per day have been proposed.[193] Pediatric doses of aspirin are not based on studies of the effect on platelet function in pediatric patients.[194] The PFA-100 sometimes is used to monitor aspirin therapy in pediatric patients, although no data support improved patient outcomes from this practice.[150] The VerifyNow aspirin assay (Accumetrics, Inc) is a point-of-care device that has been used to monitor aspirin therapy in adults, but its use for monitoring aspirin in children has not been reported.[195] Neither the PFA-100 nor the VerifyNow can be recommended for monitoring aspirin therapy in children at this time.

1.5.2 Adverse Effects: Neonates may be exposed to aspirin because of maternal ingestion (eg, treatment of preeclampsia). Clearance of aspirin is slower in neonates, potentially placing them at risk for bleeding for longer periods of time. However, in vitro studies have not demonstrated an additive effect of aspirin on platelet hypofunction in newborns, and evidence linking maternal aspirin ingestion to bleeding in newborns is weak.[196] In neonates, additive antiplatelet

effect must be considered if concurrent indomethacin therapy is required.

In older children, aspirin rarely causes important hemorrhage, except in the presence of an underlying hemostatic defect or in children also treated with anticoagulants or thrombolytic therapy. The relatively low doses of aspirin used as antiplatelet therapy, compared with the much higher doses used for antiinflammatory therapy, seldom cause other side effects. For example, although aspirin is associated with Reye syndrome, this appears to be a dose-dependent effect of aspirin and usually is associated with doses >40 mg/kg.[197-202]

Recommendation

1.5. We suggest that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day (Grade 2C)**.**

1.6 Dipyrimadole

Dipyridamole frequently is used as a second-line antiplatelet agent or in combination with aspirin therapy. Doses of 2 to 5 mg/kg per day are common.[203-205] Little in the literature is available on the use of dipyrimadole in children.

1.7 Clopidogrel

1.7.1 Therapeutic Range, Dose Response, and Monitoring: Clopidogrel is being used with increasing frequency in children. Initial anecdotal use reported a dose of 1 mg/kg per day to be effective and safe. Dosing strategies involved rounding of doses to one-quarter or one-half tablets (75-mg tablets). Regular monitoring of liver and renal function was recommended. The Platelet Aggregation Inhibition on Children on Clopidogrel (PICOLO) study reported that clopidogrel 0.20 mg/kg per day in children aged birth to 24 months with cardiac disease, 80% of whom were also receiving aspirin at a mean dose of 9 mg/kg per day, achieved a platelet inhibition level (as measured by percent inhibition of adenosine diphosphate-induced platelet aggregation) similar to that which was targeted in adult studies using 75 mg/d.[206] No other studies have reported laboratory monitoring of clopidogrel in children.

1.7.2 Adverse Effects: Clinically significant bleeding episodes were infrequent in the PICOLO trial. High rates of excessive skin bruising have been reported when clopidogrel is used in combination with aspirin, and major bleeding is reported in children receiving concomitant warfarin therapy.[207] Other studies have reported lower rates, but all studies to date have been small and retrospective.[208] Overdose has been reported with minimal adverse effects.[209]

1.7.3 Other Antiplatelet Agents: Ticlopidine, another thienopyridine, is given in doses of 10 mg/kg per day po q12h (maximum, 250 mg/dose). However, no data support the use of this drug in children.

The clinically available glycoprotein IIb/IIIa antagonists include IV abciximab, eptifibatide, and tirofiban.[210] In one study, children with Kawasaki disease who were treated with abciximab in addition to standard therapy demonstrated greater regression in coronary aneurysm diameter at early follow-up than patients who received standard therapy alone.[211] This study compared abciximab to historical controls, and all patients received additional anticoagulant therapy.

Treatment of Bleeding Due to Antiplatelet Agents—Antiplatelet agents alone rarely cause serious bleeding in children. More frequently, antiplatelet agents are one of several other causes of bleeding, such as an underlying coagulopathy and other antithrombotic agents. Transfusions of platelet concentrates and the use of products that enhance platelet adhesion (plasma products containing high concentrations of von Willebrand factor or D-des amino arginine vasopressin) may be helpful.

1.8 Thrombolysis in Neonates and Children

1.8.1 Background: At birth, plasma concentrations of plasminogen are $\sim$50% of adult values (21 mg/100 mL).[212-214] The decreased levels of plasminogen in newborns slows the generation of plasmin[215] and reduces the thrombolytic effects of streptokinase, urokinase and tissue plasminogen activator (tPA) in an in vitro fibrin clot system.[34] A similar response occurs in children with acquired plasminogen deficiency. Supplementation with plasminogen increases the thrombolytic effect of all three agents[34,216]

In pediatric patients, tPA is the agent of choice.[34,216-220] Reasons for this preference include a previous US Food and Drug Administration warning regarding urokinase, experimental evidence of improved clot lysis in vitro compared with urokinase and streptokinase, fibrin specificity, and low immunogenicity.[221,222] However, tPA is considerably more expensive than either streptokinase or urokinase, and the increased in vitro clot lysis by tPA has not been demonstrated in clinical trials in children. There is minimal experience with other thrombolytic agents in children.[217,219,223] A survey showed no consensus in indications for thrombolysis, dose, mode of delivery, or duration of therapy.[220]

Success rates for thrombolysis in pediatric patients vary. Albisetti[217] described complete resolution in 64% of 413 children receiving streptokinase, urokinase, or tPA (53%, 43%, and 69%, respectively).

Twenty-one percent of children had no response to thrombolytics. Nowak-Göttl et al,[218] in a review of thrombolysis in neonates, reported overall thrombolytic patency rates ranging from 39% for children with aortic thrombosis to 86.5% for children with cardiac diseases. The collected data suggested no difference in efficacy among streptokinase, urokinase, and tPA. Differences in success rates were also reported for thrombolysis in venous vs arterial thrombosis in children.[224] Most studies that reported success or failure of thrombolysis used thrombus resolution as an outcome measure, with methods of detection ranging from clinical assessment to radiologic assessment. One series of nine patients used the presence or absence of postthrombotic syndrome (PTS) as an outcome measure.[225] The likelihood of positive reporting bias and the lack of control groups of patients who did not receive thrombolytics make the interpretation of these data very difficult.[219]

1.8.2 Contraindications: Manco-Johnson et al[226] described specific contraindications for children, which included prematurity (< 32 weeks gestation). However, thrombolytics have been successfully given to increasingly premature babies[227-232]; the number of such patients remains small. Clinicians should, in each case, make an individual assessment of the risk-benefit ratio of thrombolysis.[219]

1.8.3 Therapeutic Range and Monitoring of Thrombolytic Agents: There is no therapeutic range for thrombolytic agents. The correlation between hemostatic variables and efficacy/safety of thrombolytic therapy is too weak to have useful clinical predictive value.[233] However, in patients with bleeding, the choice and doses of blood products can be guided by appropriate hemostatic monitoring. The single most useful assay is fibrinogen level, which usually can be obtained rapidly and helps to determine the need for cryoprecipitate or plasma replacement. A commonly used lower limit for fibrinogen level is 1.0 g/L. The aPTT may not be helpful in the presence of low fibrinogen levels, concurrent UFH therapy, and presence of fibrin/fibrinogen degradation products.[233] Measurement of fibrin degradation products or D-dimers are helpful in determining whether a fibrinolytic effect is present. Maintaining a platelet count $> 100 \times 10^9$ during thrombolysis has also been recommended.[226]

1.8.4 Doses: Eight case series have reported using thrombolysis for treatment of non-CNS venous and arterial thrombosis in children with consistent regimes. Variable success rates are reported[222,224,229,234-238] and have been summarized recently.[219] The most common dose and duration of tPA was 0.5 mg/kg per h infused for 6 h.[222,224]

Thrombolytic agents are used in low doses to restore catheter patency. Once again, tPA is the most commonly used agent; however, use of urokinase and recombinant urokinase (rUK) have also been reported.[239-248]

1.8.5 Route of Administration: No published studies have compared local to systemic thrombolytic therapy in children.[249] At this time, there is no evidence to suggest an advantage of local over systemic thrombolytic therapy in children with thrombotic complications.[217] In addition, the small vessel size in children may increase the risk of local vessel injury during catheter-directed therapy. The theoretical advantages of catheter-directed thrombolysis include the ability to deliver low doses of thrombolytic agent directly into the thrombus.[219] Local therapy may be appropriate for catheter-related TE when the catheter is already in situ. There are more-recent small case series reporting catheter-directed thrombolysis in children.[225,250,251]

1.8.6 Concurrent Heparin Therapy: Manco-Johnson et al[236] described the use of systemic urokinase infusions together with low-dose heparin infusions (10 units/kg per h) for 48 h followed by therapeutic heparinization and warfarinization in children presenting with a first episode of DVT. Concurrent low-dose heparin followed by therapeutic heparinization has since been described in other single-center studies.[224,225,229,237] Although concurrent LMWH has also been reported,[237] given the bleeding risks of thrombolysis, easily reversible anticoagulation seems more appropriate.

1.8.7 Adverse Effects of Thrombolytic Therapy: Thrombolytic therapy has significant bleeding complications in children. Early literature reviews (including 255 patients) reported an incidence of bleeding requiring treatment with packed RBCs of ~20%.[216] The most frequent problem was bleeding at sites of invasive procedures. A large single-institution study reported bleeding in 68% of patients, with bleeding requiring transfusion occurring in 39%.[222] Prolonged duration of thrombolytic infusion was associated with increased bleeding.

Zenz et al,[238] reported bleeding requiring transfusion in three of 17 (18%) patients treated for between 4 and 11 h and minor bleeding in another nine (54%). Another recent prospective study reported bleeding requiring transfusion in three of 26 (11.5%) patients and minor bleeding episodes in 11 (42%).[224] In another review, Zenz et al[232] reported intracerebral hemorrhage (ICH) in 14 of 929 (1.5%) patients. When subdivided according to age, ICH was identified in two of 468 (0.4%) children after the neonatal period, one of 83 (1.2%; 95% CI, 0.3%-6.5%) term infants, and 11 of 86 (13.8%; 95% CI, 6.6%-21.7%) preterm

infants. However, in the largest study of premature infants included in this review, the incidence of ICH was the same in the control arm that did not receive thrombolytic therapy. A retrospective analysis of 16 newborns who received tPA reported one death from bleeding.[234] Albisetti[217] reviewed the literature and calculated overall incidences (with any thrombolytic agent) of minor and major hemorrhage as 22% and 15%, respectively, with the use of tPA being associated with incidences of 26% minor and 17% major hemorrhage.

1.8.8 Treatment of Bleeding Due to Thrombolytic Therapy: Before thrombolytic therapy is used, clinicians should correct other concurrent hemostatic problems, such as thrombocytopenia or vitamin K deficiency. Clinically mild bleeding (eg, oozing from a wound or puncture site) can be treated with local pressure and supportive care. Major bleeding may be treated by stopping the infusion of thrombolytic agent; administering cryoprecipitate (usual dose of 1 unit/5 kg or 5-10 mL/kg), an antifibrinolytic, or both; and administering other blood products as indicated.

1.9 Vena Caval Interruption

There are case reports and series reporting the use of inferior vena cava (IVC) filters in children as young as 6 years of age.[252-257] Increasingly, temporary filters are used so that they can be retrieved once the risk of PE is reduced or the contraindication to anticoagulation has resolved. Temporary filters have been left in situ for >140 days.[258] Raffini et al[259] reported an institutional program that resulted in 5% of children presenting with DVT having IVC filters inserted with minimal adverse outcomes. Chaudry et al[260] reported the use of filters in the internal jugular veins as well as in the IVC. There are no specific guidelines for the use of filters in children and the risk-benefit ratio needs to be considered individually in each case. The risks will depend in part on patient factors and in part on the institutional expertise in placing and retrieving filters.

1.10 Surgical Therapy

Surgical thrombectomy, rarely used in children, is restricted to situations such as IVC thrombosis in association with intravascular extension of Wilm tumor, acute thrombosis of Blalock-Taussig shunts, life-threatening intracardiac thrombosis immediately after complex cardiac surgery, prosthetic valve thrombosis, septic thrombosis, and peripheral arterial thrombosis secondary to vascular access in neonates.[261-273] There are no specific guidelines for the use of thrombectomy in children, but there is general consensus that the TE recurrence rate and risk of long-term vascular damage is high. Clinicians should consider the risk-benefit ratio individually in each patient, and all patients should be strongly considered for anticoagulation after the procedure.

