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Antithrombotic Therapy in Neonates and Children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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Antithrombotic Therapy in Neonates and Children*

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

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

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

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

Summary of Recommendations

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

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

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

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

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

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

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

In children with deep vein thrombosis (DVT):

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

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

1.2.3. We suggest children with idiopathic thromboembolism (TE) receive anticoagulant therapy for at least 6 months, using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0), or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C).

Underlying values and preferences: The suggestion to use anticoagulation therapy to treat idiopathic DVTs in children for at least 6 months rather than on a lifelong basis places a relatively high value on avoiding the inconvenience and bleeding risk associated with antithrombotic therapy, and a relative low value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor.

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

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

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

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

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

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

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CVL access is required and the CVL is still functioning, we suggest that the CVL remain *in situ* and the patient be anticoagulated (Grade 2C).

1.2.9. For children with a first CVL-related DVT, we suggest initial management as for secondary TE as previously described. We suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5 to 1.9) or LMWH (anti-FXa level range, 0.1 to 0.3) be given until the CVL is removed (Grade 2C)**. If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVL is removed but at least for a minimum of 3 months** (Grade 2C).

1.3.1. In children with DVT, we suggest that thrombolysis therapy not be used routinely (Grade 2C)**. If thrombolysis is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen** (Grade 2C).

1.4.1. If life-threatening VTE is present, we suggest thrombectomy (Grade 2C).

1.4.2. We suggest, following thrombectomy, anticoagulant therapy be initiated (Grade 2C).

1.4.3. In children > 10 kg body weight with lower-extremity DVT and a contraindication to anticoagulation, we suggest placement of a temporary inferior vena cava (IVC) filter (Grade 2C).

1.4.4. We suggest temporary IVC filters be removed as soon as possible if thrombosis is not present in the basket of the filter, and when the risk of anticoagulation decreases (Grade 2C).

1.4.5. In children who receive an IVC filter, we recommend appropriate anticoagulation for DVT (see Section 1.2) as soon as the contraindication to anticoagulation is resolved (Grade 1B).

1.5.1. In children with cancer, we suggest management of VTE follow the general recommendations for management of DVT 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]**.**

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

1.5.2. We suggest clinicians not use primary antithrombotic prophylaxis in children with cancer and central venous access devices (Grade 2C).

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

Remark: Depending on the age of the patient, it may be more appropriate to follow adult guidelines for management of VTE in the setting of APLAs.

1.7.1. For neonates or children with unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the IVC, we suggest supportive care with monitoring of the RVT for extension or anticoagulation with UFH/LMWH or LMWH in therapeutic doses; we suggest continuation for 3 months (Grade 2C).

1.7.2. For unilateral RVT that extends into the IVC, we suggest anticoagulation with UFH/LMWH or LMWH for 3 months (Grade 2C).

1.7.3. For bilateral RVT with various degrees of renal failure, we suggest anticoagulation with UFH and initial thrombolytic therapy with tPA, followed by anticoagulation with UFH/LMWH (Grade 2C).

Remark: LMWH therapy requires careful monitoring in the presence of significant renal impairment.

1.8.1. In children with CVLs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B).

1.8.2. In children receiving long-term home total parenteral nutrition, we suggest thromboprophylaxis with VKAs with a target INR of 2.5 (range 2.0–3.0) [Grade 2C].

1.8.3. For blocked CVLs, we suggest tPA or recombinant urokinase to restore patency (Grade 2C)**. If 30 min following local thrombolytic instillation CVL patency is not restored, we suggest a second dose be administered. If the CVL remains blocked following two doses of local thrombolytic agent, we suggest investigations to rule out a CVL-related thrombosis be initiated** (Grade 2C).

1.9 For pediatric patients having a modified Blalock-Taussig shunt, we suggest intraoperative therapy with UFH followed by either aspirin (1 to 5 mg/kg/d) or no further antithrombotic therapy compared to prolonged LMWH or VKAs (Grade 2C).

1.10 For patients who underwent the Norwood procedure, we suggest UFH immediately after the procedure, with or without ongoing antiplatelet therapy (Grade 2C).

1.11 In patients who have bilateral cavopulmonary shunts, we suggest postoperative UFH (for additional information, see Section 1.11: Primary Prophylaxis for Glenn or Bilateral Cavopulmonary Shunts in Children) [Grade 2C].

1.12 For children after Fontan surgery, we recommend aspirin (1 to 5 mg/kg/d) or therapeutic UFH followed by VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1B]**.**

Remark: The optimal duration of therapy is unknown. Whether patients with fenestrations require

more intensive therapy until fenestration closure is unknown.

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

1.14 We suggest that pediatric patients with cardiomyopathy receive VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) no later than their activation on a cardiac transplant waiting list (Grade 2C).

Underlying values and preferences: Our suggestion for administration of VKAs places a high value on avoiding thrombotic complications, and a relatively low value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring in children who are eligible for transplant, which is a potentially curative therapy.

1.15 In children with primary pulmonary hypertension, we suggest anticoagulation with VKAs commencing when other medical therapy is commenced (Grade 2C).

1.16 For children with biological prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population (see chapter by Salem et al in this supplement).

1.17 For children with mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population with respect to the intensity of anticoagulation therapy (see chapter by Salem et al in this supplement).

1.17.2. For children with mechanical prosthetic heart valves who have had thrombotic events while receiving therapeutic antithrombotic therapy, or in patients in whom there is a contraindication to full-dose VKAs, we suggest adding aspirin therapy (Grade 2C).

1.18.1. Following ventricular assist device (VAD) placement, in the absence of bleeding we suggest administration of UFH targeted to an anti-factor Xa of 0.35 to 0.7 u/mL (Grade 2C).

We suggest starting UFH between 8 h and 48 h following implantation (Grade 2C).

1.18.2. We suggest antiplatelet therapy (either aspirin, 1 to 5 mg/kg/d and/or dipyridamole 3 to 10 mg/kg/d) to commence within 72 h of VAD placement (Grade 2C).

1.18.3. We suggest that once clinically stable, pediatric patients be weaned from UFH to either LMWH (target anti-FXa 0.5 to 1.0 U/mL) or VKA (target INR 3.0; range, 2.5 to 3.5) until transplanted or weaned from VAD (Grade 2C).

1.19.1. For neonates and children requiring cardiac catheterization (CC) via an artery, we recommend administration of IV UFH prophylaxis (Grade 1A).

1.19.2. We recommend the use of UFH doses of 100 to 150 U/kg as a bolus (Grade 1B). **We suggest further doses of UFH rather than no further therapy in prolonged procedures** (Grade 2B).

1.19.3. We recommend against the use of aspirin therapy for prophylaxis for CC (Grade 1B).

1.20.1. For pediatric patients with a femoral artery thrombosis, we recommend therapeutic doses of IV UFH (Grade 1B). **We suggest treatment for at least 5 to 7 days** (Grade 2C).

1.20.2. We recommend administration of thrombolytic therapy for pediatric patients 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 (Grade 1B).

1.20.3. For children with femoral artery thrombosis, we suggest surgical intervention when there is a contraindication to thrombolytic therapy and organ or limb death is imminent (Grade 2C).

1.20.4. We suggest for children in who thrombolysis or surgery is not required, conversion to LMWH to complete 5 to 7 days of treatment (Grade 2C).

1.21.1. For pediatric patients with peripheral arterial catheters *in situ*, we recommend UFH through the catheter, preferably by continuous infusion (5 U/mL at 1 mL/h) [Grade 1A].

1.21.2. For children with a peripheral arterial catheter-related TE, we suggest immediate removal of the catheter (Grade 1B). **We suggest UFH anticoagulation with or without thrombolysis, or surgical thrombectomy** (Grade 2C).

1.22.1. To maintain umbilical artery catheter (UAC) patency, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration 0.25 to 1 U/mL) [Grade 2A].

1.22.2. For neonates with UAC-related thrombosis, we suggest therapy with UFH or LMWH for at least 10 days (Grade 2C).

1.22.3. For neonates with UAC-related thrombosis, we recommend UAC removal (Grade 1B).

1.22.4. For neonates with UAC-related thrombosis with potentially life-, limb-, or organ-threatening symptoms, we suggest thrombolysis with tPa. When thrombolysis is contraindicated, we suggest surgical thrombectomy (Grade 2C).

1.23 We suggest UACs placement in a high position rather than a low position (Grade 2B).

1.24 Neonatal Aortic Thrombosis: Spontaneous (for additional information, see Section 1.24 *Neonatal Aortic Thrombosis–Spontaneous*).

1.25 In patients undergoing hemodialysis, we suggest against routine use of VKAs or LMWH for

prevention of thrombosis related to central venous lines or fistulas (Grade 2C).

1.26 We suggest the use of UFH or LMWH in hemodialysis (Grade 2C).

1.27.1. In children with Kawasaki disease, we recommend aspirin in high doses (80 to 100 mg/kg/d during the short-term phase, for up to 14 days) as an antiinflammatory agent, then in lower doses (1 to 5 mg/kg/d for 6 to 8 weeks) as an antiplatelet agent (Grade 1B).

1.27.2. In children with Kawasaki disease, we suggest against concomitant use of ibuprofen or other nonsteroidal antiinflammatory drugs during aspirin therapy (Grade 2C).

1.27.3. In children with Kawasaki disease, we recommend IV gamma globulin (2 g/kg, single dose) within 10 days of the onset of symptoms (Grade 1A).

1.27.4. In children with giant coronary aneurysms following Kawasaki disease, we suggest warfarin (target INR 2.5; INR range, 2.0 to 3.0) in addition to therapy with low-dose aspirin be given as primary thromboprophylaxis (Grade 2C).

1.28.1. For neonates with CSVT without significant ICH, we suggest anticoagulation, initially with UFH, or LMWH and subsequently with LMWH or VKA for a minimum of 6 weeks, and no longer than 3 months (Grade 2C).

1.28.2. For children with CSVT with significant hemorrhage, we suggest radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus propagation is noted (Grade 2C).

1.29.1. 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).

1.29.2. We suggest that if after 3 months of therapy there is incomplete radiologic recanalization of CSVT or ongoing symptoms, administration of a further 3 months of anticoagulation (Grade 2C).

1.29.3. For children with CSVT with significant hemorrhage, we suggest radiologic monitoring of the thrombosis at 5 to 7 days. If thrombus propagation is noted at that time, we suggest anticoagulation (Grade 2C).

1.29.4. We suggest children with CSVT in the context of a potentially recurrent risk factors (for example nephrotic syndrome, L asparaginase therapy) should receive prophylactic anticoagulation at times of risk factor recurrence (Grade 2C).

1.29.5. 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).

1.30.1. In the absence of a documented ongoing cardioembolic source, we recommend against anticoagulation or aspirin therapy for neonates with a first AIS (Grade 1B).

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

1.31.1. For children with non–sickle-cell disease-related acute AIS, we recommend UFH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes have been excluded (Grade 1B).

1.31.2. We recommend, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis (1 to 5 mg/kg/d) for a minimum of 2 years (Grade 1B).

1.31.3. We suggest for AIS secondary to dissection or cardioembolic causes, anticoagulant therapy with LMWH or VKAs for at least 6 weeks, with ongoing treatment dependent on radiologic assessment (Grade 2C).

1.31.4 We recommend against the use of thrombolysis (tPA) for AIS in children, outside of specific research protocols (Grade 1B).

1.31.5. We recommend, for children with sickle-cell disease and AIS, IV hydration and exchange transfusion to reduce sickle hemoglobin levels to at least < 30% total hemoglobin (Grade 1B).

1.31.6. For children with sickle-cell disease and AIS, after initial exchange transfusion we recommend a long-term transfusion program (Grade 1B).

1.31.7. In children with sickle-cell anemia who have transcranial Doppler velocities > 200 cm/s on screening, we recommend regular blood transfusion, which should be continued indefinitely (Grade 1B).

1.31.8. We recommend that children with moyamoya be referred to an appropriate center for consideration of revascularization (Grade 1B).

1.31.9. For children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs), we suggest changing to clopidogrel or anticoagulant (LMWH or VKA) therapy (Grade 2C).

1.32.1. For neonates with homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of fresh frozen plasma q12h or protein C concentrate, when available, at 20 to 60 U/kg until the clinical lesions resolve (Grade 1B).

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

There are statements that appear in which the evidence is based on generalization of evidence from only remotely similar pediatric and adult clinical

situations combined with the experience of expert authors of these guidelines, and the experience of other carefully selected experts in the topic areas. Such are intended to provide guidance to physicians in areas where there is minimal direct evidence to guide clinical practice decisions and care management. No weak recommendations should be used for the development of performance measures.

Advances in tertiary care pediatrics have resulted in increasing numbers of children requiring antithrombotic therapy. Because thromboembolism (TE) events in pediatrics are rare enough to make management studies a challenge, recommendations for antithrombotic therapy in pediatrics are largely extrapolated from recommendations for adults.[1–3] Intervention trials are now both feasible and urgently needed to provide validated guidelines for antithrombotic therapy in neonates and children. However, data suggests that additional research is required to understand the basic pharmacokinetics and pharmacodynamics of antithrombotic drugs in children, as significant differences in antithrombotic activity, and impact on monitoring tests occur in children compared to adults.[4,5] Such differences likely impact on the efficacy and safety of antithrombotic drugs in children. Since the first publication of this chapter in the 1995 *CHEST* Antithrombotic Supplement,[6] investigators have initiated fewer than 10 multinational randomized controlled intervention trials assessing specific aspects of anticoagulant therapy in childre, and most of these have failed to enrol adequate patients to answer the primary study question.[7–9] The majority of the pediatric literature supporting the recommendations in this publication are uncontrolled studies, case reports or *in vitro* experiments.