2.0 Recommendations for Antithrombotic Therapy in Specific Clinical Situations

2.1 VTE in Neonates

Two prospective registries from Canada and Germany collected data on neonatal venous thrombosis, whereas a study from The Netherlands included data from both neonates and older children.[20-22] The Canadian registry reported mortality according to the site of the thrombosis; deaths were most frequent (33%) in patients with right atrial/superior vena caval involvement, but it was not clear how many of these events were directly attributable to thrombosis.[21] In the German registry, there was one death due to right atrial/superior vena caval thrombosis, and in the Dutch study, there were no deaths directly attributable to the presence of thrombosis.[20,22] Morbidity following these events is very poorly characterized but includes the development of PTS. Specific complications such as chylothorax may also occur depending on the site of the thrombosis. Portal hypertension, which may lead to splenomegaly and gastroesophageal varices, may occur after umbilical venous catheter (UVC) thrombosis.[274,275] Because the majority of sick neonates have patent foramen ovale (PFO), paradoxical emboli causing stroke are described.[276]

The incidence of recurrent VTE, PTS, or other more-specific complications is unknown in treated or untreated neonates. The following recommendations are necessarily based on extrapolation of principles of therapy from adult guidelines, limited clinical information from registries, individual case studies, and knowledge of current common clinical practice. They incorporate the principles of use of anticoagulants and thrombolytics in children as described earlier in this article. Options for treatment include supportive care only, anticoagulant therapy with either UFH or LMWH, thrombolytic therapy, and surgery.

Important issues when considering treatment options in this age group include the site, extent, and clinical consequences of the thrombosis and the risks of bleeding complications associated with the use of anticoagulant or thrombolytic therapy. The latter will vary considerably with gestational age, birth weight, and comorbidities, such as lung disease, necrotizing enterocolitis (NEC), sepsis, and intraventricular hemorrhage (IVH). Management should be individualized with appropriate consideration of the risk-benefit ratio for each case. Given the particular risk of paradoxical

emboli at the time of central venous access device (CVAD) removal in neonates with CVAD-related VTE,[276] many clinicians advocate delay in CVAD removal until 3 to 5 days of anticoagulant therapy have been given.

As described previously, the majority of studies for anticoagulation in neonates have been part of larger studies reporting on children in general and report use of twice-daily enoxaparin targeted to an anti-Xa range (measured 4-6 h after dose) of 0.5 to 1.0 units/mL.[100,101,103-111] One study reported once-daily and bid enoxaparin targeted to a range of 0.5 to 0.8 units/mL measured 2 h after dose.[52] The relationship between the target therapeutic range and the clinical outcomes is unknown in neonates.[111,123-125]

Recommendation

2.1. We suggest that CVADs or UVCs associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ (Grade 2C)**. We suggest either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis rather than no follow-up** (Grade 2C)**; however, in previously untreated patients, we recommend the start of anticoagulation if extension occurs** (Grade 2C)**. We suggest that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations** (Grade 2C)**. If either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation, we suggest a prophylactic dose of anticoagulation until such time as the CVAD or UVC is removed** (Grade 2C)**. We suggest against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs** (Grade 2C)**. We suggest if thrombolysis is required, tPA is used rather than other lytic agents** (Grade 2C)**, and we suggest plasminogen (FFP) administration prior to commencing therapy** (Grade 2C)**.**

2.2-2.3 Renal Vein Thrombosis in Neonates

Renal vein thrombosis (RVT) in neonates is the most common type of spontaneous venous thrombosis.[14,20,21,277] Approximately 25% of cases are bilateral and 52% to 60% extend into the IVC.[14,278] Overall survival now approaches 100%.[278-282] Clinical sequelae in survivors include chronic renal impairment and hypertension.[278-283] Lau et al[279] reviewed all English-language reports of neonatal RVT from 1992 to 2006. There was no difference in renal outcomes irrespective of whether the infant received no therapy, UFH, or LMWH, with ~70% of affected kidneys having irreversible renal atrophy.[279] Approximately 20% of children had hypertension on long-term follow-up, and 3% of children developed chronic renal failure. Recurrent thrombosis rates appear low. Thrombophilic abnormalities did not predict recurrence or outcome; hence, their presence or absence are not useful in determining initial therapy. Because the existing direct evidence suggests no benefit, anticoagulant and thrombolytic therapy remains controversial.

Recommendations

2.2. For unilateral RVT in the absence of renal impairment or extension into the IVC, we suggest either (1) supportive care with radiologic monitoring for extension of thrombosis (if extension occurs, we suggest anticoagulation) or (2) anticoagulation with UFH/LMWH or LMWH in therapeutic doses rather than no therapy. If anticoagulation is used, we suggest a total duration of between 6 weeks and 3 months rather than shorter or longer durations of therapy (Grade 2C)**. For unilateral RVT that extends into the IVC, we suggest anticoagulation with UFH/LMWH or LMWH for a total duration of between 6 weeks and 3 months** (Grade 2C)**.**

2.3. For bilateral RVT with evidence of renal impairment, we suggest anticoagulation with UFH/LMWH or initial thrombolytic therapy with tPA followed by anticoagulation with UFH/LMWH (Grade 2C)**.**

2.4-2.5 CVAD Prophylaxis in Neonates

In discussing anticoagulant CVAD prophylaxis, one must consider two separate scenarios. The first is the use of infusions or locks to keep the CVAD patent, and the second is the use of systemic anticoagulation to prevent large-vessel thrombosis.

A 2008 Cochrane review of peripherally placed central venous catheters in neonates confirms the value of UFH continuous infusion at 0.5 units/kg per h compared with no treatment.[284] This review considered two eligible randomized trials,[285] which included 267 neonates. There was reduced risk of catheter occlusion (typical risk ratio [RR], 0.28; 95% CI, 0.15-0.53; number needed to treat, 5; 95% CI, 3-8) and no difference in the duration of catheter patency; however, one study evaluated time to catheter removal, censoring patients whose catheter was removed because of therapy completion or death, and identified benefit with heparin (adjusted hazard ratio, 0.55; 95% CI, 0.36-0.83).[285] This finding could be due to a higher incidence of elective removal of

catheters in neonates at the completion of therapy in the heparin group (63% vs 42%; $P = .002$).[285] The other study detected no statistically significant differences between heparin and placebo when evaluating time to blockage ($P = .3$) and time to sepsis ($P = .1$) separately.[286] No statistically significant differences were observed in the risk of thrombosis (RR, 0.93; 95% CI, 0.58-1.51), catheter-related sepsis (RR, 1.96; 95% CI, 0.50-7.60), or new appearance or extension of IVH (RR, 0.87; 95% CI, 0.25-3.03).[284] A subsequent randomized controlled trial (RCT) demonstrated reduced infection with 0.5 units/mL heparin through a neonatal long line compared with no heparin (RR, 0.57; 95% CI, 0.32-0.98; number needed to treat, 9; 95% CI, 5-212).[287]

The local administration of thrombolytics is effective in restoring patency to blocked vascular catheters. Both tPA and urokinase have been shown to restore patency in 50% to 90% of CVADs; tPA has been increasingly used relative to urokinase in children during the past decade in doses ranging from 0.1 to 2 mg. Studies have included few neonates.[239-248]

There are no published studies comparing the use of intermittent local thrombolysis as primary prophylaxis for CVAD patency. There are no studies that consider the use of systemic heparin or LMWH as primary prophylaxis for CVADs in neonates as distinct from older children.

Recommendation

2.4. For neonates with CVADs, we recommend to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over no prophylaxis (Grade 1A) **or intermittent local thrombolysis** (Grade 2C)**. For neonates with blocked CVADs, we suggest local thrombolysis after appropriate clinical assessment** (Grade 2C)**.**

2.6 Thromboprophylaxis for Blalock-Taussig Shunts and Modified Blalock-Taussig Shunts

Blalock-Taussig shunts (subclavian-to-pulmonary artery shunt) are a form of palliative surgery used to enhance pulmonary artery blood flow. Modified Blalock-Taussig shunts (MBTSs), in which a plastic (Gortex; W. L. Gore & Associates, Inc) tube graft is taken from the side of the subclavian artery and anastomosed to the pulmonary artery, are now standard therapy.[288] Thrombotic occlusion of MBTS has an incidence of 1% to 17%. Smaller shunt size, smaller infant size, and increased perioperative hemoglobin level are risk factors for occlusion of MBTS within 24 h.[289-291]

Postdischarge occlusion is also reported.[290,292] In a study of 146 infants aged ≤60 days who underwent MBTS and were discharged from the hospital alive, 21 (14%) died after discharge.[292] Autopsies in 15 children attributed death to shunt thrombosis in five infants (33%) and to myocardial infarction in two (13%). The mortality of patients discharged on aspirin (11%) was almost identical to that of patients discharged on no antithrombotic therapy (12.3%).[292] Wells et al[291] described the histologic appearance of 155 MBTSs electively taken down at a mean of 8 months of age and reported that 21% had >50% stenosis; however, the role of thrombosis vs myofibroblastic proliferation in causing the obstruction was unclear.

A retrospective series of 546 MBTS procedures reported no significant differences between heparin and no heparin in early failure rate (1.4% vs 3.4%, $P = .29$), in later failure rate (9.1% vs 13.6%, $P = .17$), or between aspirin and no aspirin (11.0% vs 6.7%, $P = .18$),[293] and Li et al[294] reported reduced thrombosis in a large cohort of patients treated with aspirin for 12 months after shunt surgery. In another, much smaller case study, aspirin was reported to decrease the incidence of stent thrombosis after MBTS surgery.[295] Mullen et al[296] reported the safety of MBTS without postoperative heparin therapy. No data support the use of ongoing anticoagulant therapy (heparin, LMWH, or VKAs) after MBTS surgery. No published RCTs guide the antithrombotic medical management of patients with MBTSs.

Recommendation

2.6. For neonates and children having MBTS, we suggest intraoperative UFH therapy (Grade 2C)**. For neonates and children after MBTS surgery, we suggest either aspirin or no antithrombotic therapy as compared with prolonged LMWH or VKAs** (Grade 2C)**.**

2.7 Therapy for Blocked Blalock-Taussig Shunts and MBTSs

Options for acute management of a thrombosed MBTSs include reoperation with shunt takedown and replacement, balloon angioplasty with or without percutaneous catheter thrombectomy, or thrombolysis.[297-299] There are insufficient data to recommend any one specific therapy over another.

2.8 Thromboprophylaxis for Stage 1 Norwood Procedures

Given that the standard Norwood procedure involves an MBTS and that the shunt size often is small (3.0 or 3.5 mm), prophylactic antithrombotic recommendations following Norwood procedure are based on those for MBTSs.[300,301] Whether a different strategy is required for Sano modifications of Norwood procedure is unknown.[302]

2.9-2.10 Therapy for Femoral Artery Thrombosis in Neonates and Children

Femoral artery thrombosis is most commonly seen as a complication of cardiac catheterization (CC). Few studies have considered neonates and children separately. Short-term consequences of femoral artery thrombosis include threatened limb viability and morbidity associated with anticoagulant or thrombolytic therapy. Long-term consequences of femoral artery thrombosis include leg-length discrepancies, muscle wasting, claudication, and loss of arterial access.[303-306] Symptomatic ischemia may occur at times when the child experiences rapid growth, as occurs in the first year of life and during puberty.[305]

Descriptions of treatment of femoral artery thrombosis in neonates or older children with thrombolytic therapy, anticoagulation, thrombectomy or observation (no active therapy) consist exclusively of case series without comparison groups.[238,307-322] The general practice in the majority of children's hospitals is to initiate therapy with UFH for patients with post-cardiac catheter femoral artery thrombosis. Previous studies have reported that ~70% of thromboses will resolve with UFH alone.[238] A recent report suggested that LMWH may be a safe alternative in this situation, although the possible need for thrombolysis or surgery makes LMWH a less attractive option.[103] If < 4 h have passed since the CC-related UFH bolus was given, then UFH may be commenced as a continuous infusion without a bolus. In acute limb-threatening thrombosis, indirect evidence from adults supports the use of thrombolytic or surgical interventions.

Recommendations

2.9. For neonates and children with acute femoral artery thrombosis, we recommend therapeutic doses of IV UFH as initial therapy compared with aspirin or no therapy (Grade 1B) **or LMWH** (Grade 2C)**. We suggest subsequent conversion to LMWH, or else continuation of UFH, to complete 5 to 7 days of therapeutic anticoagulation as compared with a shorter or longer duration** (Grade 2C)**.**

2.10. For neonates and children with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial UFH therapy and who have no known contraindications, we recommend thrombolysis (Grade 1C)**. For neonates and children with femoral artery thrombosis, we recommend surgical intervention compared with UFH therapy alone when there is a contraindication to thrombolytic therapy and organ or limb death is imminent** (Grade 1C)**.**

2.11 Prophylaxis for Peripheral Arterial Catheters in Neonates and Children

The majority of studies in this area have examined interventions to prolong catheter patency as distinct from avoiding occlusive arterial thrombosis.[323-326] Studies in pediatric intensive care have not separated children from neonates. Catheter patency was significantly prolonged for UFH concentration of 5 units/mL compared with 1 unit/mL,[323] UFH with normal saline vs dextrose flushes,[324] and papaverine-supplemented compared with placebo-supplemented solutions[326] (Table 7).

Recommendation

2.11. For neonates and children with peripheral arterial catheters in situ, we recommend UFH continuous infusion at 0.5 units/mL at 1 mL/h compared with normal saline (Grade 1A)**.**

2.12 Therapy for Peripheral Artery Thrombosis Secondary to Peripheral Artery Catheters in Neonates and Children

Peripheral artery thrombosis in neonates and children is almost always due to arterial puncture or catheters.[327] Tarry et al[328] identified 44 cases of peripheral arterial TEs secondary to catheterizations or arterial punctures in children with nephrotic syndrome. Friedman et al[309] reported the use of microvascular surgery in a heterogeneous group of neonates with vascular injury. Albisetti et al[329] reported 54 arterial thromboses in 51 children of whom 96% had peripheral artery thrombosis. One case series of predominantly neonates proposed an algorithm to assist in determining the role of surgery vs thrombolysis and anticoagulation.[263]

Recommendation

2.12. For neonates and children with a peripheral arterial catheter-related TE, we suggest immediate removal of the catheter (Grade 2B)**. For neonates and children with a symptomatic peripheral arterial catheter-related TE, we suggest UFH anticoagulation with or without thrombolysis or surgical thrombectomy and microvascular repair with subsequent heparin therapy** (Grade 2C)**.**

2.13-2.14 Prophylaxis of Umbilical Arterial Catheters in Neonates

The incidence of symptomatic thrombosis of umbilical arterial catheters (UACs) is 1% to 3%,[330-332] with studies using sequential imaging and autopsy data reporting a higher incidence.[333,334] Factors increasing

Table 7—*[Recommendation 2.11] Prophylaxis for Peripheral Arterial Catheters in Neonates and Children*

Study	Design	Age	Groups	No. Patients	Duration of Catheter Patency	Comments
Heulitt et al[326]/1993	RCT	Ages 3 wk to 18 y	1 unit/mL heparin: 1. placebo 2. papaverine (60 mg/500 mL)	1. n = 124 2. n = 115	Time until catheter failure was longer in patients receiving papaverine (log-rank, $P = .02$)	Catheter failure: 1. 22% 2. 7% $P = .02$
Rais-Bahrami et al[324]/1990	RCT	Newborns	Infusion 1-2 mL/h heparin 1 unit/mL: 1. heparinized normal saline 2. heparinized 5% dextrose water	1. n = 30 2. n = 30	Mean hours: 1. 78.1 h 2. 44.8 h NS	Mean hours for infants requiring premature removal of catheters: 1. n = 16, 107 h 2. n = 21, 39 h $P < .001$
Butt et al[323]/1987	RCT	Children	Heparin concentration/infusion rate: 1. 1 unit/mL, 1 mL/h 2. 1 unit/mL, 2 mL/h 3. 5 unit/mL, 1 mL/h	1. n = 164 2. n = 152 3. n = 154	Geometric mean of hours: 1. 33.5 h 2. 40.8 h 3. 43.5 h	Nonelective removal: 2 vs 1, NS 3 vs 1, $P < .002$
Selldén et al[325]/1987	Retrospective cohort	Patients aged < 1 y; radial arterial catheters	1. Intermittent flushing 2. Continuous infusion	1. n = 296 catheters 2. n = 42 catheters	Mean days: 1. 2.8 d 2. 6.3 d $P < .001$	Catheter removal because of malfunction: 1. 76% 2. 52% $P < .01$

NS = not significant. See Table 1 legend for expansion of other abbreviation.

risk include longer catheter duration[333] and the positioning of the UAC tip, which are routinely described as high or low. The high position is at the level of the T6 to T9 thoracic vertebral bodies. In this position, the catheter tip is placed above the celiac axis, superior mesenteric artery, and renal arteries and is, therefore, above the diaphragm. The low position is at the level of the L3 to L4 lumbar vertebral bodies, and the position is therefore below these major vessels but above the aortic bifurcation. Barrington[285] conducted a systematic review of five RCTs and one alternate-assignment trial comparing outcomes of clinical ischemic events, aortic thrombosis, IVH, mortality, NEC, hypertension, and hematuria. Clinical ischemic events (RR, 0.53; 95% CI, 0.44-0.63; consistent across five studies included) and aortic thrombosis (RR, 0.31; 95% CI, 0.11-0.86; one study with 62 infants) were less likely with high vs low UAC placement; other outcomes were not significantly different between high and low placement.[285]

The short-term consequences of UAC-related thrombosis depend on the extent of the thrombosis but include lower-limb ischemia,[330,332,335] congestive cardiac failure, impaired renal function, and hypertension.[336] Embolic events are also reported, and UAC thrombosis has been linked to the development of NEC.[337,338] Longer-term outcomes include death,[339] persistent renovascular hypertension, and lower-limb growth abnormalities.[340]

Six RCTs addressed the use of low-dose heparin infusions in neonates with UACs,[341-346] which was the subject of a systematic review by Barrington.[347] Five studies compared the use of UFH in the UAC infusate with or without additional UFH in flush solutions vs no UFH, whereas one compared the use of UFH in the infusate vs UFH in the flush solution. End points assessed in these studies included catheter patency, aortic occlusion, other ischemic events, coagulation abnormalities, IVH, and hypertension. Two studies used objective imaging to assess the incidence of thrombosis.[344,345] A reduced incidence of catheter occlusion was consistent in the studies (four used UFH 1 unit/mL, and one used UFH 0.25 units/mL[341]), with a pooled relative risk of 0.19 (95% CI, 0.10-0.33). Despite the consistent reduction in catheter occlusion, none of these studies were able to demonstrate that UFH had any effect on aortic thrombosis or other ischemic events. There was also no significant difference in the incidence of IVH.

McDonald et al[348] reported the use of full systemic UFH vs low-dose UFH in an RCT that included only 19 infants. Although there was a trend toward a reduced incidence of aortic thrombosis, this did not achieve statistical significance, and data on the incidence of IVH and other coagulation abnormalities were not reported.

The association between the use of UFH and the occurrence of IVH in preterm neonates remains controversial. In the review by Barrington,[347] no association between heparin exposure and IVH was identified. However, five of six studies in this review included infants of various gestational ages, some of whom may have been at relatively low risk for IVH, contrasting with other published data.[349,350] Lesko et al[349] reported a fourfold increase in IVH in low-birth-weight infants in a case control study; however, the CIs were relatively wide (OR, 3.9; 95% CI, 1.4-11.0). In addition, the median birth weight was lower in the UFH group, which also had a higher incidence of concomitant illnesses. Malloy and Cutter,[350] also reported higher UFH exposure in low-birth-weight infants with IVH. Again, confounding factors related to the severity of illness were not included in the model used for analysis.

Recommendations

2.13. For neonates with UACs, we suggest UAC placement in a high rather than low position (Grade 2B)**.**

2.14. For neonates with UACs, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25-1 unit/mL, total heparin dose of 25-200 units/kg per day) to maintain patency (Grade 2A)**.**

2.15 Treatment of Aortic Thrombosis

Non-UAC-associated or spontaneous aortic thrombosis is a rare event.[351-361] Many published cases have evidence of extensive thrombosis involving either the abdominal or the thoracic aorta, the later sometimes mimicking coarctation at presentation.[362] The outcome of these events is variable, but overall mortality appears to be relatively high.

A review summarized the management of aortic thrombosis.[363] Therapeutic options include heparin or LMWH, thrombolytic therapy, and surgical thrombectomy.[310,335,336,352,358,361,362,364-371] There are insufficient data to recommend any one treatment over others.

2.16 Prophylaxis for Cardiac Catheterization in Neonates and Children

The femoral artery is the most common access site for CC in neonates and children, although radial access has been reported in older children.[372] Although a number of studies have analyzed infants (aged <1 year) compared with older children, the available data do not allow separate consideration of neonates from children.

The incidence of femoral artery thrombosis in the absence of any thromboprophylaxis after CC is ~40%,[373,374] with younger children (ie, aged <10 years) having an increased incidence compared with older children.[373,374] Patient size, patient hemodynamic status, operator technique, larger catheter size, total time of arterial cannulation, and procedural vs diagnostic catheters are all factors that affect the risk for arterial thrombosis.[313]

Taylor et al[306] described 58 children aged <5 years at the time of catheterization and who were evaluated 5 to 14 years later using arterial duplex scanning and lower-extremity radiographs of bone length. Arterial occlusion was present in 33% of patients. Celermajer et al[303] reported that $>30\%$ of previously catheterized children and adolescents presented with vascular access problems at subsequent catheterizations because of an occluded vessel, a stenosed vessel, or scar tissue.

Five prospective trials examined the value of prophylaxis to prevent femoral artery thrombosis.[373-377] Freed et al[373] demonstrated that prophylactic anticoagulation therapy with aspirin does not significantly reduce the incidence of femoral artery thrombosis. Anticoagulation therapy with 100 to 150 units/kg UFH reduces the incidence from 40% to 8%. A randomized trial of 366 children suggested that a 50-unit/kg bolus of heparin may be as effective as a 100 units/kg when given immediately after arterial puncture (9.8% vs 9.3% incidence of arterial thromoboses); however, the CIs around the estimate are wide (0.6%; 95% CI, −5.5%-6.6%).[377]

Recommendation

2.16. For neonates and children requiring CC via an artery, we recommend administration of IV UFH as thromboprophylaxis over no prophylaxis (Grade 1A) **or aspirin** (Grade 1B)**. For neonates and children requiring CC via an artery, we recommend the use of UFH doses of 100 units/kg as a bolus compared with a 50-unit/kg bolus** (Grade 1B)**. In prolonged procedures, we suggest further doses of UFH rather than no further therapy** (Grade 2B)**.**

2.17 Cerebral Sinovenous Thrombosis in Neonates

The incidence of cerebral sinovenous thrombosis (CSVT) in neonates is at least 2.6 per 100,000.[378] Premature and term neonates are affected,[379] and CSVT can occur antenatally.[380] Seizures and lethargy are frequent, and focal neurologic deficits rare.[381,382] Venous infarcts are present in $>50\%$, of which the majority are hemorrhagic.[383,384] IVH is also frequent. Among term neonates with IVH, underlying CSVT is documented in nearly one-third (31%) and is more likely when thalamic hemorrhage is present ($P = .03$).[385]

Reported outcomes after neonatal CSVT include death in 7% to 19% and neurologic impairments in 36% to 79% of survivors.[383,384,386] Adverse neurologic outcomes include cognitive and motor deficits and in 20% to 40%, epilepsy.[387] The presence of infarcts at diagnosis and perinatal complications predict worse outcome.[388,389]

Although overt, recurrent CSVT is rare in neonates, propagation of the initial thrombus after diagnosis of CSVT is a concern. A cohort study reported asymptomatic propagation in the first week after diagnosis in 11 of 44 (25%) neonates treated without anticoagulation.[390]

There are no RCTs[391]; however, data on the safety of anticoagulation in neonates with CSVT are available.[378,383,384,392] There are significant geographic differences in physician decisions to treat neonates with CSVT with anticoagulants, with European and Canadian physicians much more likely to treat than US physicians.[392] In a consecutive cohort treatment safety study using standardized protocols for anticoagulation of neonatal CSVT, bleeding occurred in three of 37 (8%) treated neonates but was not fatal in any.[390] A subsequent report from the same authors reported nonfatal ICH in 14% of neonates with pretreatment ICH and only 2% in those without pretreatment ICH.[393] The most common anticoagulant used is LMWH.[386,392,394] LMWH has been reported to be safe even in the presence of significant thalamic hemorrhage.[395]

The optimal dose and duration of anticoagulant treatment is not known. However, neonates recanalize faster than older children, and the rate of recanalization is greatest in the first 3 months after diagnosis. About 50% of neonates have fully recanalized by 6 weeks to 3 months after diagnosis, and recanalization is observed in 65% by 6 months and 75% by 1 year.[390] Therefore, one approach is to assess for recanalization at 6 weeks and if complete, to stop anticoagulants, or if incomplete, to continue for an additional 6 weeks (3 months anticoagulation) and then stop. Early neurosurgical intervention may be necessary for even mild ventriculomegaly due to obstructive hydrocephalus.