This chapter is divided into two parts. The first section details the evidence showing that the interaction of antithrombotic agents with the hemostatic system of the young differs from adults. This section describes the pediatric specific aspects of mechanisms of action, therapeutic ranges, dose regimes, 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.

Throughout this chapter, the term *pediatric patients* refers to all neonates and children (birth to 16 years of age). The term *neonates* refers to infants from birth to 28 days corrected for gestational age. *Children* refers to patients aged 28 days to 16 years of age. The age at which adolescents should be considered adults from the perspective of treatment guidelines remains controversial. In addition to chronological age, clinicians need to consider factors such as physical development, stage of puberty, as well as emotional and intellectual development. In most pediatric centers, children are transitioned to adult services after they leave school, or between 16 and 18 years of age, although 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.

Antithrombotic Therapy in Pediatric Patients

A multitude of important variables make the use of antithrombotic drugs in pediatric patients different from adults. First, the epidemiology of TE in pediatric patients is vastly different from that seen in adults.[10–21] Second, the hemostatic system is a dynamic evolving entity that not only likely affects the frequency and natural history of TEs in children, but also the response to therapeutic agents.[22] Third, the distribution, binding, and clearance of antithrombotic drugs are age dependent. Fourth, the frequency and type of intercurrent illnesses and concurrent medications varies with age. Fifth, the need for general anesthesia to perform many diagnostic studies in pediatric patients impacts 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 antithrombotic therapy. Frequently, the practical ability to deliver the drug determines the choice of antithrombotic agent. Often, the only vascular access available is used for drug delivery, and so accurate monitoring of blood anticoagulant levels is difficult. Seventh, specific pediatric formulations of antithrombotic drugs are not available, making accurate, reproducible dosing difficult. This is especially the case for vitamin K antagonists (VKAs) [no suspension/liquid preparation] and low-molecular-weight heparin (LMWH) [available most readily in predosed syringes based on adult weights]. Eighth, dietary differences, makes the use of oral VKAs particularly difficult. This is especially true in neonates because breast milk and infant formulas have very different vitamin K levels, Finally, compliance issues are vastly different in, for example, small infants who cannot understand the need for therapy, adolescents who intellectually comprehend but emotionally are unable to cooperate, and children in dysfunctional families who suffer the effects of inad-

Table 1—*Question Definition and Eligibility Criteria*

Section	Population		Intervention or Exposure/Comparison	Outcome	Methodology	Exclusion Criteria
1.1	Neonates (prem and term up to 28 d corrected age)	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/VKAs or LMWH compared with each other or no therapy/ placebo)	Mortality PE Paradoxical stroke Postphlebitic syndrome Recurrence	RCT Observational studies	Thrombectomy Thrombolysis
1.2	Children (day 28 to 16 yr)	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/VKAs or LMWH compared with each other or no therapy/ placebo)	Mortality PE Paradoxical stroke Postphlebitic syndrome Recurrence	RCT Observational studies	Thrombectomy Thrombolysis Children with cancer, leukemia, or APLA
1.3	Children (day 28 to 16 yr)	DVT (CVL and non-CVL related), PE	Thrombolysis (compared with no therapy/placebo or anticoagulation alone)	Mortality PE Paradoxical stroke Postphlebitic syndrome Recurrence Major bleeding	RCT Observational studies	
1.4	Children (day 28 to 16 yr)	DVT (CVL and non-CVL related), PE	Thrombectomy or IVC filter (compared with each other, or anticoagulation or no therapy/placebo)	Mortality PE Paradoxical stroke Postphlebitic syndrome Recurrence	RCT Observational studies	
1.5	Children (day 28 to 16 yr) with cancer or leukemia	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/VKAs or LMWH) (compared with each other or no therapy/ placebo)	Mortality PE Paradoxical stroke Postphlebitic syndrome Recurrence	RCT Observational studies	
1.6	Children (day 28 to 16 yr) with APLA or lupus anticoagulant	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/VKAs or LMWH) (compared with each other or no therapy/ placebo)	Mortality PE Paradoxical stroke Postphlebitic syndrome Recurrence	RCT Observational studies	
1.7	Neonates (prem and term up to 28 d corrected age)	Unilateral or bilateral; RVT (with or without IVC extension)	Thrombolysis vs anticoagulation; anticoagulation vs no treatment	Mortality Renal failure Hypertension Extension	RCT Observational studies	
1.8	Neonates (prem and term up to 28 d corrected age); children (day 28 to 16 yr)	Central VAD	Local heparin (1–2 U/mL infusion), heparin lock, intermittent local thrombolysis, systemic heparin or LMWH prophylaxis (compared with each other or no therapy/ placebo)	Patency Sepsis DVT PE ICH	RCT Observational studies	

Table 1—*Continued*

Section	Population		Intervention or Exposure/Comparison	Outcome	Methodology	Exclusion Criteria
1.9	Neonates (prem and term up to 28 d corrected age), children (day 28 to 16 yr)	Blalock-Taussig shunt	Heparin or LMWH vs aspirin prophylaxis; aspirin prophylaxis vs no treatment	Intracardiac thrombosis Mortality Tissue loss ICH	RCT Observational studies	
1.10	Neonates (prem and term up to 28 d corrected age)	Stage 1 Norwood	Heparin or LMWH prophylaxis (compared to each other or no therapy/ placebo)	Intracardiac thrombosis Mortality Tissue loss ICH	RCT Observational studies	
1.11	Children (day 28 to 16 yr)	Glenn or BCPS	Heparin or LMWH prophylaxis (compared to each other or no therapy/ placebo)	Intracardiac thrombosis Mortality Tissue loss ICH Ischemic stroke Fontan surgery	RCT Observational studies	
1.12	Children (day 28 to 16 yr)	Fontan surgery	Heparin/LMWH and VKAs, aspirin (compared with each other or no primary prophylaxis)	Intracardiac thrombosis Mortality Fontan take down Stroke	RCT Observational studies	
1.13	Children (day 28 to 16 yr)	Endovascular stents	Heparin or LMWH or aspirin prophylaxis (compared with each other or no therapy/ placebo)	Patency Mortality Pulmonary emboli Ischemic stroke	RCT Observational studies	
1.14	Children (day 28 to 16 yr)	Dilated cardiomyopathy	VKAS or aspirin prophylaxis (compared with each other or no therapy/placebo)	Mortality Thrombosis Ischemic stroke	RCT Observational studies	
1.15	Children (day 28 to 16 yr)	Primary pulmonary hypertension	Prophylaxis; VKAs (compared with no therapy/placebo)	Mortality Thrombosis Heart/lung transplantation	RCT Observational studies	
1.16	Children (day 28 to 16 yr)	Biological prosthetic heart valves	VKAs or aspirin (compared with each other or no therapy/placebo)	Mortality Valve replacement Thrombosis Stroke	RCT Observational studies	
1.17	Children (day 28 to 16 yr)	Mechanical prosthetic heart valves	No therapy, antiplatelet agents, heparin/VKAs, antiplatelet agents, and VKAs	Mortality Valve replacement Thrombosis Stroke	RCT Observational studies	
1.18	Children (day 28 to 16 yr)	Thoratec or Berlin heart	VKAs or LMWH, antiplatelet agents prophylaxis (compared with each other or no therapy/placebo)	Mortality Thrombosis Stroke Blocked circuit requiring repeat surgery	RCT Observational studies	
1.19	Neonates (prem and term up to 28 d corrected age); children (day 28 to 16 yr)	Cardiac catheter	Heparin prophylaxis compared with no therapy/placebo	Femoral artery thrombosis	RCT Observational studies	

Table 1—*Continued*

Section	Population		Intervention or Exposure/Comparison	Outcome	Methodology	Exclusion Criteria
1.20	Neonates (prem and term up to 28 d corrected age); children (day 28 to 16 yr)	Femoral artery thrombosis	Thrombolysis, anticoagulation (heparin/VKAs or LMWH), thrombectomy (compared with each other or no therapy/placebo)	Claudication Leg shortening Limb loss	RCT Observational studies	
1.21	Neonates (prem and term up to 28 d corrected age); children (day 28 to 16 yr)	Peripheral arterial thrombosis	Thrombolysis vs thrombectomy; thrombolysis or thrombectomy; anticoagulation vs no therapy	Tissue loss Growth failure	RCT Observational studies	
1.22	Neonates (prem and term up to 28 d corrected age)	Aortic thrombosis (UAC related)	Heparin prophylaxis; thrombolysis; anticoagulation vs no prophylaxis	Patency Aortic thrombosis ICH NEC Mortality	RCT Observational studies	
1.23	Neonates (prem and term up to 28 d corrected age)	UAC	Exposure; high position (>T10) vs low position (L3–L5)	Aortic thrombosis NEC ICH	RCT Observational studies	
1.24	Neonates (prem and term up to 28 d corrected age)	Aortic thrombosis (spontaneous)	Thrombolysis or anticoagulation compared with each other or no treatment	Mortality Limb loss Renal impairment Hypertension NEC ICH	RCT Observational studies	
1.25	Children (day 28 to 16 yr)	Hemodialysis	Continuous VKAs or LMWH (compared with each other)	Mortality Thrombosis Shunt dysfunction Shunt infection	RCT Observational studies	
1.26	Children (day 28 to 16 yr)	Hemodialysis	Procedural UFH or LMWH (compared with each other)	Thrombosis Shunt dysfunction Dialysis failure	RCT Observational studies	
1.27	Children (day 28 to 16 yr)	Kawasaki disease	Aspirin, IVIG, aspirin and IVIG, no treatment	Coronary aneurysms Myocardial infarction Mortality	RCT Observational studies	
1.28	Children (day 28 to 16 yr)	Kawasaki disease with coronary aneurysms	Vitamin K antagonists, aspirin (compared with each other or no treatment)	Myocardial infarction Mortality Hemorrhage	RCT Observational studies	
1.29	Neonates (prem and term up to 28 d corrected age)	CSVT	Heparin or LMWH or VKAs compared with each other or no treatment	Mortality Functional status ICH	RCT Observational studies	

Table 1—*Continued*

Section	Population		Intervention or Exposure/Comparison	Outcome	Methodology	Exclusion Criteria
1.30	Children (day 28 to 16 yr)	CSVT	Heparin or LMWH or VKAs compared with each other or no treatment	Mortality Functional status ICH	RCT Observational studies	
1.31	Neonates (prem and term up to 28 d corrected age)	AIS	Heparin or LMWH vs aspirin or no treatment	Mortality Functional status ICH	RCT Observational studies	
1.32	Children (day 28 to 16 yr)	AIS	Heparin or LMWH vs aspirin or no treatment	Mortality Functional status ICH	RCT Observational studies	
1.33	Neonates (prem and term up to 28 d corrected age)	Purpura fulminans	Protein C replacement, VKAs, or LMWH compared to each other or no treatment	Mortality Vision Neurologic outcome Thrombosis	RCT Observational studies	

*IVIG = IV immunoglobulin; prem = premature.

equate 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.

The same limitations of extrapolation from adults apply to diagnosis as well as therapy of TE in children. This chapter focuses on therapy. For discussion of the issues related specifically to diagnosis, readers can consult several studies and reviews.[9,23–45]

In summary, the management of TEs in children differs significantly from that in adults. When there are no formal studies to support a recommendation, clinical experience becomes very important. The authors suggest that where possible, pediatric hematologists with experience in TEs manage pediatric patients with TE. When this is not possible, a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist provides a reasonable alternative.

Heparin and LMWH in Neonates and Children

Heparin

Unfractionated heparin (UFH), or standard heparin, remains a commonly used anticoagulant in pediatric patients. In tertiary pediatric hospitals, approximately 15% of inpatients are exposed to UFH each day.[46]

Mechanism of Action: The chapter by Hirsh et al in this supplement describes the mechanism of action of UFH. Table 2 lists the specific factors that may alter the activities of UFH in children.

Therapeutic Range: The recommended therapeutic range for the treatment of venous TEs in adults is an activated partial thromboplastin time (aPTT) that reflects a heparin level by protamine titration of 0.2 to 0.4 U/mL or an anti-factor (F) Xa level of 0.35 to 0.7 U/mL.[47] The aPTT therapeutic ranges are universally calculated using adult plasma. Recent data suggest that extrapolating the aPTT range from adults to pediatric patients is unlikely to be valid. For example, baseline aPTTs in pediatric patients, especially neonates, are often increased compared to adults. Therefore, the therapeutic ranges represent a reduced relative increment in aPTT values in pediatric patients having heparin therapy compared to adults.[22] *In vitro* and *in vivo* data also support that the aPTT that correlates to an anti-factor Xa (anti-FXa) level of 0.35 to 0.7 U/mL varies significantly with age.[5,48]

Table 2—*Factors in Children That Affect the Action of UFH

UFH Factor	Age-Related Difference	Evidence
UFH acts via antithrombin-mediated catabolism of thrombin and factor Xa	Reduced levels of antithrombin	Strong: multiple studies[22,118,143]
	Reduced capacity to generate thrombin	Strong: multiple studies[502,503]
	Age-related difference in anti-FXa: anti IIa activity	Weak[4]
UFH is bound to plasma proteins, which limits free active UFH	Alterations in plasma binding	Weak[5,48]
Endothelial release of TFPI	Age-related differences in amount of TFPI release for same amount of UFH	Weak[5]

*TFPI = tissue factor pathway inhibitor.

A recent study has demonstrated significant differences in the results of anti-FXa assays in children depending on the commercial kit being used. This has implications not only for the use of anti-FXa as a direct measure of UFH activity, but also for the determination of aPTT therapeutic ranges.[48] However, as yet there are no clinical outcome data to support changes in clinical practice based on the variation in the anti-FXa activity. In the absence of further information, extrapolation of the adult therapeutic range to pediatric patients remains necessary.

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[49] Bolus doses of 75 to 100 U/kg result in therapeutic aPTT values in 90% of children at 4 to 6 h after bolus. Maintenance UFH doses are age dependent, with infants (up to 2 months corrected for gestational age) having the highest requirements (average 28 U/kg/h) and children >1 year of age having lower requirements (average 20 U/kg/h). The doses of UFH required for older children are similar to the weight-adjusted requirements in adults (18 U/kg/h).[50] There is little or no data to define optimal prophylactic doses of UFH. Clinicians commonly use a dose of 10 u/kg/h as a continuous infusion.[51]

Pharmacokinetics: Studies of UFH in newborns are limited but show that the clearance is faster than for older children due to a larger volume of distribution,[52,53] and that the dose of UFH required achieve a therapeutic aPTT is also increased compared to older children.[49] Pharmacokinetic studies in piglets also show that the clearance of UFH is faster than for adult pigs due to a larger volume of distribution.[54]

Monitoring: The lack of certainty around the use of aPTT and anti-FXa assays in children as described in the section on therapeutic ranges combine to make recommendations about optimal monitoring of UFH problematic. While there is no published data to support the practice, many clinicians use anti-FXa assays preferentially in children <1 year old or in children in pediatric ICUs. This relates to the lack of correlation between the anti-FXa and the aPTT seen in these patient groups. Previously, clinicians had noted difficulty making appropriate dosage adjustment of IV UFH therapy in children[50,55]; however, investigations have validated UFH dosing nomograms in children (Table 3).[49]

Adverse Effects: One cohort study reported bleeding in 1.5% (95% confidence interval [CI], 0.0–8.3%) of children treated with UFH for deep venous thrombosis (DVT)/pulmonary embolus (PE).[49] However, many children were treated with subtherapeutic doses of UFH (compared to the target aPTT) in this study.[49] A more recent single-center cohort study reports a major bleeding rate of 24% in children in pediatric intensive care receiving UFH therapy.[56] Further studies are required to determine the true frequency of UFH-induced bleeding in optimally treated children. There are only three case reports of pediatric UFH-induced osteoporosis. In two of these, the patient received concurrent steroid therapy.[57–59] The third received high-dose IV UFH therapy for a prolonged period.[60] However, given the convincing relationship between UFH and osteoporosis in adults, clinicians should avoid long-term use of UFH in children when alternative anticoagulants are available.

A number of case reports of pediatric heparin-induced thrombocytopenia (HIT) have described patients ranging in age from 3 months to 15 years.[61–65] 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. Studies specifically examining the frequency of HIT in children have varied in their reported results, likely related to differences in patient inclusion and laboratory tech-

Table 3—*Protocol for Systemic Heparin Administration and Adjustment for Pediatric Patients

APTT, s	Bolus, U/kg	Hold, min	Rate Repeat Change, %	aPTT, h
< 50	50	0	+ 10	4
50–59	0	0	+ 10	4
60–85	0	0	0	Next day
86–95	0	0	− 10	4
96–120	0	30	− 10	4
>120	0	60	− 15	4

*(1) Loading dose: heparin 75 U/kg IV over 10 min; (2) initial maintenance dose: 28 Us/kg/h for infants < 1 yr old, and 20 U/kg/h for children > 1 yr old; (3) adjust heparin to maintain aPTT 60–85 s (assuming this reflects an anti-FXa level of 0.35 to 0.70); (4) obtain blood for aPTT 4 h after administration of the heparin loading dose and 4 h after every change in the infusion rate; (5) when aPTT values are therapeutic, a daily CBC and aPTT. Reproduced with permission from Michelson et al[6]/1995.

Table 4—*Reversal of Heparin Therapy

Time Since Last Heparin Dose, min	Protamine Dose, mg/100 U Heparin
< 30	1.0
30–60	0.5–0.75
60–120	0.375–0.5
> 120	0.25–0.375

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

niques.[46,66–70] Reported rates vary from almost nonexistent in unselected heparinized children,[46] up to 2.3% in children in the pediatric ICU.[67] A high index of suspicion is required to diagnose HIT in children because many patients in the neonatal/pediatric ICUs who are exposed to UFH have multiple potential reasons for thrombocytopenia and/or thrombosis. Danaparoid, hirudin, and argatroban are alternatives to UFH in children with HIT.[61,62,64,71–74]

Treatment of Heparin-Induced Bleeding: As in adults, if anticoagulation with UFH needs to be discontinued for clinical reasons, termination of the UFH infusion will usually suffice because of the rapid clearance of UFH. If an immediate effect 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). Protamine sulfate can be administered in a concentration of 10 mg/mL at a rate not to exceed 5 mg/min. Patients with known hypersensitivity reactions to fish, and those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.

LMWH

Despite their unproven efficacy, LMWHs have rapidly become the anticoagulant of choice in many pediatric patients, both for primary prophylaxis and treatment of TE. The potential advantages of LMWH for pediatric patients include minimal monitoring requirements (important in pediatric patients with poor or nonexistent venous access); lack of interference by other drugs or diet (compared to VKAs); reduced risk of HIT; and probable reduced risk of osteoporosis with long term use compared to UFH. However, the predictability of the anticoagulant affect with weight-adjusted doses appears to be reduced compared to adults, presumably due to altered plasma binding.[3,75]

Throughout these guidelines, we use the term *LMWH* and present dosing schedules for a number of different LMWHs. However, the majority of all clinical data with respect to LMWH use in pediatric patients is from studies that used enoxaparin.[76–84]

Mechanism of Action: In vitro, thrombin generation is similar in adults and children at the same concentration of LMWH. However, at 0.25 U/mL LMWH, thrombin generation was delayed and reduced by approximately half in newborns compared to adults. These differences were matched by reductions in rates of prothrombin consumption.[85]

Therapeutic Range: Therapeutic doses of LMWH are extrapolated from adults and are based on anti-FXa levels. The guideline for therapeutic LMWHs is an anti-FXa level of 0.50 to 1.0 U/mL in a sample taken 4 to 6 h following a subcutaneous injection. The clinical significance of the *in vitro* data described previously has not been established. The target anti-factor Xa assay (anti-FXa) range for prophylactic LMWH is again mostly extrapolated from adult data, although the PROTEKT trial used a range of 0.1 to 0.3 anti-FXa units.[8]

Doses: The doses of LMWH required in pediatric patients to achieve adult therapeutic anti-FXa levels have been assessed for enoxaparin, reviparin, dalteparin, and tinzaparine (Table 5).[86–88] In general, peak anti-FXa levels occur 2 to 6 h following a subcutaneous LMWH injection. While the doses listed were the initial doses reported to most likely attain the therapeutic range, considerable interpatient dose differences were reported, suggesting that routine monitoring of anti Xa levels in children and

neonates remains necessary. Infants less than approximately 2 to 3 months of age or < 5 kg have increased requirements per kg likely due to their larger volume of distribution. Alternative explanations for the increased requirement of LMWH per body weight in young children include altered heparin pharmacokinetics[89] and/or a decreased expression of anticoagulant activity of heparin in children due to decreased plasma concentrations of antithrombin. IV dosing has been reported in one neonate: Enoxaparin at 1 mg/kg q8h was required to maintain therapeutic levels.[76] A nonrandomized prospective cohort study has reported once daily enoxaparin at a dose of 1.5 mg/kg/dose to be as effective as 1 mg/kg q12h in children with DVT after the initial 7 to 14 days of twice-daily treatment in terms of efficacy and safety end points, but this study was underpowered.[78] Table 5 presents the doses required for prophylactic LMWH for enoxaparin, reviparin, and dalteparin.[86–88]

Adverse Events: Although the risk of major bleeding in neonates remains uncertain, studies have reported the risk of bleeding in neonates as part of larger patient populations. One pilot study reported no bleeding in seven infants < 2 months of age (0%; 95% CI, 0–47%).[89] In a larger series, 4 of 37 infants had major bleeding (10.8%; 95% CI, 3–25.4%).[83] Bleeding occurred locally (at the site of subcutaneous catheters in two newborns with little subcutaneous tissue), and into preexisting abnormalities in the CNS in a further two newborns. These data suggests that subcutaneous catheters should be used with caution in newborns with little subcutaneous tissue. In a single institution cohort study of 146 courses of therapeutic enoxaparin given to children, major bleeds occurred in 4.8% (95% CI, 2–9.6%) of patients.[83] In a randomized trial (n = 37) of reviparin, major bleeding occurred in 8.1% of patients (95% CI, 1.7–21.9%).[9] There are no data on the frequency of osteoporosis, HIT, or other hypersensitivity reactions in children exposed to LMWH.

Table 5—*Doses of LMWH Used in Pediatric Patients*

Variables	Data
Weight-dependent dose of reviparin, U/kg q12h	
Initial treatment	
Weight < 5 kg	150
Weight > 5 kg	100
Initial prophylactic	
Weight < 5 kg	50
Weight > 5 kg	30
Age-dependent dose of enoxaparin, mg/kg q12h*	
Initial treatment	
Age < 2 mo	1.5
Age > 2 mo	1.0
Initial prophylactic	
Age < 2 mo	0.75
Age > 2 mo	0.5
Pediatric (all ages) dose of dalteparin, U/kg q24h†	
Initial treatment	129 ± 43
Initial prophylactic	92 ± 52
Age-dependent dose of tinzaparin, U/kg q24h	
Initial treatment	
0–2 mo	275
2–12 mo	250
1–5 yr	240
5–10 yr	200
10–16 yr	175

*Enoxaparin has 110 anti-FXa U/mg.[86]
†Dalteparin has 100 anti-FXa U/mg; mean ± SD.

Treatment of LMWH-Induced Bleeding: Equimolar concentrations of protamine sulfate neutralize LMWHs anti-FIIa activity but result in only partial neutralization of its anti-FXa activity.[90] However, in animal models, LMWH associated bleeding is completely reversed by protamine sulfate.[91–94] The dose of protamine sulfate required is dependent on the dose of LMWH used. Repeat doses of protamine may be required after subcutaneous LMWH. Protocols for reversal have been published.[91]

VKAs in Neonates and Children

VKAs

VKAs function as anticoagulants by reducing the functional plasma concentration of vitamin-K dependent factors (II, VII, IX, and X). 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, which makes formula-fed infants resistant to VKAs. In contrast, breast milk has low concentrations of vitamin K, making breast-fed infants very sensitive to VKAs.[95,96] The latter can be compensated for by feeding breast-fed neonates 1 to 2 ounces 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, frequent changes in medications, and diet.[97] Poor venous access is often an issue for newborns. Finally,

although there is substantial information on the use of VKAs in children > 3 months of age, there is essentially no efficacy or safety information specific to their use in neonates.

Therapeutic Range: The capacity of plasma from children receiving VKAs to generate thrombin is delayed and decreased by 25% compared to plasmas from adults with similar INRs.[98] This raises the issue of whether the optimal INR therapeutic range for children will 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 compared to adults at similar INR values.[98] Despite this, 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).

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 (Table 6).[1] The published age-specific weight-adjusted doses for children vary due to the different study designs, patient populations, and possibly the small number of children studied. The largest cohort study (n = 319) found infants required an average of 0.33 mg/kg and teenagers 0.09 mg/kg of warfarin to maintain an INR of 2.0–3.0.[99] For adults, weight-adjusted doses for VKAs are not precisely known but are in the range of 0.04 to 0.08 mg/kg for an INR of 2.0 to 3.0.[100] The mechanisms responsible for the age dependency of VKA doses are not completely clear.

Monitoring: Monitoring oral anticoagulant therapy in children is difficult and requires close supervision with frequent dose adjustments.[1,99,101] Approximately 10 to 20% of children can be safely monitored monthly.[1]

Point of Care Monitoring in Neonates and Children

Whole blood INR monitors use various techniques to measure the time from application of fresh samples of capillary whole blood to coagulation of the sample. The monitors include a batch specific calibration code that converts the result into a calculated INR. There are two "point-of-care" monitors evaluated in the pediatric population the CoaguChek S (Boehringer; Mannheim, Germany) and the Pro-Time Microcoagulation System (International Technidyne Corporation; Edison, NJ). Both monitors were shown to correlate well with INRs from venous samples analyzed in a coagulometer. The correlations were achieved when the whole blood monitors were used in the outpatient laboratory and at home settings. Parents and patients undertook a formal education program prior to using the monitors. The major advantages identified by families included reduced trauma of venipunctures, minimal interruption of school and work, ease of operation, and portability.[102–105] However, the cost per test when using whole-blood INR monitors is substantially increased compared to testing performed using venipuncture and a laboratory INR determination. The recently released CoaguChek XS as yet has not been validated in the pediatric population. At this time, no studies have demonstrated the accuracy of point-of-care monitors for UFH or LMWH therapy.