Recommendation

2.17. For neonates with CSVT without significant ICH, we suggest anticoagulation, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months rather than shorter or longer treatment duration (Grade 2C)**. For neonates with CSVT with significant hemorrhage, we suggest either (1) anticoagulation or (2) supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted as compared with no therapy** (Grade 2C)**.**

2.18-2.20 Arterial Ischemic Stroke in Neonates

The diagnosis of neonatal arterial ischemic stroke (AIS) is very challenging because the clinical presentation is nonspecific, and routine imaging studies may miss AIS in neonates.[396] MRI with diffusion-weighted imaging usually is diagnostic for AIS.[397,398]

The incidence of acute neonatal AIS is one in 4,000 live births.[399] A form of perinatal stroke with delayed diagnosis has been referred to as presumed perinatal AIS.[400,401] Such infants are neurologically normal in the first month of life, demonstrate early hand preference or other signs of hemiparesis typically between 4 and 12 months of age, and have a CT scan showing a remote lesion consistent with prenatal or perinatal AIS. A variety of risk factors have been described for term and preterm neonates.[402-406] In term infants with AIS, the typical distribution is the middle cerebral artery, more commonly left than right, and small artery infarcts can occur. Hemorrhagic conversion is well recognized.

Neurologic deficits or epilepsy occur in 50% to 75% of survivors; sensorimotor deficits and feeding problems are most common.[400,407,408] Outcomes may be worse in preterm neonates.[409] Long-term follow-up is critical because later deficits with brain maturation often emerge.[410] Radiographic features may predict outcomes.[411,412] Recurrent stroke is very rare after AIS in the neonatal period.[413-415]

Recommendations

2.18. For neonates with a first AIS in the absence of a documented ongoing cardioembolic source, we suggest supportive care over anticoagulation or aspirin therapy (Grade 2C)**.**

2.19. For neonates with a first AIS and a documented cardioembolic source, we suggest anticoagulation with UFH or LMWH (Grade 2C)**.**

2.20. For neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C)**.**

2.21 Neonates With Purpura Fulminans

Purpura fulminans is an acute, lethal syndrome of disseminated intravascular coagulation characterized by rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis.[416-419] The skin lesions start as small, ecchymotic areas that increase in a radial fashion, become purplish black with bullae, and then turn necrotic and gangrenous. The lesions

occur mainly on the extremities but can occur on the buttocks, abdomen, scrotum, and scalp.

The syndrome is due to homozygote protein C (most commonly) or protein S deficiency or compound heterozygous states with undetectable plasma levels of the respective protein.[420-434] Rarely have other causes been described.[435] The classic clinical presentation consists of cerebral or ophthalmic damage (or both) that occurred in utero. In up to 70% of cases, purpura fulminans occurs within hours or days of birth, and, on rare occasions, large-vessel thrombosis occurs. The diagnosis is based on the appropriate clinical picture; a very-low or undetectable protein C/protein S level; heterozygous deficiency of the same protein in the parents; and, ideally, identification of the molecular defect. The presence of very-low levels of protein C/protein S in the absence of clinical manifestations and of a family history cannot be considered diagnostic because physiologic plasma levels can be as low as 0.12 units/mL.

Although clinicians have used numerous forms of initial therapy, 10 to 20 mL/kg of FFP every 6 to 12 h is usually the form of therapy that is most readily available.[436,437] Plasma levels of protein C achieved with these doses of FFP vary from 15% to 32% at 30 min after the infusion and from 4% to 10% at 12 h.[426] Plasma levels of protein S (which is entirely bound to C4b) are 23% at 2 h and 14% at 24 h, with an approximate half-life of 36 h.[438,439] Doses of protein C concentrate have ranged from 20 to 60 units/kg. In one study, a dose of 60 units/kg resulted in peak protein C levels of >0.60 units/mL.[426] Replacement therapy should be continued until all the clinical lesions resolve, which is usually at 6 to 8 weeks. In addition to the clinical course, plasma D-dimer concentrations may be useful for monitoring the effectiveness of protein C replacement.

The modalities used for the long-term management of infants with homozygous protein C/protein S deficiency include oral anticoagulation therapy, replacement therapy with either FFP or protein C concentrate, and liver transplantation.[419,437,440] To avoid skin necrosis when oral anticoagulation therapy is initiated, replacement therapy should be continued until the INR is therapeutic. The optimal therapeutic range is unknown; ranges from 2.5 to 4.5 have been reported. The risks of oral anticoagulation therapy include bleeding with high INRs and recurrent purpuric lesions with low INRs. Frequent monitoring of INR values is required if these complications are to be avoided.

Recommendation

2.21. For neonates with clinical presentations of homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of FFP every 12 h or protein C concentrate, when available, at 20 to 60 units/kg until the clinical lesions resolve (Grade 1A)**. For neonates with homozygous protein C deficiency, after initial stabilization, we recommend long-term treatment with VKA** (Grade 1C)**, LMWH** (Grade 1C)**, protein C replacement** (Grade 1B)**, or liver transplantation** (Grade 1C) **compared with no therapy.**

2.22 DVT and PE in Children

Unlike adults, 95% of VTEs in children are secondary to an identifiable risk factor.[13,22,151,441-443] The most common risk factor is the presence of a CVAD.[13,22,441,444-447] When spontaneous thrombosis occurs in children, it is usually in the lower limbs.[17] Recurrent VTEs occur in 7.5% of children.[13,17,22,441]

Prospective studies reveal that asymptomatic central venous line-related thrombosis occur frequently in children.[113,445,448] Radiographically confirmed asymptomatic CVAD-related thromboses in children are of clinical importance for a number of reasons. First, CVAD-related VTEs are associated with CVAD-related sepsis.[447] Second, CVAD-related thrombosis is a common source for PE in children,[17,449,450] which may be fatal.[446] Third, recurrent CVAD-related clot may result in loss of venous access that may be necessary for life-saving intervention such as organ transplantation.[17,22,451] Finally, many children have persistent right-to-left intracardiac shunts through which paradoxical embolism may occur.[17,446]

PTS occurs in 12% to 65% of children following venous thrombosis.[451,452] Although treatment studies have included this as an outcome measure, delay in initial treatment and recurrent thrombosis are reported risk factors.[452]

There has been one multicenter randomized trial of anticoagulation for VTE in children.[151] The REVIVE (Reviparin in Venous Thromboembolism) trial randomized children (aged >3 months) with a first VTE to receive either UFH and then VKAs (target INR, 2.5) for 3 months or an LMWH (reviparin) adjusted to achieve a target anti-Xa level of 0.5 to 1.0 units/mL for 3 months. The study was closed early because of slow recruitment prior to completion of target recruitment. As a result, the study failed to demonstrate or exclude a reduction or increase in recurrence (OR, 0.53; 95% CI, 0.05-4.00) or bleeding (OR, 0.41; 95% CI, 0.04-2.76).

Table S1 summarizes the other studies evaluating treatment of venous thrombosis in children (see "Acknowledgments" for more information on accessing this supplemental table). Many of the recommendations rely on indirect evidence for treatment of DVT and PE in adults.

Recommendations

2.22.1. In children with first VTE (CVAD and non-CVAD related), we recommend acute anticoagulant therapy with either UFH or LMWH (Grade 1B)**. We recommend initial treatment with UFH or LMWH for at least 5 days** (Grade 1B)**. For ongoing therapy, we suggest LMWH or UFH. 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 INR has not exceeded 2.0 compared with no therapy** (Grade 1B)**.**

2.22.2. We suggest that children with idiopathic VTE receive anticoagulant therapy for 6 to 12 months compared with no therapy (Grade 2C)**.**

Underlying values and preferences: Families who place a high value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor and a lower value on avoiding the inconvenience of therapy or potential impact of therapy on growth and development and bleeding risk associated with antithrombotic therapy are likely to choose to continue anticoagulant therapy beyond 6 to 12 months.

2.22.3. In children with secondary VTE (ie, VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for 3 months (Grade 2C) **as compared with no further therapy. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing asparaginase therapy, we suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved** (Grade 2C)**.**

2.22.4. In children with recurrent idiopathic VTE, we recommend indefinite treatment with VKAs (Grade 1A)**.**

2.22.5. In children with recurrent secondary VTEs with an existing reversible risk factor for thrombosis, we suggest anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy (Grade 2C)**.**

2.22.6. In children with a CVAD in place who have a VTE, if a CVAD 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 rather than no anticoagulation prior to removal** (Grade 2C)**. If CVAD access is required, and the CVAD is still functioning, we suggest that the CVAD remain in situ and the patient be given anticoagulants** (Grade 2C)**. For children with a first CVAD-related VTE, we suggest initial management as for secondary VTE as previously described.**

2.22.7. In children with CVAD in place who have a VTE and in whom the CVAD remains necessary, we suggest after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed (Grade 2C)**. If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE** (Grade 2C)**.**

2.23 Thrombolysis in Pediatric Patients With DVT

A number of case series have described thrombolysis for DVT in children.[222,226,235-238,329,453-460] A retrospective cohort found improved outcomes with respect to PTS when children received thrombolysis rather than anticoagulation alone.[461] Thrombolysis has been given systemically as catheter-directed doses, alone, and in combination with mechanical thrombolysis.[250,461-464] A number of reviews have summarized the experience of catheter-directed and systemic thrombolysis for DVT in children.[219,465,466] The risk-benefit ratio in terms of improved thrombosis outcome vs bleeding risk remains uncertain, as does the optimal dose and delivery technique. On the basis of adult data, the use of thrombolysis may be best restricted to limb- or life-threatening thrombosis.[467]

Recommendation

2.23. In children with VTE, we suggest that thrombolysis therapy be used only for life- or limb-threatening thrombosis (Grade 2C)**. If thrombolysis is used in the presence of physiologically low levels or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen** (Grade 2C)**. In children with VTE in whom thrombolysis is used, we suggest systemic thrombolysis or catheter-directed thrombolysis depending on institutional experience and, in the latter case, technical feasibility.**

2.24 Thrombectomy and IVC Filter Use in Pediatric Patients With DVT

Case reports and small case series in children report the use of thrombectomy for massive VTE or

PE[468-471] or for life-threatening thrombosis (Fontan circuit).[270,311,314,319,469,471,472] Recent reviews have also described both open and percutaneous methods of thrombectomy.[465,466] Thrombectomy may be an appropriate first-line therapy in children postcardiac surgery who have significant thrombus in the surgical field, especially if a shunt is acutely compromised.