Table 6—*Protocol for Oral Anticoagulation Therapy to Maintain INR 2–3 for Pediatric Patients

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

*Reproduced with permission from Michelson et al.[6]

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 is < 3.2% per patient-yr (13 case series).[2] In one large cohort (391 warfarin-years, variable target range), the bleeding rate was 0.5% per patient-year.[104] In a randomized trial (n = 41; target INR range, 2.0–3.0 for 3 months) bleeding occurred in 12.2% (95% CI, 4.1–26.2).[9] A more recent single-center study, with a nurse-coordinated anticoagulant service, has reported bleeding rates of 0.05% per patient-year.[106] Nonhemorrhagic compli-

cations of VKAs, such as tracheal calcification or hair loss, have been described on rare occasions in young children.[107,108] Two cohort studies have described reduced bone density in children on warfarin for > 1 year. However, these were uncontrolled studies, and the role of the underlying disorders in reducing bone density remains unclear.[109,110]

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. There are only limited data available in children, but IV vitamin K in doses of 30 μg/kg have been used previously.[111] In the presence of significant bleeding, immediate reversal using fresh frozen plasma (FFP) or prothrombin complex concentrates or recombinant factor VIIa may be required.

Alternative Thrombin Inhibitors

A small number of case reports have documented the use of danaparoid, hirudin, and argatroban in pediatric patients,[61,63,71,72,112] most commonly in children with HIT. No further data are available at this time. A standard protocol for danaparoid dosing in children is available (Table 7).[2]

Table 7—*Protocol for the Use of Danaparoid in Pediatric Patients**

Protocol	Action
Loading dose	30 U/kg body weight IV
Initial maintenance dose	1.2–2.0 U/kg/h IV
Monitoring	Anti-FXa activity can be monitored immediately following the bolus dose q4h until steady state is reached and then daily to maintain a therapeutic range of 0.4–0.8 U/mL[504]

*Danaparoid consists mainly of heparan sulphate, a small quantity of dermatan sulphate, and a minor amount of chondroitin sulphate, and does not contain any heparin fragments. Danaparoid has a much higher anti-Xa/anti-IIa ratio compared to heparin or LMWH. Danaparoid has a decreased cross-reactivity rate (< 10%) with heparin-induced antibody as compared to LMWH (> 90%). Danaparoid is predominantly removed from the circulation through the kidney. Consequently, danaparoid is contraindicated in patients with severe impaired renal function. Although subcutaneous danaparoid is frequently used in adults,[65] there is no published pediatric dose information.

Antiplatelet Drugs in Neonates and Children

Background: Compared to adult controls, neonatal platelets are hyporeactive to thrombin, adenosine diphosphate/epinephrine, and thromboxane A_2.[113,114] This hyporeactivity of neonatal platelets is the result of a defect intrinsic to neonatal platelets.[113,114] Paradoxically, the bleeding time is short in newborns due to increased RBC size, high hematocrit, and increased levels of multimeric forms of von Willebrand factor.[115–117] The bleeding time was prolonged, relative to adults, throughout childhood in two of three studies.[118–120]

The platelet function analyzer (PFA-100; Dade International; Miami, FL) is an *in vitro* method for assessing primary hemostasis that utilizes citrated whole blood[121] and reports closure times related to either collagen and epinephrine (10 μmol/L) or collagen and adenosine diphosphate (50 μmol/L) stimulus. Cord blood samples from term neonates have shorter closure times than samples from older children or adults.[122–124] The shorter closure time correlates with the higher hematocrit and increased von Willebrand factor activity (measured by ristocetin cofactor assay) in cord blood.[123] Investigators have found that the PFA-100 quantifies an individual's response to aspirin therapy and can be effective in monitoring the compliance of aspirin therapy in adult patients.[125] A review summarizes antiplatelet therapy in children.[126]

Aspirin

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, although empiric low doses of 1–5 mg/kg/d have been proposed.[126] Pediatric doses of aspirin are not based on studies of the effect on platelet function in pediatric patients.[127] The PFA-100 is often used to monitor aspirin therapy in pediatric patients, although there are no data that support improved patient outcomes from this practice.[2] The Verify NOW aspirin assay (Accumetrics; San Diego, CA) 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.[128]

Adverse Effects: Neonates may be exposed to aspirin due to maternal ingestion (*eg*, treatment for 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 the hypofunction of newborn platelets, and evidence linking maternal aspirin ingestion to bleeding in newborns is weak.[129] 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 rela-

tively low doses of aspirin used as antiplatelet therapy, as compared to 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 is usually associated with doses > 40 mg/kg.[130–135]

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/or 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.

Other Antiplatelet Agents

Historically, the second most commonly used antiplatelet agent in children is dipyridamole in doses of 2–5 mg/kg/d.[136–138] However, clopidogrel is being used with increasing frequency in children. Initial anecdotal use reported a dose of 1 mg/kg/d to be effective and safe. Dosing strategies involved rounding of doses to quarter or half tablets (75-mg tablets). Regular monitoring of liver and renal function was recommended. Most recently, there has been a preliminary report of a prospective, international, multicenter, randomized placebo-controlled trial (Platelet Inhibition in Children on Clopidogrel) that evaluated the pharmacodynamics of clopidogrel in 116 children (0 to 24 months old) with modified Blalock-Taussig shunts (MBTS) or another cardiac condition with a risk for thrombosis.[139] This study concluded that clopidogrel is well tolerated in children, and that a dose of 0.2 mg/kg/d achieves a platelet inhibition level similar to that in adults taking the standard dose of 75 mg/d. This study also demonstrated that clopidogrel can be safely used in combination with aspirin in children.

Ticlopidine, another thienopyridine, is given in doses of 10 mg/kg/d po q12h (maximum 250 mg/dose), However, there are no data to support the use of this drug in children.

The clinically available glycoprotein IIb-IIIa antagonists include IV abciximab, eptifibatide, and tirofiban.[140] 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.[141] This study compared abciximab to historical controls, and all patients received additional anticoagulant therapy.

Thrombolytic Agents and Thrombectomy in Neonates and Children

Background: At birth, plasma concentrations of plasminogen are approximately 50% of adult values (21 mg/100 mL).[142–144] The decreased levels of plasminogen in newborns slows the generation of plasmin[145] and reduces the thrombolytic effects of streptokinase (SK), urokinase (UK) and tissue plasminogen activator (tPA) in an *in vitro* fibrin clot system.[146] A similar response occurs in children with acquired plasminogen deficiency. Supplementation of plasmas with plasminogen increases the thrombolytic effect of all three agents.[146,147]

No studies have compared the efficacy, safety, or cost of different thrombolytic agents in children. Although SK is the cheapest of the three agents, SK has the potential for allergic reactions and may be less effective in children with physiologic or acquired deficiencies of plasminogen for the reasons outlined above.

tPA has become the agent of choice in pediatric patients for several reasons, including a previous US Food and Drug Administration warning regarding UK, experimental evidence of improved clot lysis *in vitro* compared to UK and SK, fibrin specificity, and low immunogenicity.[148,149] However, tPA is considerably more expensive than either SK or UK, and the increased *in vitro* clot lysis by tPA has not been demonstrated in clinical trials in children. There is minimal or no experience with other thrombolytic agents in children.[150]

Success rates for tPA in pediatric patients vary. A prospective study using 0.5 mg/kg/h of systemic tPA for 6 h with concurrent UFH (10 U/kg/h) and FFP supplementation prior to the tPA reported complete thrombus resolution in 81% of arterial thrombosis (n = 16), compared to 0% of venous thrombosis (n = 10).[151] Zenz et al[152] described a regimen that used a dose of 0.5 mg/kg/h for the first hour followed by 0.25 mg/kg/h until clot lysis occurred or treatment had to be stopped because of bleeding complications. Complete clot lysis was achieved in 16 of 17 patients within 4 to 11 h after the start of treatment. In one patient, only partial lysis occurred. After complete lysis, rethrombosis developed in one patient 15 h after the end of treatment.

Contraindications: There are well-defined contraindications to thrombolytic therapy in adults.[153] Clinicians should consider similar problems in children as relative but not absolute contraindications to thrombolytic therapy.

Therapeutic Range and Monitoring of Thrombolytic Agents: There is no therapeutic range for thrombolytic agents. The correlation between hemo-

static variables and efficacy/safety of thrombolytic therapy is too weak to have useful clinical predictive value.[153] 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 the fibrinogen level, which can usually be obtained rapidly and helps to determine the need for cryoprecipitate and/or plasma replacement. A commonly used lower limit for fibrinogen level is 100 mg/dL. The aPTT may not be helpful in the presence of low fibrinogen levels, concurrent UFH therapy, and presence of fibrin/fibrinogen degradation products.[153] Measurement of fibrin degradation products and/or d-dimers are helpful in determining whether a fibrinolytic effect is present.

Dose Response: Thrombolytic agents are used in low doses, usually to restore catheter patency, and in higher doses to lyse large-vessel TE or PE. Table 8 presents the most commonly used local and systemic dose regimens for thrombolytic therapy in pediatric patients. These protocols come from case series.[147,154] The optimal doses for each of UK, SK, and tPA are not known for pediatric patients. Based on data in adults from the Thrombolysis in Myocardial Infarction II trial, in which doses of 150 mg rtPA caused more bleeds into the CNS than 100 mg[155] (1.5% vs 0.5% respectively), it seems probable that there is an upper dose limit based on safety.

Route of Administration: No published studies have compared local to systemic thrombolytic therapy in children.[156] At this time, there is no evidence to suggest that there is an advantage of local over systemic thrombolytic therapy in children with thrombotic complications. In addition, the small vessel size in children may increase the risk of local vessel injury during catheter-directed therapy. Local therapy may be appropriate for catheter-related TE when the catheter is already *in situ*. There are isolated case reports of thrombolysis via multiple-lumen catheters use in children.[157] There are no reported cases of pulse spray thrombolysis in children.

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 approximately 20% in pediatric patients.[147] The most frequent problem was bleeding at sites of invasive procedures that required treatment with blood products. A more recent study reported bleeding in 68% of patients, with bleeding requiring transfusion occurring in 39%.[149] Prolonged duration of thrombolytic infusion was associated with increased bleeding.

Zenz et al,[152] in a prospective study using the protocol described earlier, reported bleeding requiring transfusion in 3 of 17 patients (18%) treated for between 4 to 11 h, and minor bleeding in another 9 patients (54%). Another recent prospective study, using a defined protocol, that included: (1) concurrent UFH therapy (10 U/kg/h), (2) fixed tPA infusions at 0.5mg/kg/h for 6 h with no extensions beyond 6 h, and (3) FFP (10 mL/kg) given a half hour before each tPA infusion to ensure adequate

Table 8—*Thrombolytic Therapy for Pediatric Patients

Therapy	Action
I. Local instillation of tPA	
Weight < 10 kg	
Single-lumen CVL	0.5 mg diluted in 0.9% NaCl to volume required to fill line
Double-lumen CVL	0.5 mg per lumen diluted in 0.9% NaCl to fill volume of line; treat one lumen at a time
SC port	0.5 mg diluted with 0.9% NaCl to 3 mL
Weight > 10 kg	
Single-lumen CVL	1.0 mg in 1.0 mL 0.9% NaCl; use amount required to fill volume of line, to maximum of 2 mL = 2 mg
Double-lumen CVL	1.0 mg/mL; use amount required to fill volume of line, to a maximum of 2 mL = 2 mg per lumen; treat one lumen at a time
SC port	2.0 mg diluted with 0.9% NaCl to 3 mL
II. Systemic thrombolytic therapy†	
UK	
Load	4,400 U/kg
Maintenance	4,400 U/kg/h for 6–12 h
Monitoring	Fibrinogen, TCT, prothrombin time, APTT
SK	
Load	2,000 U/kg
Maintenance	2,000 U/kg/h for 6–12 h
Monitoring	Fibrinogen, TCT, prothrombin time, APTT
tPA	
Load	None
Maintenance	0.1–0.6 mg/kg/h for 6 h
Monitoring	Fibrinogen, TCT, prothrombin time, APTT

*SC port = subcutaneous port; TCT = thrombin clotting time; values provided are starting suggestions, as some patients may respond to longer or shorter courses of therapy. Reproduced with permission from Michelson et al[6]/1995.

†Start heparin therapy either during, or immediately upon completion of thrombolytic therapy. A loading dose of heparin may be omitted. The length of time for optimal maintenance is uncertain.

plasminogen and fibrinogen, reported bleeding requiring transfusion in 3 of 26 patients (11.5%) and minor bleeding episodes in 11 patients (42%; venipuncture sites and epistaxis).[151] In another review, Zenz et al[158] reported intracranial hemorrhage (ICH) in 14 of 929 (patients 1.5%) analyzed. There was no information provided about concurrent UFH administration in this study. When subdivided according to age, ICH was identified in 2 of 468 children (0.4%) after the neonatal period, 1 of 83 term infants (1.2%; 95% CI, 0.3–6.5%), and 11 of 86 preterm infants (13.8%; 95% CI, 6.6–21.7%). 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.[159]

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 (such as 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 bag/5 kg, or 5 to 10 mL/kg), or an antifibrinolytic (or both) and administering other blood products as indicated.

Vena Caval Interruption

In addition to pharmacologic therapy, venous interruption devices (inferior vena cava [IVC] filters) are used for specific clinical indications in adults. A handful of anecdotal reports of successful and failed IVC filters in children have been published.[160] Temporary filters are often used in children and removed when the risk of PE is reduced.[161] A case series described the safety of temporary filters in 10 patients.[162] 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.

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.[163] There are no controlled data to compare the value of conservative therapy, and it is unlikely such data will become available. In most cases, concurrent or subsequent anticoagulation therapies were used.[164–168] There are no specific guidelines for the use of thrombectomy in children, but there is general consensus that in many situations the TE recurrence rate and risk of long-term vascular damage is high. Clinicians should consider the risk/benefit ratio individually in each patient.

1.0 Specific Indications for Antithrombotic Therapy

The following section describes the evidence for the use of anticoagulant therapy in specific clinical circumstances. In addition, there remain a number of less common clinical situations in neonates and children in which the question of optimal antithrombotic management is important; however, the literature consists of only a few case reports, so there are insufficient data to distinguish between any of the potential therapeutic options. One example of such a situation is portal vein thrombosis. Differences in etiology and pathophysiology of the thrombosis reduce the usefulness of extrapolation of therapeutic guidelines for adults in many of these circumstances.

1.1 Neonatal DVT: Central Venous Line and Non-Central Venous Line Related

Background: The incidence of thromboembolic events in the pediatric age group is highest in neonates and infants < 1 year of age.[10–19] Much of the published data regarding the epidemiology of neonatal venous thromboembolism (VTE) has come from national registry studies. Two neonatal registries from Canada and Germany prospectively collected data on neonatal thrombosis, while a third from the Netherlands included data from both neonates and older children.[11–13] The Canadian registry reported 97 cases of which 64 (66%) had venous involvement. Based on data reported from Southern Ontario, the incidence of clinically apparent thrombosis was 2.4 per 1,000 admissions to the neonatal ICUs.[11] The German neonatal registry reported 79 cases of symptomatic thrombosis, including stroke.[12] VTE accounted for 76% of cases. The overall incidence of symptomatic events was 0.51 per 10,000 births. In the Dutch study, the incidence of neonatal VTE was 0.07 per 10,000 children, but 35% of these events were asymptomatic.[13]

Neonatal VTE is frequently associated with the

presence of significant underlying risk factors. As in older children, central venous lines (CVLs) are the single most important contributing factor. Excluding cases of renal vein thrombosis (RVT), CVL-related thrombosis accounted for 89% and 94% of VTEs in the Canadian and Dutch registries, respectively.[11,13] These events involve the large vessels most frequently used for catheterization including the umbilical vein. Neonatal VTE related to the use of the umbilical venous catheter (UVC) has been the subject of studies involving sequential imaging. Using venography, Roy et al documented UVC-associated thrombosis in 14 of 48 neonates (29%).[171,172] Sepsis, perinatal asphyxia and congenital heart disease are other recognized risk factors for neonatal VTE, and multiple risk factors often coexist in these infants.

The morbidity and mortality attributable to neonatal VTE are not well defined. The Canadian registry reported mortality according to the site of the thrombosis; deaths were most frequent in patients with right atrial/superior vena caval involvement (33%), but it was not clear how many of these events were directly attributable to thrombosis.[11] In the German registry, there was one death due to right atrial/superior vena caval thrombosis, and in the Dutch studies there were no deaths directly attributable to the presence of thrombosis.[12,13] Morbidity following these events is very poorly characterized but includes the development of postthrombotic syndrome (PTS). The clinical sequelae of thrombosis depends on the site of the VTE. Specific complications such as chylothorax may also occur depending on the site of the thrombosis. Portal hypertension, which may lead to splenomegaly, and varices, may occur following UVC thrombosis[173,174] The majority of sick neonates have patent foramen ovale. Paradoxical emboli causing stroke are described and may occur as the clinical presentation of the VTE. In addition, paradoxical emboli may occur at the time of CVL removal in neonates with CVL-related VTE.

Evidence: There are no published randomized controlled trials (RCTs) and no large cohort studies that report on the outcomes of different treatment modalities in the management of neonatal VTE. 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. 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 CVL removal in neonates with CVL-related VTE, many clinicians advocate delay in CVL removal until 3 to 5 days of anticoagulant therapy have been given. There are no clinical studies to support the validity of this practice, although anecdotally, the frequency of paradoxical emboli is said to be reduced.

Recommendations

In neonates with VTE (CVL and non-CVL related):
1.1.1. We suggest that CVLs or UVCs associated with confirmed thrombosis be removed, if possible, after 3 to 5 days of anticoagulation (Grade 2C)**.**
1.1.2. We suggest either initial anticoagulation, or supportive care with radiologic monitoring (Grade 2C)**; however, we recommend subsequent anticoagulation if extension of the thrombosis occurs during supportive care** (Grade 1B)**.**
1.1.3. We suggest anticoagulation should be with either: (1) LMWH given twice daily and adjusted to achieve an anti-FXa level of 0.5 to 1.0 U/mL: or (2) UFH for 3 to 5 days adjusted to achieve an anti-FXa of 0.35 to 0.7 U/mL or a corresponding aPTT range, followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months (Grade 2C)**.**
1.1.4. We suggest that if either a CVL or a UVC is in still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH be given to prevent recurrent VTE until such time as the CVL or UVC is removed (Grade 2C)**.**
1.1.5. We recommend against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 1B)**.**
1.1.6. We suggest that, if thrombolysis is required, the clinician use tPA and supplement with plasminogen (FFP) prior to commencing therapy (Grade 2C)**.**

1.2 DVT in Children

Infants < 1-year of age and teenagers have the highest incidence of thrombosis in the pediatric population.[10,13,14,175] However, the incidence of

symptomatic VTE in children is significantly less than the incidence in adults and reported to be approximately 5.3 per 10,000 hospital admissions. Unlike adults, 95% of VTEs in children are secondary to serious conditions such as cancer, trauma/surgery, congenital heart disease, and systemic lupus erythematosus.[9,10,13,14,176] Children most often have one or more (median 2) risk factors[10,13,14,16] predisposing them to thrombosis. The most common risk factor is the presence of a CVL.[10,13–15,177–179] When spontaneous thrombosis occurs in children, it is usually in the lower limbs[16]; however, the true incidence is unknown. Recurrent VTEs are reported to occur in 7.5% of children.[10,13,14,16]

Prospective studies reveal that asymptomatic CVL-related thrombosis occurs in children with various illnesses including congenital heart disease, malignancy, and trauma.[8,33,179] Line patency may be compromised when CVL-related thrombosis is present (unable to withdraw, and or infuse), or the line may continue to function with difficulty.

Radiographically confirmed asymptomatic CVL-related thromboses in children are of clinical importance for a number of reasons. First, there is increasing evidence that CVL-related VTEs are associated with CVL-related sepsis. In a metaanalysis, prophylactic UFH therapy reduced CVL-related VTE (relative risk [RR], 0.43; 95% CI, 0.23–0.78) as well as decreased bacterial colonization (RR, 0.18; 95% CI, 0.06–0.60), and probably CVL-related bacteremia (RR, 0.26; 95% CI, 0.07–1.03).[178] Second, CVL-related thrombosis is the most common source for PE in children,[16,180] which may be fatal.[15] Third, recurrent CVL-related clot may result in loss of venous access that may be necessary for life-saving intervention such as organ transplant.[13,16,181] Finally, many children have persistent right to left intracardiac shunts, where thrombus may embolize across and to the brain causing embolic stroke.[15,16]

PTS is defined as swelling, skin pigmentation, pain, and ulceration of the limb secondary to DVT. PTS occurs in up to 65% of children following venous thrombosis.[181] At present, there is no properly validated outcome measure for PTS in children; however, 10–20% of children with PTS have two or more of these symptoms, and in some children these symptoms reduce their quality of life.[15,16]

Evidence: There has been one multicenter randomized trial of anticoagulation for VTE in children.[9] The Reviparin in Venous Thromboembolism (REVIVE) trial[9] randomized children (> 3 months of age) with a first VTE to receive either UFH and then VKAs (target INR 2.5) for 3 months, or a LMWH (reviparin) adjusted to achieve a target anti-FXa level of 0.5 to 1.0 U/mL for 3 months. The outcome measures were symptomatic recurrent thrombosis occurring in the following 3 months after treatment completion. The study was closed early due to slow recruitment prior to completion of target recruitment, leaving the study underpowered (78 patients) for the primary outcome measure. The point estimates in the reviparin group for recurrence (5.6%) and major bleeding (5.6%) were reduced compared to the UFH/VKA group (12.5% for recurrence and 12.5% for major bleeding). However, the OR for recurrence was 0.53 (95% CI, 0.05–4.00; Fisher exact test, 2p = 0.677). Similarly, the OR for bleeding was 0.41 (95% CI, 0.04–2.76; Fisher exact test, 2p = 0.44). The remaining studies evaluating treatment for venous thrombosis in children are described in Tables 9, 10.

Recommendations

In children with VTE (CVL and non-CVL related): first TE for children:

1.2.1. In children with thrombosis, we recommend anticoagulant therapy with either UFH or LMWH (Grade 1B)**.**

Remark: Dosing of IV UFH should prolong the aPTT to a range that corresponds to an anti-FXa level of 0.35 to 0.7 U/mL, whereas LMWH should achieve an anti-FXa level of 0.5 to 1.0 U/mL 4 h after an injection for twice-daily dosing.

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

1.2.3. We suggest children with idiopathic TE receive anticoagulant therapy for at least 6 months, using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C)**.**

Underlying values and preferences: The suggestion to use anticoagulation therapy to treat idiopathic DVTs in children for at least 6 months rather than on a lifelong basis places a relatively high value on avoiding the inconvenience and bleeding risk associated with antithrombotic therapy, and a relative low value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor.

Table 9—*Studies Assessing Anticoagulation for VTE in Children: Summary Evidence Profile (Section 1.2.1)**

Study/yr	Design	Treatment Target Levels	Patients, No.	Follow-up, yr	Thromboembolic Events, No. (%)	Major Hemorrhage, No. (%)	Comments
Goldenberg et al[505]/2005	Case series	LMWH Target INR 0.5–1.2 VKA target INR 2–3	11 LMWH n = 4 VKA n = 1 Lemierre syndrome n = 6	Median: 1 (7 wk–12 mo)	No reported events	No reported events	Case series At follow up 4–6 mo after diagnosis Persistent thrombosis, n = 2 Recanalization n = 4
Revel Vilk et al[84]/2004	Case series	Enoxaparin; Target anti-FXa 0.5–1.0 U/mL Duration 5–616 d of enoxaparin Previous anticoagulation and/or lytic	245 Age 33 d–17.3 yr 56% neonates VTE 84% Arterial TE 5%	Mean follow-up 3 d–6.6 yr (median 6 mo) 190 had evaluable ultrasounds	PE developed in 5	No events reported	22% had no serial ultrasounds to assess thrombus following treatment Collaterals 20% Clot resolution 53% No change 34% Partial resolution 25%
Massicotte et al[9]/2003	RCT	UFH/warfarin target INR 2–3, 46% in TTR Reviparin target anti-FXa 0.5–1.0, 75% in range	78 100% follow-up 56 completed study	3 mo therapy = 123 mo	4 (10) 2 (5.6)	5 (12.5) 2 (5.6)	Underpowered
Streif et al[77]/2003	Cohort	LMWH target 0.5–1.0	62	1.2/100 treatment-yr	3	4	
Hofmann et al[506]/2001	Retrospective case series	Nadroparin, n = 66 Enoxaparin, n = 13 Target 0.5–1.0	66 13 48 female 31 male Age 2 wk–19 yr Mean 11.8 yr	62 short-term prophylaxis (1–2 wk) 13 long-term therapy and follow-up	1	0	No reocclusion, n = 4 Recanalization, n = 2 Reocclusion, n = 1 Unable to separate which patients received enoxaparin vs nadroparin
Dix et al[83]/2000	Case series	Enoxaparin Target anti-FXa 0.5–1.0 U/mL 46 switched to warfarin Low-risk prophylactic target anti-FXa 0.1–0.4	138 146 courses of therapy 86 VTE Age 1 d–18 yr Median 3.5 yr Mean 6.1 yr	Duration of therapy: 74 < 20 d Median follow-up 6 mo	2 (2.3) recurrent/new VTE when patient subtherapeutic	7 (4) major 25 (17) minor on LMWH	12 unavailable for follow-up Transfer to other hospitals 2 deaths directly related to therapy (1 hemorrhage; 1 TE)
Punzalan et al[507]/2000	Case series	Enoxaparin target anti-FXa 0.5–1.2 Enoxaparin and or lytic therapy	6 prospective 13 retrospective VTE n = 14 Primary prophylaxis n = 5	Not reported	No new/recurrent VTE	No major hemorrhage	Unable to determine which patients were treated for VTE vs primary prophylaxis
Nohe et al[87]/1999	Case series	Dalteparin 129 ± 43 U/k/d Target anti-FXa 0.4–1.0 U/mL	48 VTE, n = 19	Not reported	None reported	None reported	6 complete recanalization 5 partial recanalization 7 no recanalization