Reports of successful and failed IVC filters in children have been published.[253,254,256-258,260,469,473-476] Raffini et al reported,[259] in a prospective cohort study, that 5% of children with DVT required IVC filters. The filter usually is placed through the femoral or jugular approach and may remain in situ for life or may be temporary. Removable filters are preferable, and they may remain in situ for up to 5 months.[258] Vena cava filter placement is restricted to children who weigh > 10 kg because of the size of the IVC and the available filters. In addition, the availability of a skilled pediatric interventional radiologist with experience in this field will be a major determinant of the risk-benefit ratio in individual patients. The complications of filter placement include extension of preexisting thrombosis up to the level of the filter, thrombus formation within the filter basket, and perforation of the IVC.[477-479]

Recommendation

2.24. In children with life-threatening VTE, we suggest thrombectomy (Grade 2C)**. In children who have had a thrombectomy, we suggest anticoagulant therapy as per recommendation (Recommendations 2.22)** (Grade 2C)**. In children > 10 kg body weight with lower-extremity VTE and a contraindication to anticoagulation, we suggest placement of a retrievable IVC filter** (Grade 2C)**. In children who receive a filter, we suggest that the filter be removed as soon as possible if thrombosis is not present in the basket of the filter and when contraindication to anticoagulation is resolved** (Grade 2C)**. In children who receive an IVC filter, we recommend appropriate anticoagulation for VTE (see Recommendation 1.2) as soon as the contraindication to anticoagulation is resolved** (Grade 1C)**.**

2.25 DVT in Children With Cancer

One RCT (the REVIVE study) compared LMWH and UFH/warfarin in the treatment of DVT in 78 children, but only 30% were cancer patients.[151] The CIs were consistent with substantial benefit and substantial detriment. LMWH is the preferred anticoagulant in many pediatric cancer patients because of the ease of maintaining the anticoagulation therapy around the usual frequent procedures, such as lumbar punctures.[480]

The rates of thrombosis in childhood cancer are much lower than in adults.[480-487] Furthermore, many childhood cancers have high cure rates, so active cancer may not be an ongoing factor once treatment is under way. Finally, therapy for childhood cancer is often intense and associated with significant thrombocytopenia, increasing the bleeding risks of anticoagulant therapy.[488] Thus, children with cancer and VTE may not benefit from antithrombotic therapy beyond 3 months, providing that other risk factors have resolved.[489]

There is only one case report of a pediatric patient with cancer developing thrombosis before the diagnosis of cancer.[490] This suggests that other risks factors play a significant role in the development of VTE in this population. For example, the risk of VTE in children with cancer varies considerably with the chemotherapeutic protocol being used.[487,491] The presence of CVADs also appears to greatly increase the rate of thrombosis.[486,487,491] Further, specific host factors may be important.[492] Thus, although the optimal duration of therapy is unknown, the control of reversible risk factors seems to be associated with a considerable reduction in risk of thrombosis recurrence and, therefore, important to consider in determining the duration of therapy. However, there remains little direct evidence to support recommendations.[487,493]

Recommendation

2.25. In children with cancer, we suggest that management of VTE follow the general recommendations for management of VTE in children. We suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (eg, use of asparaginase) (Grade 2C)**.**

Remarks: The presence of cancer, the need for surgery, chemotherapy, or other treatments may modify the risk-benefit ratio for treatment of VTE, and clinicians should consider these factors on an individual basis.

2.26 Children With Antiphospholipid Antibodies and DVT

Antiphospholipid antibodies (APLAs) are associated with an increased risk of thrombosis in children,[494-496] although whether this risk is similar to that of adults remains uncertain.[497-499] There is no direct evidence to guide the optimal therapy for DVT in children with APLAs or to support or refute the role of primary prophylaxis.

Recommendation

2.26. For children with VTE in the setting of APLAs, we suggest management as per

general recommendations for VTE management in children.

2.27 Children With DVT and Positive Inherited Thrombophilia Testing

The impact of a variety of inherited thrombophilia markers on the risk of recurrence for pediatric venous thrombosis has long been debated and was the subject of a meta-analysis[500] and review article.[501] The literature on which these reviews were based were cohort and case-control studies as well as case series, and there remain many questions about the optimal testing strategy and the impact of results on therapeutic decisions. There are insufficient data to support the presence or absence of thrombophilia markers as a determinant of intensity or duration of therapy and as distinct from the presence or absence of clinical precipitants of thrombosis (ie, spontaneous vs secondary thrombosis).

Recommendation

2.27. For children with VTE independent of the presence or absence of inherited thrombophilic risk factors, we suggest that the duration and intensity of anticoagulant therapy as per Recommendation 2.22.

2.28 Children With VTE and Structurally Abnormally Venous Systems

Structural venous abnormalities as precipitants of venous thrombosis in childhood are well described, although patients with such abnormalities often do not present until adult life. In the lower venous system, the most common abnormalities are interrupted or duplex IVC, presumably secondary to disrupted embryonic development of the IVC itself.[502-509] However, in the upper venous system, thoracic outlet syndrome, eponymously named Paget-Schroetter syndrome, are believed to be due to chronic trauma to the subclavian vein secondary to reduced anatomic space for the vein usually as a result of an abnormal relationship with the first rib, abnormal fibrous bands or muscle development in athletes.[510-519] Management of the venous thrombosis and the underlying structural abnormality has included acute anticoagulation; both local and systemic thrombolysis through a number of techniques; percutaneous angioplasty; thrombectomy; venous reconstruction; and in the case of Paget-Schroetter syndrome, decompression of the thoracic inlet through removal of relevant bone and muscle. No randomized trials have been conducted.

Recommendation

2.28. For children with first VTE secondary to structural venous abnormalities, we suggest anticoagulation as per other "spontaneous" VTE (Recommendations 2.22) and consideration of subsequent percutaneous or surgical interventions depending on patient factors and institutional experience. For children with recurrent VTE secondary to structural venous abnormalities, we suggest indefinite anticoagulation unless successful percutaneous or surgical interventions can be performed (Grade 2C)**.**

2.29 Children With Right Atrial Thrombosis

Right atrial and intracardiac thromboses are most commonly diagnosed in children who have CVADs extending into the right atrium.[273,520] The epidemiology and risk associated with right atrial thrombosis appears to be different in children compared with adults.[273] The natural history appears to be resolution irrespective of therapy, and many children are asymptomatic. Risk stratification based on clot size and mobility appears to be useful.[273,520] For low-risk patients with a clot < 2 cm in size, nonmobile, and attached to the atrial wall, not pedunculated or snake shaped, then removal of the CVAD with or without anticoagulation appears appropriate. For high-risk thrombosis cases, systemic anticoagulation should be offered. Thrombolysis or percutaneous or surgical thrombectomy have considerable risks and should be considered on an individualized basis.[273]

Recommendation

2.29. For children with right atrial thrombosis related to CVAD, we suggest removal of the CVAD with or without anticoagulation depending on the individual risk factors compared with leaving the CVAD in situ (Grade 2C)**. For children with large (> 2 cm), mobile, right atrial thrombosis, we suggest anticoagulation with appropriately timed CVAD removal and consideration of surgical intervention or thrombolysis based on individualized risk-benefit assessment compared with no anticoagulation therapy** (Grade 2C)**.**

2.30-2.34 Children With CVADs

Loss of CVAD patency most often is due to intraluminal occlusion with either thrombus or chemical deposition, although it may be secondary to large-vessel thrombosis involving the vein in which the CVAD is situated. CVAD patency is necessary for therapy to be effectively given through the CVAD. Blocked CVADs may be at increased risk of infection and lead to increased anesthetic and surgical exposure when they require replacement. Primary prophylaxis to maintain patency has usually considered intermittent CVAD heparin or saline flushes, continuous

CVAD heparin, or saline infusions. Taurolidine-citrate locks have been compared with heparin locks and shown to reduce rates of bloodstream infection.[521] Restoration of CVAD patency has usually involved intermittent bolus dosing of a variety of agents, with failure to restore patency being defined as the CVAD removal and replacement rate. Primary prophylaxis to avoid large-vessel thrombosis around the CVAD usually involves systemic anticoagulation and needs to be considered separately.

Studies that have addressed the issue of CVAD patency include a trial that evaluated the use of saline vs combination saline and 1 unit/mL UFH in a single-center, blinded randomized clinical trial.[522] The study failed to demonstrate or exclude a beneficial or detrimental effect on CVAD patency between the two groups (RR, 7.63; 95% CI, 0.4-144.9).

An unblinded, randomized crossover study in which 14 children received UFH 50 units/kg flush vs standard care every 12 h failed to demonstrate or exclude a beneficial or detrimental effect on CVAD patency.[523] A literature review by Kannan[524] provided no evidence to support heparin over normal saline as an intermittent flush.

In contrast, a meta-analysis of studies in adults with CVADs reported benefit of heparin compared with saline in terms of thrombosis, bacterial colonization, and possible bacteremia.[447] More than 40% of children with cancer had CVAD occlusions despite weekly heparin locks.[525] In the hemodialysis setting, alteplase 1 mg/mL was shown to be more effective than heparin 5,000 units/mL in reducing intraluminal clot between hemodialysis sessions.[526] A multicenter study of 577 pediatric cancer patients with CVADs reported that urokinase administration every 2 weeks reduced both CVAD occlusion rates and catheter-related infections compared with heparin administration.[527] Most other studies that have reported the use of local thrombolytic agents reported therapy for CVAD blockage and, hence, restoration of patency.[241,243,246,528]

Recommendation

2.30. For CVADs, we suggest flushing with normal saline or heparin or intermittent recombinant urokinase (rUK) to maintain patency as compared with no therapy (Grade 2C)**. For blocked CVADs, we suggest tPA or rUK to restore patency** (Grade 2C)**. If after at least 30 min following local thrombolytic instillation CVAD patency is not restored, we suggest a second dose be administered. If the CVAD remains blocked following two doses of local thrombolytic agent, we suggest radiologic imaging to rule out a CVAD-related thrombosis** (Grade 2C)**.**

There are two RCTs reporting thromboprophylaxis of CVADs to prevent CVAD-related DVT.[113] The PROTEKT Study randomized 186 children aged ≥ 3 months with varying underlying conditions to reviparin (n = 92) (anti-Xa levels, 0.1-0.3 units/mL) vs standard care (n = 94) (up to 3 units/kg per h UFH).[113] The incidence of asymptomatic CVAD-related thrombosis was 14.1% (11/78) in the reviparin group vs 12.5% (10/80) in the standard care group (OR, 1.15; 95% CI, 0.42-3.23).[113] The study was closed early because of slow patient recruitment. Schroeder et al[47] reported a single-center RCT comparing 10 units/kg per h continuous UFH infusion to placebo in 90 children aged < 1 year with CVADs postcardiac surgery. There was no difference in CVAD-related thrombosis in the treatment or placebo groups (15% vs 16%; difference of 1%; 95% CI, −14%-16%). The study was closed after an interim analysis showed futility.

The incidence of CVAD-related thrombosis varies with the underlying patient population, and this has led to some more-specific disease-related studies to examine the role of primary prophylaxis. CVAD-related thrombosis is reported to be common in children with cancer.[484,485] There are two RCTs that studied thromboprophylaxis in children with cancer. The Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) trial studied the use of antithrombin concentrate vs no therapy in 85 patients with pediatric acute lymphoblastic leukemia (ALL) treated with asparaginase.[486] Seven of 25 (28%) patients treated with antithrombin compared with 22 of 60 (37%) not treated had thrombosis (difference, −9%; 95% CI, −30%-13%), but the study was not powered to show efficacy. Ruud et al[529] studied the use of warfarin compared with no therapy in the prevention of CVAD-related thrombosis in children with cancer. The study enrolled 73 children, and 15 of 31 (48%) on warfarin and 17 of 42 (40%) on no therapy developed a VTE (difference, 12%; 95% CI, −15%-31%). The study was terminated without full recruitment after an interim study showed futility.

Cohort studies and case series have also addressed this issue. Elhasid et al[107] found LMWH (mean dose, 0.84 mg/kg once daily) to be apparently safe when compared with historical controls in preventing thrombosis in 41 patients with ALL. Nowak-Göttl et al[530] gave LMWH (dose, 1 mg/kg once daily) as primary thromboprophylaxis to children and adolescents with Ewing sarcoma (n = 36) and osteogenic sarcoma (n = 39). None of the patients developed TE complications during the postoperative period. Meister et al[531] reported that enoxaparin (1 mg/kg per day) in addition to antithrombin supplementation reduced the rate of thrombosis in children with ALL and CVADs

being treated in the BFM (Berlin-Frankfurt-Münster) 95 of 2,000 studies compared with antithrombin alone (nine of 71 [13%] with antithrombin alone and zero of 41 [0%] with enoxaparin alone; difference, 13%; 95% CI, 5%-20%). None of these series is adequate to address the question of efficacy because of sample size and study design.[487]

Recommendation

2.31. For children with short- or medium-term CVADs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B)**.**

The incidence of CVAD-related VTE in children receiving long-term total parenteral nutrition (TPN) varies from 1% based on clinical diagnosis to 35% based on ventilation perfusion scans or echocardiography to 75% based on venography.[444,532-538] Two studies have reported the use of VKA primary prophylaxis in this group of patients.[444,535] However, VKA primary prophylaxis commonly is used for children receiving long-term home parenteral nutrition, despite the lack of similar practice in adults.

Recommendation

2.34. For children receiving long-term home TPN, we suggest thromboprophylaxis with VKAs (Grade 2C)**.**

2.35 Glenn Procedure or Bilateral Cavopulmonary Shunt

Glenn successfully performed the classic cavopulmonary anastomosis in 1957 as palliation for tricuspid atresia. The bidirectional Glenn procedure is now frequently used as an intermediate step in patients with single ventricles prior to definitive Fontan surgery (following Blalock-Taussig shunts in hypoplastic right-side hearts and following stage I Norwood procedure in hypoplastic left-side hearts). Thrombotic complications following the Glenn shunt procedure are infrequent.[539-544] No published data support the need for routine thromboprophylaxis. However, once again, the fact that many patients subsequently proceed to Fontan procedures has led to some suggestions that thromboprophylaxis is warranted after a Glenn shunt to reduce the risk of thrombosis in the pulmonary vasculature, hence increasing the likelihood of successful conversion to a full Fontan circuit. Current clinical practices vary, and include no anticoagulation, UFH followed by aspirin, and UFH followed by warfarin therapy. There is no evidence to support a preference for any of these approaches. Recommendations for patients undergoing a bilateral cavopulmonary shunt (BCPS) procedure are therefore based on generalization from other major vascular procedures in infants and children.

Recommendation

2.35. For children who have a BCPS, we suggest postoperative UFH (Grade 2C)**.**

2.36 Fontan Surgery

The Fontan procedure, or a modified version, is the definitive palliative surgical treatment of most congenital univentricular heart lesions.[545,546] TE remains a major cause of early and late morbidity and mortality. Reported incidences of VTE and stroke ranged from 3% to 16% and 3% to 19%, respectively, in retrospective cohort studies where thrombosis was the primary outcome and from 1% to 7% in retrospective studies assessing multiple outcomes.[547,548] TE may occur any time after Fontan procedures but often present months to years later.[549] No predisposing factors have been identified with certainty, although this may be due to inadequate power and the retrospective nature of the studies.

Transesophageal echocardiography is more sensitive than transthoracic echocardiography for the diagnosis of intracardiac and central venous thrombosis.[550-552] MRI has been reported to be useful in noncomparative studies.[553] Despite aggressive therapy, TE following Fontan procedures carries a high mortality and responds to therapy in $<50\%$ of cases.[554,555] There is no consensus in the literature or in routine clinical practice about the optimal type or duration of antithrombotic therapy to prevent such events.[271,542,556,557] Consequently, a wide variety of prophylactic anticoagulant regimes are in use.

There are very few studies that compare treatment options.[547,548] Some cohort studies report anticoagulation or aspirin to be better than no therapy in terms of thrombotic complications,[558] although others question this finding.[559] The only randomized trial performed compared aspirin (5 mg/kg per day) to initial UFH followed by warfarin (target INR, 2.5; range, 2.0-3.0) as primary prophylaxis for 2 years post-Fontan surgery. The study found no difference in thrombosis (cumulative thrombosis rates, 19% at 2 years) or bleeding.[560] No studies comparing optimal duration of therapy have been performed.

Recommendation

2.36. For children after Fontan surgery, we recommend aspirin or therapeutic UFH followed by VKAs over no therapy (Grade 1C)**.**

2.37 Endovascular Stents

Endovascular stents are used with increasing frequency in the management of vascular problems, including

congenital heart lesions, such as branch pulmonary artery stenosis, pulmonary vein stenosis, or coarctation of the aorta; traumatic arterial injuries; arterial dissection; cerebral vascular abnormalities; renovascular disease; APLA syndrome; surgical stenosis; and venous disease.[561-573] Although stents can be successfully used in infants aged < 1 year, the small vessel size increases the risk of thrombosis.[574] There are no studies assessing the role of anticoagulation or antiplatelet therapy to avoid stent occlusion in children. Clinicians commonly administer UFH at the time of stent insertion followed by aspirin therapy.

Recommendation

2.37. For children having endovascular stents inserted, we suggest administration of UFH perioperatively (Grade 2C)**.**

2.38 Dilated Cardiomyopathy

The etiology of cardiomyopathy in children is quite different from adults. Postviral and idiopathic cardiomyopathies occur in otherwise well children, whereas dilated cardiomyopathy occurs frequently during the end stage of muscular dystrophies. Thrombosis remains a significant cause of morbidity and mortality.[262,575,576] In a cross-sectional study of children awaiting cardiac transplant, 31% had acute PE confirmed by ventilation/perfusion scan or angiography.[577] A series of 66 patients with dilated cardiomyopathy reported a prevalence of thrombosis of 14%.[578]

There are no studies of anticoagulant prophylaxis in pediatric patients. However, based on adult studies and the apparent risk of PE and stroke in children with cardiomyopathy, primary prophylaxis with warfarin (target INR, 2.5; range, 2.0-3.0) often is used.[579]

Recommendation

2.38. For pediatric patients with cardiomyopathy, we suggest VKAs no later than their activation on a cardiac transplant waiting list (Grade 2C)**.**

Underlying values and preferences: Parents who place a high value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring and a lower value on the uncertain reduction in thrombotic complications are unlikely to choose VKA therapy for their children who are eligible for transplant.

2.39 Primary Pulmonary Hypertension

Relatively little evidence directly addresses the role of anticoagulant therapy as primary prophylaxis in children with pulmonary hypertension.[580-582] However, on the basis of adult data and the basic pathophysiology of the disease, clinicians commonly administer anticoagulant prophylaxis in children with primary pulmonary hypertension.[580,583,584] The ACCP guidelines for medical management of primary pulmonary hypertension in adults recommend routine anticoagulant prophylaxis with VKAs, although there is variation with respect to the target range recommended. The guidelines acknowledge that some centers use a target INR of 2.0 (range, 1.7-2.5), whereas others use a target INR of 2.5 (range, 2.0-3.0). The ideal time to commence anticoagulant therapy in children is uncertain; starting at the same time as vasodilator or other medical therapy is common.[585-587] Some authors have suggested that the presence of reduced cardiac output or polycythemia is required to justify anticoagulant therapy.[581]

Recommendation

2.39. For children with primary pulmonary hypertension, we suggest starting anticoagulation with VKAs at the same time as other medical therapy (Grade 2C)**.**

2.40-2.42 Biologic and Mechanical Prosthetic Heart Valves

Biologic prosthetic heart valves may be surgically placed in infants and children with congenital or acquired heart disease when their innate tricuspid, pulmonary valve, or both are not surgically repairable.[588] Mechanical valves are preferred for mitral and aortic replacement, given the catastrophic consequences of valve failure in these anatomic positions.[589] Patients with biologic prosthetic heart valves usually receive an antiplatelet agent. TE and bleeding events are uncommon with this therapy.[590-594]

There is no direct evidence describing optimal thromboprophylaxis in children with bioprosthetic heart valves. Recommendations, therefore, must rely on indirect evidence from adults and the associated recommendations.[595]

Mechanical prosthetic heart valves may be surgically placed in infants and children with congenital or acquired heart disease when their innate valve is not surgically repairable.[596] Thrombotic complications associated with mechanical prosthetic heart valves are well described in adults. For this reason, clinicians generally use VKAs to prevent complications, which include TE, valve thrombosis, and ischemic stroke.

In children, optimal strategies for thromboprophylaxis for mechanical heart valves are less clear. Studies in children typically consists of retrospective case series, with many of the studies including small numbers of infants and children, a spectrum of age ranges, and varied valve positions and types.

Antithrombotic regimens described to prevent TE complications range from no anticoagulation to the use of antiplatelet agents or VKAs. The outcome events reported include TE (valve thrombosis and stroke), bleeding, and mortality.

The incidence of TE in children with mechanical valves is reported to be as high as 68% per patient-year in children who receive acetylsalicyclic acid (ASA)[597] and 27% per patient-year for children who received no drug therapy.[597] Bleeding, when reported, is extremely rare.[203,594,598-603] When VKAs are prescribed, the incidence of TE is reduced, but there is an increased bleeding incidence.[203,590,594,599,600,602-613] A series of 32 children routinely treated with phenprocoumon collected over a 22-year period reported a 10-year freedom of 89.1% (1.2%/patient-year) from any anticoagulation-related adverse event.[614]

There are few prospective studies and no RCTs in children. Recommendations are therefore based on the high-quality evidence supporting anticoagulant thromboprophylaxis in adults and the available evidence in children.

Recommendations

2.40-2.42. For children with biologic or mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population.[595]

2.43 Bacterial Endocarditis

Infective endocarditis in children most frequently affects children with underlying congenital heart disease or previous cardiac surgery. One of the major sequelae of infective endocarditis is embolic phenomenon and stroke.[615-617] Embolic complications may occur in as many as 30% of patients with infective endocarditis.[618] There remains debate about the role of urgent surgical intervention for infective endocarditis in children.[619,620] For those children managed conservatively, the presence or risk of emboli often leads to the question of the role of anticoagulation. Emboli are usually septic and may represent vegetations with or without thrombin deposition.

There are no comparative data with respect to the value of anticoagulation over and above antibiotics alone, and data on this subject in adults is conflicting. The role of anticoagulation must be considered on a case-by-case basis, incorporating the assumed embolic risks, potential need for surgery, and bleeding risks. There appears to be a small role for thrombolysis or potential benefit from antiplatelet agents.

2.44 Ventricular Assist Devices

Ventricular assist devices (VADs) are being used more often in children with cardiac failure (congenital or acquired) as either bridge to transplantation or to cardiac recovery.[621-626] There are a variety of VADs available, many specifically developed for pediatric use.[621]

Studies of these devices in infants and children are mainly retrospective case series with outcomes being survival to transplant or to cardiac recovery.[622,626-642] Reported survival to transplant or to cardiac recovery ranges from 50%[630] to 83%.[628] There are no good-quality studies evaluating the safety and efficacy of anticoagulant or antiplatelet therapy in children on VAD support to reduce TE. There is no standardized antithrombotic regimen; however, on the basis of adult data and the catastrophic consequences of circuit occlusion or embolic complications, anticoagulant therapy in combination with antiplatelet therapy seems preferable over no therapy.