Table 9—*Continued*

Study/yr	Design	Treatment Target Levels	Patients, No.	Follow-up, yr	Thromboembolic Events, No. (%)	Major Hemorrhage, No. (%)	Comments
Streif et al[99]/1999	Prospective cohort	Warfarin n = 52 target INR 1.4–1.8 n = 263 target INR 2–3 n = 208 primary prophylaxis n = 144 secondary prophylaxis 49–61% TTR	319 352 courses of therapy 391 treatment-yr Age 1 mo–18 yr	Not reported	2 1.3% per patient-yr	2 (INR 1.7); 0.5%/patient-yr (INR 2–3)	36% of children had CHD (n = 114)
Massicotte et al[89]/1996	Case series	Enoxaparin Target anti-Xa 0.5–1.0	25 n = 14 VTE n = 9 CNS n = 2 CHD prophylaxis	Variable duration of therapy; range 10–50 d	No new/recurrent VTE	2	
Andrew et al[49]/1994	Prospective cohort	UFH Target PTT 55–85 s 52/65 (73%) of PTTs corresponded to anti-FXa and within therapeutic range	65 Follow-up n = 65 45% < 1 yr old 56% 1–18 yr DVT/PE n = 30 (9 < 1 yr) Arterial thrombosis n = 11	Not reported	2	1	
Andrew et al[1]/1994	Registry	Warfarin (1) target INR 2–3 for 3–6 mo followed by target INR 1.3–1.8 secondary prophylaxis (2) target 1.3–1.8 primary prophylaxis (3) target 2.5–3.5 (mechanical valves); primary prophylaxis n = 59; secondary prophylaxis n = 56; duration of therapy: n = 37 3–6 mo, n = 38 6 mo, n = 40 life long	115 Secondary prophylaxis, n = 54 Primary prophylaxis, n = 61 n = 21 (target INR 1.3–1.8) n = 18 (target INR 2.5–3.5)	18 mo	4 new/recurrent thrombosis when warfarin discontinued	2	

*CHD = congenital heart disease; PTT = partial thromboplastin time; TTR = time in therapeutic range.

Table 10—*Studies Reporting Anticoagulation for VTE in Children: Methodologic Quality (Section 1.2.2)

Study/yr	Design	Patients, No.	Intervention/Control	Internal/Control Setting Similar	Internal/Control Time Frame Similar	Adjustment	Effectively Blinded Assessment of Outcome	Follow-up	Comments
Goldenberg et al[505]/ 2005	Case series	11	LMWH or VKA	No control	No control	No adjustment	Not blinded	Incomplete	
Revel Vilk et al[84]/2004	Retrospective cohort	245	Enoxaparin Target LMWH 0.5–1.0 U/mL 5–616 d/enoxaparin Previous anticoagulation and/or lytic	No control	No control	No adjustment	Not blinded	Follow-up on 190 patients Mean follow-up 3 d–6.6 yr (median 6 mo)	
Massicotte et al[9]/2003	RCT, REVIVE	78	Reviparin 100 U/kg anti-FXa 0.5–1.0 for 3 mo vs UFH/VKA	> 3 mo–< 18 yr; first DVT/PE; heterogeneous underlying diagnosis	Same	No adjustment	Blinded effectively	LMWH 8 patients withdrew 1 death	Study closed early due to slow recruitment
Streif et al[77]/2003	Prospective cohort	62	Enoxaparin; target antiXa 0.5–1.0	No control	No control	No adjustment	Not blinded	Not reported	
Hofmann et al[506]/ 2001	Retrospective cohort	79 Nadroparin, n = 66 Enoxaparin, n = 13	62 short term (1–2 wk) 13 long-term therapy Various cointerventions	No control	No control	No adjustment	Not blinded	Variable	Cannot separate which patients received enoxaparin vs nadroparin
Dix et al[83]/ 2000	Prospective cohort	138 146 courses of therapy	Enoxaparin Primary prophylaxis 1.0–1.5 mg/kg/dose Target anti-FXa 0.5–1.0 U/mL 46 switched to warfarin Low-risk prophylactic target anti-FXa 0.1–0.4 Duration of therapy: n = 74 = < 20 d of treatment	No control	No control	No adjustment	Not blinded	Median follow-up 6 mo 12 not available for follow-up	
Punzalan et al[507]/ 2000	Case series	Prospective, n = 6 Retrospective, n = 13 Total VTE, n= 14 Prophylaxis, n= 5	Enoxaparin 1 mg/kg q12h target anti-FXa 0.5–1.2 Enoxaparin and or lytic therapy	No control	No control	No adjustment	Not blinded	Not reported	

Table 10—*Continued*

Study/yr	Design	Patients, No.	Intervention/Control	Internal/Control Setting Similar	Internal/Control Time Frame Similar	Adjustment	Effectively Blinded Assessment of Outcome	Follow-up	Comments
Nohe et al[87]/1999	Case series	19	Dalteparin 129 + 43 U/k/d Target anti-FXa 0.4–1.0 U/mL	No control	No control	No adjustment	Not blinded	Incomplete	
Streif[99]/1999	Prospective cohort	319; 352 courses of therapy; 391 treatment-yr; age 1 mo–18 yr	Warfarin Primary prophylaxis, n = 208 Secondary prophylaxis, n = 144 49–61% TTR	No control	No control	No adjustment	Not blinded	Variable duration	
Massicotte et al[89]/1996	Prospective cohort	14	Enoxaparin 1 mg/kg/dose q12h; target anti-FXa 0.5–1.0	No control	No control	No adjustment	Not blinded	Clinical	
Andrew et al[49]/1994	Prospective cohort	65	UFH 50 U/k/h bolus > 20 U/kg/h Target PTT 55–85 s 73% of PTTs corresponded to anti-FXa and within therapeutic range	Age-matched controls Newborn to 18 yr Heterogeneous underlying diagnosis	Same	No adjustment	Not blinded	Complete	
Andrew et al[1]/1994	Prospective cohort	115	Warfarin Primary prophylaxis, n = 59 Secondary prophylaxis, n = 56 Duration of therapy: 3–6 mo, n = 37; > 6 mo, n = 38; life long, n = 40	No control	No control	No adjustment	Not blinded	None unavailable for follow-up	

*See Table 9 for expansion of abbreviation.

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

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

Recurrent Idiopathic TE for Children

Recommendation

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

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

Recurrent Secondary TE for Children

Recommendations

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

In addition, with specific respect to the management of CVL-related thrombosis:

1.2.8. If a CVL is no longer required, or is nonfunctioning, we recommend it be removed (Grade 1B). **We suggest at least 3 to 5 days of anticoagulation therapy prior to its removal** (Grade 2C). **If CVL access is required and the CVL is still functioning, we suggest that the CVL remain *in situ* and the patient be anticoagulated** (Grade 2C).

1.2.9. For children with a first CVL-related DVT, we suggest initial management as for secondary TE as previously described. We suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5–1.9) or LMWH (anti-FXa level range, 0.1 to 0.3) be given until the CVL is removed (Grade 2C). **If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVL is removed but at least for a minimum of 3 months** (Grade 2C).

1.3 Use of Thrombolysis in Pediatric Patients With DVT

Evidence for this intervention is limited to case series of small number of patients.[149,152,182–194] Reports are limited to the use of alteplase with various dosing regimens ranging from what is deemed to be a low dose (0.01 mg/kg/h)[182] to high dose (0.1–0.6 mg/kg/h).[149] In these studies, the bleeding risk ranges from 3 to 27%, while reported efficacy of resolution of thrombosis ranged from 40 to 97%. However, a more recent series has reported 0% successful thrombolysis in VTE in children.[151] There are no reports of the impact of recombinant tPA (rtPA) on long-term outcome, including PTS.

Recommendation

1.3.1. In children with DVT, we suggest that thrombolysis therapy not be used routinely (Grade 2C). **If thrombolysis is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen** (Grade 2C).

1.4 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,[195–197] or for life-threatening thrombosis (Fontan circuit).[167,197–202] Reports include few outcomes following thrombectomy other than ischemic stroke in one neonate.[195]

A handful of anecdotal reports of successful and failed IVC filters in children have been published.[160] Recently, a case series described the safety of temporary filters in 10 patients.[162] Guidelines for use of vena caval filters rely on these reports and on indirect evidence from adults. Vena caval filters are used in children with venous thrombosis with contraindication to anticoagulation (active bleeding)[203,204] or failed anticoagulation.[162,198,204–208] The filter is usually placed via femoral or jugular approach and may remain *in situ* for life or may be temporary (10 days to 3 months). Vena caval filter placement is restricted to children $>$ 10 kg in weight due to the size of the IVC and the available filters. In addition, the availability of a skilled pediatric procedural 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 migration of perforation of the IVC. Overall, mortality in the children with filters was reported as 7.9%. A large retrospective review[203]

from a trauma database of 268 tertiary care pediatric centers in the United States demonstrate that children who had filters placed had more severe injuries, assessed by the Glasgow coma scale, than did children who did not receive a filter. The high association of filters placement and mortality is in all probability due to increased baseline injury severity and not as a result of the filter placement.

Recommendations

1.4.1. If life-threatening VTE is present, we suggest thrombectomy (Grade 2C)**.**
1.4.2. We suggest, following thrombectomy, anticoagulant therapy be initiated to prevent thrombus reaccumulation (Grade 2C)**.**
1.4.3. In children > 10 kg body weight with lower-extremity DVT and a contraindication to anticoagulation, we suggest placement of a temporary IVC filter (Grade 2C)**.**
1.4.4. We suggest temporary IVC filters should be removed as soon as possible if thrombosis is not present in the basket of the filter and when the risk of anticoagulation decreases (Grade 2C)**.**
1.4.5. In children who receive an IVC filter, we recommend appropriate anticoagulation for DVT (see 1.2) as soon as the contraindication to anticoagulation is resolved (Grade 1B)**.**

1.5 Pediatric Cancer Patients With DVT

1.5.1. Use of Anticoagulants as Therapeutic Agents

There is one RCT (the REVIVE study) comparing LMWH vs UFH/warfarin in the treatment of DVT in children, but the study is not specific to cancer patients. Due to slow recruitment, the investigators closed the study without attaining the target sample size. There were no efficacy or safety differences between the two groups but this may due to small sample size. However, the CLOT study demonstrated that LMWH was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding in adult patients with cancer.[209] In adults, LMWH is recommended for at least 3 months of treatment for patients with VTE and cancer (Grade 1A), followed by treatment with LMWH or VKA as long as the cancer is active (Grade 1C). LMWH is the preferred anticoagulant in pediatric cancer patients because the ease of maintaining the anticoagulation therapy around the usual frequent procedures such as lumbar punctures. It may be advisable to omit two doses of LMWH before procedures being performed and resume 12 to 24 h after the procedures. In children, chemotherapy is usually intense and causes significant thrombocytopenia for a period of time. Clinicians should maintain platelet counts $> 50 \times 10^9$/L in the first 2 weeks of the antithrombotic therapy. Beyond the first 2 weeks of anticoagulant therapy, the dose of LMWH should be adjusted according to the platelet count. Full dose anticoagulant can be administered for platelet count $> 50 \times 10^9$/L. For a platelet count from 20 to 50×10^9/L, the dose of LMWH can be halved. For a platelet count $< 20 \times 10^9$/L, LMWH should be stopped. These suggestions on the use of LMWH in pediatric cancer patients are practical but are not supported by any systematic observations.[210]

In contrast to the adult cancer patients, children with cancer and VTE may not require prolonged antithrombotic therapy beyond 3 months providing other risk factors have resolved. There is only one case report of a thrombosis developing in a pediatric cancer patient before the diagnosis of cancer.[211] This suggests other risks factors such as mechanical obstruction (*eg*, mediastinal mass), chemotherapy (*eg*, asparaginase and steroid), and central venous catheters play a significant role in the development of VTE in this population. Therefore, in pediatric cancer patients, anticoagulant therapy can be given for a minimum of 3 months and then discontinued once the other risk factors have resolved (*eg*, finish of asparaginase, resolution of mediastinal mass).