Recommendation

2.44. For children with VADs, we suggest administration of UFH (Grade 2C)**. We suggest starting UFH between 8 and 48 h following implantation** (Grade 2C)**. In addition, we suggest antiplatelet therapy (either aspirin or aspirin and dipyridamole) to commence within 72 h of VAD placement** (Grade 2C)**. For children with VAD, once clinically stable, we suggest switching from UFH to either LMWH or VKA (target INR, 3.0; range, 2.5-3.5) until transplanted or weaned from VAD** (Grade 2C)**.**

2.45-2.46 Primary Prophylaxis for Venous Access Related to Hemodialysis

CVADs and arteriovenous fistulas are frequently used to provide venous access for children during hemodialysis.[643] Hemodialysis is used more frequently than peritoneal dialysis in children.[644] Pediatric patients who receive hemodialysis through a CVAD may be at increased risk of CVAD-related DVT because of the large-bore catheters used and the fluid shifts associated with intermittent dialysis. The average survival of CVADs used for hemodialysis is reported to be < 1 year,[643] whereas arteriovenous fistulas may have as much as a 59% 5-year survival.[645] In a small historical cohort study of children with arteriovenous fistulas, primary prophylaxis with LMWH was more effective than aspirin, which in turn was more effective at preventing thrombosis than no treatment.[646]

Recommendations

2.45. For patients undergoing hemodialysis via an arteriovenous fistula, we suggest routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy (Grade 2C)**.**

2.46. For patients undergoing hemodialysis via CVAD, we suggest routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy (Grade 2C)**.**

2.47 Use of UFH or LMWH During Hemodialysis

Intermittent hemodialysis traditionally requires procedural anticoagulation to avoid thrombosis within the artificial circuit. A substantial amount of data exists in adults with respect to the benefit of using either UFH or LMWH to maintain circuit patency during hemodialysis. Both UFH[647,648] and LMWH[649,650] have been reported as safe in children with uremia. Citrate has also been reported to be safe and effective, especially in patients at higher risk of bleeding.[651] Care must be taken with dosing and monitoring heparin prophylaxis in children receiving hemodialysis because inadvertent systemic anticoagulation with clinical bleeding can occur.[652]

Recommendation

2.47. For children having hemodialysis, we suggest the use of UFH or LMWH during hemodialysis to maintain circuit patency independent of type of vascular access (Grade 2C)**.**

2.48-2.50 Kawasaki Disease

During the acute phase, Kawasaki disease may cause medium-vessel and large-vessel arteritis, arterial aneurysms, valvulitis, and myocarditis. Kawasaki disease is the leading cause of acquired heart disease in children in North America. Of particular concern are coronary artery aneurysms that may stenose or thrombose. Coronary artery aneurysms or ectasia develop in 15% to 25% of untreated children and may lead to myocardial infarction, sudden death, or chronic coronary arterial insufficiency.[653]

Treatment of Kawasaki disease in the acute phase is directed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis, whereas long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction.[653] In patients with Kawasaki disease, aspirin is initially given in high doses (80-100 mg/kg per day during the acute phase for up to 14 days) as an antiinflammatory agent and then in lower doses as an antiplatelet agent (3-5 mg/kg per day for 6 to 8 weeks) to prevent coronary aneurysm thrombosis and subsequent infarction (the major cause of death in patients with Kawasaki disease).[653] Because concomitant use of ibuprofen or other nonsteroidal antiinflammatory drugs may interfere with the effectiveness of aspirin, these agents should be avoided.[654]

A large, multicenter RCT of high-dose IV γ-globulin plus aspirin compared with aspirin alone demonstrated that coronary artery abnormalities were present in 14 of 79 (18%) children in the aspirin group compared with three of 79 (4%) children in the γ-globulin plus aspirin group ($P = .005$).[655] Recent studies have focused on trying to risk stratify patients at presentation into those who will only require IV immunoglobulin at 1 g/kg as a single dose[656] vs those who will not respond to the standard two doses of 1 g/kg and require even more-aggressive therapy.[657] Methylprednisolone in the acute phase has been shown not to be beneficial in a recent well designed RCT.[658]

In a small study, patients who were treated with abciximab demonstrated greater regression in aneurysm diameter at early follow-up than historical control patients who received standard therapy alone.[211] These findings suggest that treatment with abciximab may promote vascular remodeling and warrant further study.

Because no prospective data exist to guide clinicians in choosing an optimal regimen for the prevention of thrombosis in patients with Kawasaki disease with coronary artery disease, recommendations are based on the known pathophysiology, retrospective case series in children with Kawasaki disease, and extrapolation from experience in adults with coronary disease.[653] Therapeutic regimens used in patients with Kawasaki disease depend on the severity of coronary involvement and include antiplatelet therapy with aspirin, with or without clopidogrel or dipyridamole; anticoagulant therapy with VKAs or LMWH; or a combination of anticoagulant and antiplatelet therapy, usually VKAs plus aspirin.[653] Long-term combined VKA and aspirin is reported to be associated with a 91% cardiac event-free outcome at 10 years and a bleeding complication rate of 1.7% per year.[659] LMWH has been reported to be as effective as warfarin and may lead to increased aneurysm regression compared with warfarin. For long-term therapy, patients often are converted to warfarin therapy.[660]

When a coronary aneurysm expands rapidly, the risk of thrombosis is particularly high. For this reason, some experts advocate the use of UFH with aspirin.[653] The most common antithrombotic regimen for patients with giant aneurysms is low-dose aspirin together with warfarin, maintaining an INR of 2.0 to 2.5.[653,661] Some physicians substitute a therapeutic dose of LMWH for warfarin.[653]

For giant aneurysms with acute thrombosis, thrombolysis or surgery is reported to be useful, but there are no comparative data.[265,659,662,663] Thrombolysis usually is given as a front-loaded protocol.[661] Comprehensive guidelines have been published.[664]

Recommendations

2.48. For children with Kawasaki disease, we recommend aspirin in high doses (80-100 mg/kg

per day during the acute phase for up to 14 days) as an antiinflammatory agent, then in lower doses (1-5 mg/kg per day for 6 to 8 weeks) as an antiplatelet agent (Grade 1B)**. For children with Kawasaki disease, we recommend IV γ-globulin (2 g/kg, single dose) within 10 days of the onset of symptoms** (Grade 1A)**.**

2.49. For children with moderate or giant coronary aneurysms following Kawasaki disease, we suggest that warfarin in addition to low-dose aspirin be given as primary thromboprophylaxis (Grade 2C)**.**

2.50. For children with Kawasaki disease who have giant aneurysms and acute coronary artery thrombosis, we suggest thrombolysis or acute surgical intervention (Grade 2 C)**.**

2.51 CSVT in Children

The estimated incidence of pediatric CSVT is 0.6 per 100,000 children per year with >40% occurring in neonates as previously discussed.[383,665] Radiographic diagnosis of CSVT requires imaging of the thrombus within cerebral sinuses and veins because nearly one-half of children have normal-appearing brain parenchyma and the location and characteristics of venous infarction are very nonspecific.[381,383,666,667] Imaging of the cerebral venous system is required including magnetic resonance venography or CT venography.[379,666,668]

Clinical outcomes after pediatric CSVT include death in 9% to 29% and neurologic deficits, headaches, and seizure disorders in more than one-half of survivors.[383,668] Among neurologic deficits, cognitive and behavioral deficits are common, and motor deficits are less common. In children, radiologic recanalization as early as 2 weeks after the onset of clinical symptoms has been reported.[669] Predictors of poor outcome include presentation with venous infarcts or seizures[383] and, for death, presentation with coma.[668] In the Canadian Pediatric Ischemic Stroke Registry, nearly 25% of children showed an increased severity of neurologic deficits developing over time, reinforcing the need for long-term follow-up. In addition, 13% of children with CSVT developed recurrent cerebral or systemic thrombosis.[383]

Initial therapy for CSVT includes hydration, antibiotics or surgery for foci of cranial infection, anticonvulsants for seizures, and measures aimed at decreasing intracranial pressure, with close monitoring for optic nerve compression.[670] However, historically poor outcomes and recurrent thrombosis provide the impetus for anticoagulant therapy.[671]

Clinical trials are lacking in pediatric CSVT. Four randomized, placebo-controlled trials of heparin in adults with CSVT support a benefit of heparin.[672-676] Most guidelines recommend anticoagulation for adults with CSVT, even in the presence of hemorrhage.[677] Pooled outcome data from 150 cases of pediatric CSVT published between 1980 and 1996 showed that among 136 children who were not given anticoagulants, the frequency of death was 16%, and the frequency of poor neurologic outcome was 22% (combined poor outcome, 36.5%). Among 14 treated children mortality was 14%, and poor neurologic outcome occurred in none (combined poor outcome, 14%).[678] Sébire et al[668] reported a trend toward better survival with no cognitive sequelae with anticoagulation (OR, 3.64; 95% CI, 0.98-13.5); results failed to exclude either a beneficial or a detrimental effect on the outcome of death (OR, 0.29; 95% CI, 0.03-2.89).

Single-center and small multicenter series in children[110,378,383,666,668,679-687] have shown that IV UFH and subcutaneous LMWH can be used safely in children. Hemorrhage is uncommon in patients treated with anticoagulants in all series.

In a study combining patients from several European centers, nonadministration of antithrombotic treatment in clinical risk situations and in children with idiopathic CSVT (n = 3) was significantly associated with higher risk of recurrence ($P < .001$). The type of anticoagulation therapy administered (eg, the use of UFH and warfarin or the application of LMWH) did not influence thrombosis-free survival ($P = .54$).[685]

Most recently, a large, single-center cohort reported that 56 of 79 (71%) children with CSVT received acute anticoagulation.[393] Major hemorrhage occurred in three children, two of whom had pretreatment intracranial hemorrhage. Bleeds were all nonfatal, and clinical outcome was favorable in 50%, similar to the remaining patients (53%), which is consistent with data in adults with CSVT and hemorrhage that show that the benefit of anticoagulation still outweighs the risk.[672,673,676] Early follow-up imaging demonstrated thrombus propagation in seven of 19 (37%) children without and three of 44 (7%) children with anticoagulation (RR, 3.1; 95% CI, 1.6-5.8).[393] Propagation was associated with new venous infarcts in 40% children and moderate or severe clinical outcome (OR, 4.3; 95% CI, 1.0-19.4). The authors concluded that anticoagulation was safe and that nontreatment was associated with propagation in more than one-third of children. The presence or absence of thrombophilia should not affect decisions with regard to treatment intensity or duration.[688]

The efficacy of thrombolysis in adults with CSVT remains uncertain, although there are sufficient data to conclude that it can be given safely.[689] Evidence regarding thrombolysis in children,[690-693] mechanical dissolution of clots or thrombectomy,[694-696] and surgical

decompression[697-699] is confined to case reports that have reported apparent success in isolated cases or small series of seriously ill patients, including children, usually in coma and with extensive thrombosis of superficial and deep venous structures.[690-692]

Recommendation

2.51. For children with CSVT without significant ICH, we recommend anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation (Grade 1B)**. In children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms, we suggest administration of a further 3 months of anticoagulation** (Grade 2C)**. For children with CSVT with significant hemorrhage, we suggest initial anticoagulation as for children without hemorrhage or radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted at that time** (Grade 2C)**. In children with CSVT and potentially recurrent risk factors (eg, nephrotic syndrome, asparaginase therapy), we suggest prophylactic anticoagulation at times of risk factor recurrence** (Grade 2C)**. We suggest thrombolysis, thrombectomy, or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy** (Grade 2C)**.**

2.52 AIS in Children

Reported incidence rates for AIS varies between two and 13 per 100,000 children per year.[700-702] Outcomes from childhood AIS include death in 3% to 5% and permanent cognitive or motor disability in 30% to 80%.[671,703,704] Survival rates are significantly better than in adults, and children with stroke who do not die acutely will probably survive beyond middle age, and the treatment of the resulting comorbidity will be extremely expensive. The health burden of this disease entity is thus very large.

Initial therapy in childhood AIS aims to limit extension of occlusive thrombosis and early recurrent thrombotic stroke. Subsequently, maintenance therapy aims to prevent longer-term recurrence.[705] Mechanisms of stroke in children include cardiogenic and large-vessel dissection-related embolism; cerebral vasculopathy, which may be transient or progressive; sickle cell disease; and in situ thrombosis. The conditions underlying these three mechanisms for stroke differ markedly in children compared with adults and notably exclude atherosclerosis. Frequently, chronic diseases of childhood or acute illnesses, including systemic infection and dehydration, underlie AIS. However, up to 15% of children with AIS have no apparent risk factors.

The results of adult stroke trials testing antithrombotic treatments cannot be directly extrapolated to children because of different mechanisms for thrombus formation in adults with atherosclerosis. To date, no RCTs of antithrombotic therapy have been conducted in children with stroke. Antiplatelet, anticoagulant, and other therapies in children with AIS are selected based on the perceived mechanism for arterial thrombosis associated with the underlying risk factors. Several cohort studies of children with AIS have assessed safety and failure rates for antithrombotic agents[679,706]; however, the largest data set is from the International Pediatric Stroke Study (IPSS) group. This consortium involves > 30 centers worldwide and collects data using standardized case report forms. The IPSS has published data on children with AISs occurring between 2003 and 2007.[704] There were 661 children with AIS (640 with acute treatment data, 612 with morbidity data, and 643 with mortality data). Acute therapy included anticoagulation alone in 171 (27%) patients, antiplatelet therapy alone in 177 (28%), antiplatelet and anticoagulation in 103 (16%), and no antithrombotic treatment in 189 (30%). Subtypes associated with any use of anticoagulation were dissection (OR, 14.09; 95% CI, 5.78-37.01) and cardiac disease (OR, 1.87; 95% CI, 1.20-2.92). Factors associated with nonuse of anticoagulation included sickle cell disease subtype (OR, 0.12; 95% CI, 0.02-0.95) and the enrollment center being located in the United States (OR, 0.56; 95% CI, 0.39-0.80). Antiplatelet use was associated with Moyamoya (OR, 4.88; 95% CI, 2.13-11.12), whereas nonuse was associated with dissection (OR, 0.47; 95% CI, 0.22-0.99), low level of consciousness (OR, 0.45; 95% CI, 0.31-0.64), and bilateral ischemia (OR, 0.32; 95% CI, 0.20-0.52). Outcomes at hospital discharge included neurologic deficits in 453 (74%) patients and death in 22 (3%). In multivariate analysis, arteriopathy, bilateral ischemia, and decreased consciousness at presentation were prognostic of adverse outcome.[704]

When ASA therapy fails or is not tolerated in children with AIS, clopidogrel frequently is used. Risks of combination therapy with ASA plus clopidogrel, however, were recently highlighted by a study of 17 children who received clopidogrel (nine alone, eight concurrent with aspirin) in whom two had subdural hemorrhages (both also receiving aspirin and both having marked cerebral atrophy [1 Moyamoya, 1 progeria vasculopathy]).[707]

There are few data addressing the safety or efficacy of tPA in children with AIS, and the literature associating outcomes with this treatment consists mostly of isolated case reports.[708,709] Although rarely feasible,

older children with acute AIS may be diagnosed within the time window for this treatment.