Recommendation

1.5.1. In children with cancer, we suggest management of VTE follow the general recommendations for management of DVT 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]**.**

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

1.5.2. Use of Anticoagulant as Thromboprophylaxis

There are three RCTs studying thromboprophylaxis in children (Table 11). Two studies are specific to cancer, and one study is not. The PARKAA trial studied use of antithrombin concentrate in pediatric acute lymphoblastic leukemia patients treated with asparaginase.[21] There was a trend suggesting that the use of antithrombin may decrease the incidence of thrombosis but the study was not powered to show efficacy. Ruud et al[212] studied the use of warfarin in the prevention of CVL-related thrombosis in children with cancer. The study was terminated without

Table 11—*Use of Prophylactic Anticoagulants in Pediatric Cancer Patients: Clinical Description and Results (Section 1.5)*

Study/yr	Treatment Group	Patients, No.	Follow-up, mo	Thrombosis, No. (%)	Major Hemorrhage, No. (%)	Comments
Mitchell et al[508] (completed)/ 2003	Antithrombin	25		7 (28)	0 (0)	Study not powered to answer efficacy Open label Specific to ALL Included symptomatic and asymptomatic clots
	No antithrombin	60		22 (37)	1 (1.7)	
Ruud et al[212] (completed)/ 2006	Warfarin (INR1.3–1.9)	29	6	6 (20)	0	Study underpowered
	Control	33		8 (24)	0	
Massicotte et al[8] (completed)/ 2003	LMWH	78		11 (14.1)	0	Study underpowered Not specific to cancer Only patients with CVL included
	Standard of care	80		10 (12.5)	1	

full recruitment due to lack of efficacy. One limitation of the study was that very few patients achieved the targeted INR. The PROTEKT trial, which compared the use of LMWH (reviparin) to standard of practice, was not specific to the cancer population.[8] Again, this study was concluded early because of lack of recruitment, which thus reduced the power of the trial. There was no difference between the LMWH group compared to the standard of practice group.

Case series have also addressed this issue. Elhasid et al[80] found LMWH (mean dose, 0.84 mg/kg qd) apparently safe when compared to historical controls in preventing thrombosis in a patient with acute lymphoblastic leukemia. Nowak-Gottl et al[213] gave LMWH (dose, 1 mg/kg qd) as primary thromboprophylaxis to children and adolescents with Ewing sarcoma (n = 36) and osteogenic sarcoma (n = 39). None of their patients had any thromboembolic complications during the postoperative period.[213] None of these series are adequate to address the question of efficacy because of sample size and the design of the studies.

Recommendation

1.5.2. We suggest clinicians not use primary antithrombotic prophylaxis in children with cancer and central VADs (Grade 2C)**.**

1.6. Children With DVT and Antiphospholipid Antibodies

Studies have confirmed that APLA are associated with an increased risk of thrombosis in children, although whether this risk is similar to that described in adults remains uncertain.[214] However, there are no specific data as to optimal therapy for DVT in children with APLA, nor are there any data to support or refute the role of primary prophylaxis.

Recommendation

1.6. For children with VTE, in the setting of APLA, we suggest management as per general recommendations for VTE management in children.

Remark: Depending on the age of the patient, it may be more appropriate to follow adult guidelines for management of VTE in the setting of APLA (see chapter by Kearon et al in this supplement).

1.7 Neonatal RVT

Background: In the Canadian and German neonatal thrombosis registries, RVT accounted for 22% and 44% of reported cases, respectively.[11,12] Risk factors for RVT include maternal diabetes, dehydration, infection, asphyxia, and polycythemia.[11,12,17]

RVT usually presents soon after birth, and it is likely that a number of these events initially develop antenatally.[215,216] Hematuria, abdominal mass, and impaired renal function are common presenting features. Approximately 25% of cases are bilateral, and 52–60% are reported to have evidence of extension into the IVC.[17,216]

Overall survival following neonatal RVT is generally favorable. Four small cohort studies with variable follow-up reported 81–100% of neonates survived.[216–219] Clinical sequelae in survivors included chronic renal impairment and hypertension.[216–219]

Evidence: Although much has been learned about the epidemiology and risk factors relating to neonatal RVT, there is very limited evidence regarding opti-

mal therapy. Options include supportive care, anticoagulation, and thrombocytic therapy. No RCTs have addressed the issue of how to manage this condition, and evidence that exists comes from a small number of case series and individual case reports.

Zigman et al[216] reported on 23 cases of RVT, 83% of which occurred in neonates. In this series, 52% of patients received anticoagulation, while 48% were managed supportively. There were no deaths, but subsequent renal impairment was more frequent in those who did not receive anticoagulation (100% vs 33%).[216] Nuss[219] reported renal impairment in four of six neonates (66%) despite the use of LMWH. A small number of cases studies have documented variable outcomes following the use of thrombolytic therapy in this condition.[17,215] The use of anticoagulant and thrombolytic therapy in the management of neonatal RVT remains controversial because are limited data to suggest that the use of these agents improves long-term outcomes as compared with supportive care alone.

Recommendations

1.7.1. For unilateral RVT in the absence of renal impairment or extension into the IVC, we suggest supportive care with monitoring of the RVT for extension or anticoagulation with UFH/LMWH or LMWH in therapeutic doses, we suggest continuation for 3 months (Grade 2C)**.**

1.7.2. For unilateral RVT that extends into the IVC, we suggest anticoagulation with UFH/LMWH or LMWH for 3 months (Grade 2C)**.**

1.7.3. For bilateral RVT with various degrees of renal failure, we suggest anticoagulation with UFH and initial thrombolytic therapy with tPA, followed by anticoagulation with UFH/LMWH (Grade 2C)**.**

Remark: LMWH therapy requires careful monitoring in the presence of significant renal impairment.

1.8 Primary Antithrombotic Prophylaxis for CVL in Neonates and Children

CVLs are necessary for critical medical care in neonates and children to facilitate administration of life-saving fluids, nutrition (total parenteral nutrition), and/or medications. The consequences of CVL-related VTE in neonates and children are discussed in Sections 1.1 and 1.2, respectively. CVL patency is necessary for therapy to be effectively given through the CVL. Blocked CVLs may be at increased risk of infection, and lead to increased anesthetic and surgical exposure when they require replacement. This section considers the role of primary antithrombotic prophylaxis in pediatric patients with CVLs *in situ*. Primary prophylaxis may be considered for two separate outcomes: first to prevent CVL-related DVT, and second to maintain CVL patency.

There is one RCT reporting thromboprophylaxis of CVLs to prevent CVL-related DVT.[8] The PROTEKT study randomized 186 children ≥ 3 months of age with varying underlying diagnoses to reviparin (n = 92) [anti-FXa levels 0.1–0.3 U/mL] vs standard care (n = 94) [up to 3 U/kg/h UFH]. The incidence of asymptomatic CVL-related thrombosis was 14.1% in the reviparin group vs 12.5% in the standard care group. The study was closed early due to slow patient recruitment and did not achieve sufficient power; however, at this stage there is insufficient evidence to support recommending routine thromboprophylaxis for children with CVL *in situ*.

The incidence of CVL-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. CVLs in children with cancer have been discussed previously (see Section 1.5). The incidence of CVL-related VTE in children receiving long-term total parenteral nutrition varies from 1% based on clinical diagnosis to 35% based on ventilation perfusion scans or echocardiography, to 75% based on venography.[177,220–226] Based on the life-sustaining need for central venous access, two studies have reported the use of VKA primary prophylaxis in this group of patients.[177,226] Both studies had methodologic problems, and further comprehensive studies would be worthwhile. However, VKA primary prophylaxis is commonly used for children receiving long-term home parenteral nutrition.

Studies that have addressed the issue of CVL patency include a trial that evaluated the use of saline solution vs combination saline solution and 1 U/mL UFH in a single-center, double-blinded randomized clinical trial.[227] The study did not demonstrate a difference in CVL patency between the two groups (RR, 7.63; 95% CI, 0.4–145). An unblinded randomized crossover study in which children received UFH 50 U/kg flush vs standard care q12 h reported no difference in CVL patency (RR, 0.5; 95% CI, 0.05–4.9).[228]

A number of studies have evaluated the use of local thrombolytic agents (UK, tPA [alteplase], rtPA [reteplase]) for CVL blockage.[229–232] Most agents restored CVL patency in $> 70\%$ of CVLs after the instillation of two doses (Table 12).

Recommendations

1.8.1. In children with CVLs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B)**.**
1.8.2. In children receiving long-term home total parenteral nutrition, we suggest thromboprophylaxis with VKAs with target INR 2.5 (range 2.0–3.0) [Grade 2C]**.**
1.8.3. For blocked CVLs, we suggest tPA or recombinant UK to restore patency (Grade 2C)**. If after at least 30 min following local thrombolytic instillation CVL patency is not restored, we suggest a second dose be administered. If the CVL remains blocked following two doses of local thrombolytic agent, we suggest investigations to rule out a CVL-related thrombosis should be initiated** (Grade 2C)**.**

1.9 Primary Prophylaxis for Blalock-Taussig Shunts

Background: Blalock-Taussig shunts (subclavian to pulmonary artery shunt) are a form of palliative surgery used to enhance pulmonary artery blood flow in patients with severe or progressive cyanosis, usually secondary to pulmonary stenosis. An MBTS, in which a plastic (Gortex; WL Gore; Newark, DE) tube graft is taken from the side of the subclavian artery and is anastomosed to the pulmonary artery, has been used since 1980. Because of the short length and very high flow, acute thrombosis is less common with the MBTS compared to the classical Blalock-Taussig shunt. Nevertheless, thrombotic occlusion of the MBTS remains a problem, with an incidence between 1% and 17%. In a 155-patient study, smaller shunt size (< 4 mm) was a risk factor for occlusion of the MBTS.[233]

A retrospective review reported on 146 infants aged ≤ 60 days who underwent MBTS and were discharged from the hospital alive, 21 died after discharge (14%) and before further planned surgery.[234] Of these 21 infants, 17 (81%) were apparently clinically well before sudden death. Autopsies were obtained in 15 cases and attributed the cause of death to shunt thrombosis in 5 infants (33%) and myocardial infarction in 2 infants (13%). The mortality rate of patients discharged on aspirin (11%) was almost identical to that of patients discharged receiving no anticoagulation (12.3%).[234]

A retrospective series of 546 MBTS procedures reported an overall early failure rate of 1.4% when heparin was administered intraoperatively and for 48 h postoperatively, in contrast to an early failure rate of 3.4% when heparin was not used ($p = 0.29$).[235] Overall rates of failure during follow-up were 9.1% in heparinized patients vs 13.6% ($p = 0.17$) in nonheparinized patients. Administration of aspirin during follow-up after the MBTS procedure nonsignificantly reduced failure from 11 to 6.7%, $p = 0.176$. In another, much smaller case study, aspirin was reported to decrease the incidence of stent thrombosis after MBTS.[236]

No published RCTs are available to guide the antithrombotic medical management of MBTS patients. A current randomized, blinded, placebo-control trial (Efficacy and Safety of Clopidogrel in Neonates/Infants With Systemic to Pulmonary Artery Shunt Palliation) is currently enrolling patients (ClinicalTrials.gov Identifier: NCT00396877) to evaluate the efficacy of clopidogrel for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic to pulmonary artery shunt.

Recommendation

1.9 For pediatric patients undergoing MBTS, we suggest intraoperative therapy with UFH followed by either aspirin (1–5 mg/kg/d) or no further antithrombotic therapy compared to prolonged LMWH or VKAs (Grade 2C)**.**

1.10 Primary Prophylaxis for Stage 1 Norwoods in Neonates

The Norwood procedure is now commonly performed as the initial surgery for children with hypoplastic left heart, which was previously an almost uniformly fatal condition. Although investigators have reported thrombotic complications following Stage 1 Norwood surgery, the major causes of postoperative death remain surgical and hemodynamic factors.[237–243] The potential for thrombosis to increase pulmonary pressures and so restrict the potential for subsequent Fontan surgery is important. There are no specific studies examining the role of anticoagulant prophylaxis although common practice is to use heparin immediately post operatively followed by aspirin, as per Blalock-Taussig shunts. Recently, some centers report using aspirin and clopidogrel as combination therapy for prophylaxis of Blalock-Taussig shunts during Norwood procedures, and continue this until immediately prior to BCPS.[139] The safety and efficacy of this therapy are unproven. Recommendations for patients undergoing the Norwood procedure are therefore based on generalization from other major cardiac surgery in infants and children.