In Situ Thrombosis or Stroke of Undetermined Cause: In situ thrombosis may be idiopathic; secondary to local inflammation; or secondary to prothrombotic conditions, including iron deficiency anemia,[710-712] hyperhomocysteinemia,[712-716] elevated levels of lipoprotein(a),[218] and inherited prothrombotic disorders.[218,717,718] The overall risk of a recurrent AIS and TIA is 10% to 35%.[413,415,719-729] The recurrence risk increases in the presence of multiple stroke risk factors.[726] Genetic thrombophilia was previously reported as increasing the recurrence rate[725]; however, a more recent comprehensive study suggested that this is not the case.[688] Recurrence risk is greatest in the initial weeks and months following an index AIS but persists for at least several years.[413,725] Recurrent stroke can be silent; infarction is documented in one-third of children with cryptogenic stroke (not due to obvious preexisting diseases) undergoing repeat neuroimaging.[725]

Recommendation

2.52. For children with acute AIS with or without thrombophilia, we recommend UFH or LMWH or aspirin as initial therapy until dissection and embolic causes have been excluded (Grade 1C)**. For children with acute AIS, we suggest, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis for a minimum of 2 years as compared with no antithrombotic therapy** (Grade 2C)**. For children receiving aspirin who have recurrent AIS or TIAs, we suggest changing to clopidogrel or anticoagulant therapy with LMWH or VKA** (Grade 2C)**. For children with AIS, we recommend against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols** (Grade 1C)**.**

2.53 Embolic Stroke

Congenital heart disease and related interventions (surgery or catheterization) are associated with paradoxical embolism through intracardiac defects. In the setting of acute emolic stroke, the main principle of treatment is to prevent further embolic phenomenon. Strategies therefore target the source thrombosis, even though this may not be visualized through standard imaging techniques. Thus, anticoagulation is the preferred therapy because it is more effective than antiplatelet therapy in the treatment of intracardiac thrombosis and peripheral or central DVT.[671] The finding of a PFO on echocardiography in a child with stroke without an associated documented venous thrombosis often creates difficulties because the distinction between an in situ thrombosis as a cause of the AIS vs an embolic stroke may be impossible.[730-732]

Recommendation

2.53. For AIS secondary to cardioembolic causes, we suggest anticoagulant therapy with LMWH or VKAs for at least 3 months (Grade 2C)**. For AIS secondary to cardioembolic causes in children with demonstrated right-to-left shunts (eg, PFO), we suggest surgical closure of the shunt** (Grade 2C)**.**

2.54 Dissection

Dissection of craniocervical arteries underlies ~7% of childhood AIS.[733] In children with cerebral arterial dissection underlying AIS, the risk of recurrent strokes is ~12%.[733-735] Recurrence appears to be reduced by antithrombotic treatment[734] but is still observed during anticoagulation[733-735] or antiplatelet treatment.[734] In adults with cerebral artery dissection, a Cochrane meta-analysis that included 327 patients reported no significant difference for initial or recurrent stroke during anticoagulant treatment (five of 414) vs antiplatelet treatment (six of 157). The frequency of major hemorrhage was 0.5% during anticoagulation.[736] Subsequently, a large trial, the Spontaneous vs Traumatic Arterial Dissection (SPONTADS) study, showed recurrent stroke in two of 71 patients receiving anticoagulation treatment and one of 23 patients receiving aspirin treatment.[737] If data from the 105 SPONTADS patients are added to those pooled in the Cochrane analysis, there is a trend showing benefit of anticoagulant therapy (seven of 485 stroke on treatment) over antiplatelet therapy (seven of 180 stroke on treatment) (Fisher test $P = .066$; RR, 1.88; 95% CI, 1.10-3.23).

Recommendations

2.54. For AIS secondary to dissection, we suggest anticoagulant therapy with LMWH or VKAs for at least 6 weeks (Grade 2C)**. Ongoing treatment will depend on radiologic assessment of degree and extent of stenosis and evidence of recurrent ischemic events.**

2.55 Cerebral Vasculopathies

Cerebral vasculopathies can be inflammatory, traumatic, or idiopathic. Postvaricella angiopathy and transient cerebral arteriopathy (or nonprogressive primary angitis of the CNS) are among the most frequently seen and represent a unilateral inflammatory process involving the intracranial vessels that comprise the circle of Willis.[738] The recurrence rate for

vasculopathy may be increased compared with idiopathic stroke in children.[413,725,739] Sequential imaging studies may be required to differentiate the diagnosis, and ancillary studies (eg, varicella serology) are important. Determination of the specific subtype of vasculopathy and monitoring of cerebral vessel appearance on magnetic resonance angiography or formal angiography are critical for determining ongoing therapy requirements. In cerebral vasculitis, immunosuppressive agents may be required.[740]

Recommendation

2.55. For children with acute AIS secondary to non-Moyamoya vasculopathy, we recommend UFH or LMWH or aspirin for 3 months as initial therapy compared with no treatment (Grade 1C)**. For children with AIS secondary to non-Moyamoya vasculopathy, we suggest that ongoing antithrombotic therapy should be guided by repeat cerebrovascular imaging.**

2.56-2.57 Moyamoya Disease

The most severe childhood cerebral vasculopathy is Moyamoya, a progressive bilateral intracranial cerebral arteriopathy with severe stenosis or occlusion of the terminal internal carotid arteries, typically accompanied by basal collateral vessels.[671] Recurrent sequential infarcts, some silent, often are present at diagnosis. The mechanisms for ischemia and infarction likely involved both chronic underperfusion and thrombotic occlusion. Clinical presentations include recurrent abrupt AIS and TIA presentations and progressive cognitive loss. Children with vascular stenosis or Moyamoya have a risk of recurrence as high as 66%.[413,725,741] Direct and indirect revascularization procedures to bypass the stenotic and occluded arteries are available to increase regional cerebral blood flow and reduce the risk of recurrence,[742,743] and a meta-analysis of $>1{,}000$ children confirmed that surgery confers symptomatic benefit in almost 90% of children.[744] A summary of evidence supporting the variety of surgical interventions is available.[671] Anticoagulation is less frequently used because of concerns about bleeding; however, the use of antiplatelet therapy is common. Few data confirm benefit in either the short or long term, although some studies suggest that medical therapy is important perioperatively to reduce the risk of procedure-associated strokes, which are common.[745]

Recommendations

2.56. For children with acute AIS secondary to Moyamoya, we suggest aspirin over no treatment as initial therapy (Grade 2C)**.**

2.57. For children with Moyamoya, we suggest that they be referred to an appropriate center for consideration of revascularization.

2.58-2.59 Sickle Cell Anemia

Children with sickle cell anemia can experience stroke related to occlusion of small cerebral arteries or through the development of Moyamoya. In sickle cell anemia with stroke, reinfarction occurs in 7.06 of 100 patient-years despite treatment.[746] In children with sickle cell anemia receiving no treatment, recurrence is as high as 92%.[747-755] Children with sickle cell anemia and transcranial Doppler (TCD) velocities >200 cm/s have a 40% risk of stroke over the next 3 years.[756] An RCT found significant reduction in risk by blood transfusion every 6 weeks to decrease hemoglobin S percentage to $<30\%$.[757] Patients should receive regular transfusions indefinitely as the risk of overt stroke or reversion to high-risk TCD increases when blood transfusions stop (STOP2 [Optimizing Primary Stroke Prevention in Sickle Cell Anemia]).[758] Hydroxyurea may also reduce stroke risk in children with TCD velocities >200 cm/s.[759] Overt stroke is twice as common in children with silent or covert infarction in the context of sickle cell anemia.[746] Bone marrow transplantation[760-762] and revascularization for Moyamoya[763-766] are additional options for selected patients; however, no RCTs have been completed for these therapies. For specific recommendations related to sickle cell disease, we refer the reader to the most recent version of the more authoritative National Institutes of Health sickle cell treatment guidelines.[767]

Conclusion

The ninth edition of the antithrombotic therapy in neonates and children guidelines presents 59 recommendations linked in a transparent manner to the evidence on which the recommendations are based. The guidelines address generic issues related to the use of antithrombotic therapies in neonates and children as well as many specific clinical situations in which these therapies are considered. Although there has been considerable progress made in this field over recent years, there remain many questions and many gaps in our knowledge. However, there is no doubt that the management of thrombosis in neonates and children is an increasing problem for clinicians, and it is hoped that these guidelines will provide some degree of uniformity of approach while further research is being undertaken.

Areas of Future Research

These guidelines highlight once again the lack of evidence for many of the fundamental questions

facing clinicians dealing with TE disease in neonates and children. Immediate research priorities include the following:

1. Natural history of disease: Many thromboses in neonates, and indeed children, are now discovered incidentally or as part of routine screening. Clear evidence that all thromboses in neonates or children require treatment is lacking, and studies assessing the long-term outcomes, particularly in asymptomatic thrombosis, are required so that adequate risk-benefit assessments of treatment options can be determined. In particular, uniform assessment criteria of complications such as PTS are required.
2. Intensity of anticoagulant therapy: The efficacy and safety assessments of all anticoagulants used in neonates and children remain uncertain partly because there are no clinical outcome studies documenting optimal therapeutic strategies (and partly because there is as yet no uniform assessment of bleeding in the child treated with anticoagulation). Multiple publications now describe the inadequacies of current therapeutic ranges and of the monitoring tests used in current clinical practice. Therapeutic monitoring imposes a considerable burden of care. No viable alternative strategy has been reported. The potential for using weight-adjusted dosing without monitoring, particularly for UFH and LMWH, needs to be explored.
3. Duration of therapy: Currently, duration of therapy for venous thrombosis in neonates and children is extrapolated from adult practice, despite considerable evidence that this may not be relevant. Current clinical convention around duration of therapy for many types of arterial thrombosis seems entirely empirical. Multicenter clinical outcome studies are required to address these questions.
4. Role of nonpharmacologic interventions: Individual reports of interventional radiology or surgical therapies for thrombosis in children are increasing in frequency; however, there remain no comparative studies and, in fact, few if any consecutive cohort studies that enable patient selection criteria to be adequately determined or likely risk-benefit ratios of such interventions to be considered.
5. Nonhematologic complications of therapy: Normal long-term physical, neurologic, and psychosocial development should be the goal of all pediatric treatments. There is evidence that interventions aimed at the coagulation system may affect variable aspects of development, such as neurocognitive outcome or bone density. A greater understanding of the nonhematologic impact of anticoagulation therapies is required for holistic management of neonates and children with thrombosis.

There are many additional areas that require research to improve the outcomes for neonates and children with thrombosis, often at an individual disease level (eg, the use of antiplatelet vs anticoagulation therapy in a variety of clinical situations). However, the issues noted in this article are fundamental to progressing many other specific questions. As mentioned at the beginning of the article, new agents are now being specifically studied in children, and it is important that all these aspects are considered in study design and implementation, or else history will repeat itself, and in years to come, we will regret missed opportunities to build a sustainable evidence base on which to improve the care for neonates and children with thrombosis.

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Additional information: Table S1 can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl/e737S/suppl/DC1.

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