Table 12—*Studies Reporting the Use of Low-Dose Thrombolysis To Restore Patency to Blocked CVLs: Clinical Description and Results (Section 1.8.1)***

Study/yr	Patients, No.	Intervention	Patients per Intervention, No.	Patency, No./Total (%)	Complications	Comments
Svoboda et al[229]/2004	95 children Age 16 d–18 yr	Recombinant UK 5,000 IU/mL up to 0.2 mL lumen overfill, up to 30 min; repeated if unsuccessful; average 202 IU/kg (13–3,750 IU/kg range)	878 16 d to 96 yr 95 children 16 d–18 yr	Catheter patency restored: After single instillation (30 min): 48/95 (50.5); After up to two instillations (60 min): 72/95 (75.7)	None reported	Within 72 h of treatment +30 d events counted: major hemorrhage, nonhemorrhagic, sepsis defined
Fisher et al[230]/2004	22 Age < 1 yr–19 yr	tPA 0.22–2 mg doses Dose 1: 25–120 min dwell Dose 2: 30–60 min dwell	22	First dose: 86%; Second dose: 95%	Not stated	
Haire et al[231]/2004	180 20% ≤ 18 yr old	(1) recombinant UK 5,000 IU/mL If no response after 30 min, second dose (2) placebo	2:1	Recombinant UK 54% Placebo 30%	No major hemorrhagic events within 72 h	
Shen et al[509]/2003	995 (2–91 yr) 122 (2–18 yr old)	Alteplase: ≥ 30 kg: 2 mg in 2 mL < 30 kg: dose 110% of catheter volume ≤ 2 mL Assess at 30 min, then 120 min, and if no response, second dose and assess at 120 min	122	Patency restored in 86.9% with up to two doses tPA Patency restored with single dose (30 min) in 70/122 (57)	No death, ICH, major bleeding episodes, or TE	Pediatric subgroup analysis
Terrill et al[510]/2003	15 CVLs (n = 13 children) Age 2–18 yr	r-PA (reteplase) 4 doses: 0.1, 0.2, 0.3, then 0.4 U, observed for 1 h for adverse events	15	12/15 (80)	None reported	Average dwelling time 38 min (range 25–105 min)

Table 12—*Continued*

Study/yr	Patients, No.	Intervention	Patients per Intervention, No.	Patency, No./Total (%)	Complications	Comments
Chesler and Feusner[511]/2002	42 Cancer diagnosis < 30 kg Age 4 mo–9.5 yr	tPA 0.5 mg for 30–60 min	42	Patency restored; after single dose: 29/42(69) After up to two doses: 37/42 (88)	Not stated	14/37 reoccluded in 1 mo
de Neef et al[227]/2002	448 (arterial and venous) Venous n = 152 Age ≥ 4 wk to < 18 yr	NaCl 0.9% infusion NaCl 0.9% plus 1 IU UFH/mL infusion	66 72	No increase in risk for nonpatency in nonheparinized CVC (RR 7.63; 95% CI 0.4–145)	Not stated	Closed early; not all eligible patients included
Choi et al[232]/2001	25 (34 courses of tPA) Age 7 wk–16 yr	< 10 kg = 0.5 mg tPA; > 10 kg = 1–2 mg tPA; instilled for 1–4 h or overnight in place (80% 2–4 h)	34	29/34 (85) patency restored	1 minor bleed (hematoma)	No follow-up protocol
Jacobs et al[512]/2001	320 occluded CVLs (228 children) Age 1–18 yr	tPA 0.2–2 mg for 20 min, for 1–3 doses	380	Cumulative restoration of patency After 1 dose: 71.3% After 2 doses: 86.8% After 3 doses: 90.6%	None reported	
Fratino et al[513]/2001	482 (567 CVLs) Mechanical obstruction, n = 24 (46%)	Urokinase 25,000 U/mL to fill catheter for 15 min If not successful, UK 1,000 U/kg/h or tPA 0.05 mg/kg/h in 3-h continuous cycles (up to four cycles)	24 21	Catheter patency achieved; local UK: 3/24 (12.5); UK or tPA infusion: 5/21 (23.8)	Not reported	
Ponec et al[514]/2001	149 (12 children)	tPA for 2 h (≥ 30 kg: 2 mg/2 mL; < 30 kg: 110% of catheter volume) Placebo for 2 h	tPA, n = 75 Placebo, n = 74	Catheter patency tPA 5/6 (83) Placebo 1/6 (16)	No ICH within 5 d; no VTE; no major bleeds	
Davis et al[515]/2000	58 (pediatric and adult)	tPA 0.5–2.0 mg for 1–3 doses	Not reported	Patency restored in 96.6% (86% with 0.5 mg tPA)	Not reported	
Kleta et al[516]/1998	Not reported Age 3 mo–25 yr	tPA 0.5 mg for 20–30 min	Not reported	Patency restored 97%	Not reported	
Haire et al[517]/1994	50 (pediatric and adult)	tPA 2 mg for 1 h; UK 10,000 U for 1 h	28 22	tPA restored patency: 25/28 (89), p = 0.013 UK restored patency: 13/22 (59)	No bleeding No VTE No sepsis	

*CVC = central venous catheter. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Recommendation

1.10 For patients who underwent the Norwood procedure, we suggest UFH immediately after the procedure, with or without ongoing antiplatelet therapy (Grade 2C)**.**

1.11 Primary Prophylaxis for Glenn or BCPS in Children

Glenn successfully performed the classic cavopulmonary anastomosis in 1957 as palliation for tricuspid atresia. The bidirectional Glenn 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 heart, and following stage I Norwood in hypoplastic left hearts). Thrombotic complications following the Glenn shunt are infrequently reported.[244–246] 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 at this time. Thus, recommendations for patients undergoing BCPS are therefore based on generalization from other major vascular procedures in infants and children.

Recommendation

1.11 In patients who have BCPS, we suggest postoperative UFH (Grade 2C)**. We suggest this should be followed by no anticoagulation or antiplatelet therapy or anticoagulation with VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) to continue until the patient is ready for Fontan surgery** (Grade 2C)**.**

1.12 Primary Prophylaxis for Fontan Surgery in Children

The Fontan procedure, or a modified version, is the definitive palliative surgical treatment for most congenital univentricular heart lesions. 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 in which thrombosis was the primary outcome, and from 1 to 7% in retrospective studies assessing multiple outcomes.[247,248] TE may occur anytime following Fontan procedures but often present months to years later. 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.[36–38] Despite aggressive therapy, TE following Fontan procedures have a high mortality, and respond to therapy in $< 50\%$ of cases. There is no consensus in the literature, or in routine clinical practice, as to the optimal type or duration of antithrombotic therapy to prevent such events.[165,246,249,250] Consequently a wide variety of prophylactic anticoagulant regimes are in use. There are very few studies that compare treatment options (Tables 13). There are a number of recent reviews of thromboprophylaxis following Fontan procedures and there is a large multicenter prospective trial of prophylactic anticoagulation therapy following Fontan procedures, which is nearing completion.[247,248] The trial compares aspirin (5 mg/kg/d) to initial UFH

Table 13—*Comparative Studies of Primary Prophylaxis for Fontan Surgery in Children: Clinical Description and Results (Section 1.12.1)**

Study/yr	Intervention	Patients, No.	Follow-up, yr	Thromboembolic Events, No. (%)	Major Hemorrhage	Comments
Seipelt et al[250]/ 2002	No treatment; Aspirin 2–3 mg/kg Heparin warfarin target 2.2–2.7	45 14 26	Mean 5.3 ± 4.5 Mean 4.4 ± 2.8 Mean 3.6 ± 1.3	10 (22), 4.2/100 patient-yr 1 (7), 1.6/100 patient-yr 1(4), 1.1/100 patient-yr	None recorded	
Kaulitz et al[249]/ 2005	Aspirin, n = 86 No anticoagulation, n = 45 Warfarin, n = 11	142	Mean follow-up was 91.1 ± 43.9 mo	VTE: 8 (5.6) AIS: 2 (1.4) Majority of events during initial postoperative UFH therapy Only 2 events during later follow-up	None reported	Case series

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

followed by warfarin (target INR 2.5; range, 2.0–3.0) and primary prophylaxis, and results are expected in late 2007.

Recommendation

1.12 For children after Fontan surgery, we recommend aspirin (1–5 mg/kg/d) or therapeutic UFH followed by VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1B]**.**

Remark: The optimal duration of therapy is unknown. Whether patients with fenestrations require more intensive therapy until fenestration closure is unknown.

1.13 Primary Prophylaxis for Endovascular Stents in Children

Endovascular stents are used with increasing frequency in the management of congenital heart lesions including branch pulmonary artery stenosis, pulmonary vein stenosis, coarctation of the aorta, and to treat subsequent surgical stenosis.[251] Although stents can be successfully used in infants < 1 year of age, the small vessel size increases the risk of thrombosis. 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. Further studies are required to determine optimal prophylactic anticoagulation after such procedures.

Recommendation

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

1.14 Primary Prophylaxis for Dilated Cardiomyopathy in Neonates and Children

The etiology of cardiomyopathy in children is quite different to that seen in adults. Postviral and idiopathic cardiomyopathies occur in otherwise well children, whereas dilated cardiomyopathy occurs frequently during the end stage of muscular dystrophies. The outcome is frequently poor, and heart transplant, although potentially curative in many cases, is associated with long wait times.[252–256] In a cross-sectional study of children awaiting cardiac transplant, 31% were said to have acute PE confirmed by ventilation/perfusion scan or angiography.[257] 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 to 3.0) is often used.[258]

Recommendation

1.14 We suggest that pediatric patients with cardiomyopathy receive VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) no later than their activation on a cardiac transplant waiting list (Grade 2C)**.**

Underlying values and preferences: Our suggestion for administration of VKAs places a high value on avoiding thrombotic complications, and a relatively low value on avoiding the inconvenience, discomfort and limitations of anticoagulant monitoring in children who are eligible for transplant, which is a potentially curative therapy.

1.15 Primary Pulmonary Hypertension

There are relatively little specific data about the role of anticoagulant therapy as primary prophylaxis in children with pulmonary hypertension. However, based on adult data, and the basic pathophysiology of the disease, clinicians commonly administer anticoagulant prophylaxis. 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), while others use target INR 2.5 (range, 2.0–3.0). The ideal time to commence anticoagulant therapy in children is uncertain; however, simultaneous to the commencement of vasodilator or other medical therapy is common.[259–261]

Recommendation

1.15 In children with primary pulmonary hypertension, we suggest anticoagulation with VKAs commencing when other medical therapy is commenced (Grade 2C)**.**

1.16 Biological Prosthetic Heart Valves

Biological prosthetic heart valves may be surgically placed in infants and children with congenital or acquired heart disease when their innate tricuspid and/or pulmonary valve is not surgically repairable.[262] Mechanical valves are preferred for mitral and aortic replacement given the catastrophic consequences of valve failure in these anatomical positions. Patients with biological prosthetic heart valves

are usually provided with an antiplatelet agent. Thromboembolic and bleeding events are uncommon with this therapy.[263–267] There is no specific evidence describing optimal thromboprophylaxis in children with bioprosthetic heart valves, and as a result, clinicians should follow recommendations for adults in these circumstances (see chapter by Salem et al in this supplement).

Recommendation

1.16 For children with biological prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population (see chapter by Salem et al in this supplement).

1.17 Mechanical Prosthetic Heart Valves

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. Thrombotic complications associated with mechanical prosthetic heart valves are well described in adults. For this reason, clinicians generally use VKAs to prevent complications that 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, with varied valve positions and types. Antithrombotic regimens described to prevent TE complications range from no anticoagulation, to the use of antiplatelet agents, or VKA. The outcome events reported include TE (valve thrombosis and stroke), bleeding, and mortality (Table 14).

The incidence of TE in children with mechanical valves is reported as high as 68% per patient-year in children who received aspirin,[268] and 27% per patient-year for children who received no drug therapy.[268] Bleeding, when reported, was extremely rare.[136,267,269–274] When VKAs were prescribed, the incidence of TE was reduced, but there was an increased bleeding incidence.[136,263,267,270,271,273–283]

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

Recommendation

1.17.1 For children with mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population with respect to the intensity of anticoagulation therapy.

1.17.2. For children with mechanical prosthetic heart valves who have had thrombotic events while receiving therapeutic antithrombotic therapy, or in patients for whom there is a contraindication to full-dose VKAs, we suggest adding aspirin therapy (Grade 2C)**.**

1.18 VADs

VADs are being used more often in children with cardiac failure (congenital or acquired) as either bridge to transplantation or to cardiac recovery. Available VADs include pulsatile VADs (Medos [Stolberg, Germany]; Excor [Berlin, Germany]; Thoratec, Heartmate [Pleasanton, CA]; ABIOMED BVS 5000 [Danvers, MA][284–298]; or axial flow (MicroMed DeBakey [Houston, TX[299–301]]).

Studies in infants and children using these devices are mainly retrospective case series with outcomes being survival to transplant or to cardiac recovery. Reported survival to transplant or to cardiac recovery ranges from 50%[299] to 83%.[285] There are no good quality studies evaluating the safety and efficacy of anticoagulant and/or antiplatelet therapy in children on VAD support to reduce TE. There is no standardized antithrombotic regime; however, based on adult data and the catastrophic consequences of circuit occlusion or embolic complications, anticoagulant therapy in combination with antiplatelet therapy seems preferable over no therapy.

The only alternative to the use of VADs in cardiac failure is extracorporeal membranous oxygenation (ECMO) with an estimate of survival approximately 50% for a cardiac indication, and having 50% bleeding complications.[290] A prospective study with a head to head comparison of VAD (with a standardized anticoagulation regimen) to ECMO is needed to determine long term safety and efficacy.

Recommendations

1.18.1. Following VAD placement, in the absence of bleeding we suggest administration of UFH targeted to an anti-factor Xa of 0.35 to 0.7 U/mL (Grade 2C)**. We suggest starting UFH between 8 h and 48 h following implantation** (Grade 2C)**.**

1.18.2. We suggest antiplatelet therapy (either aspirin, 1–5 mg/kg/d and/or dipyridamole 3–10 mg/kg/d) to commence within 72 h of VAD placement (Grade 2C)**.**

1.18.3. We suggest that once clinically stable, pediatric patients be weaned from UFH to either

LMWH (target anti-FXa 0.5–1.0 U/mL) or VKA (target INR, 3.0; range, 2.5–3.5) until transplanted or weaned from VAD (Grade 2C)**.**

1.19 Cardiac Catheterization

The femoral artery is the most common access site for cardiac catheterization (CC). The development of thrombus at the puncture site and into the ileofemoral system is one of the serious complications of CC. Signs of femoral thrombosis range from a mild decrease in pulse strength as a result of partial obstruction by a thrombus to severe ischemia and potential loss of limb secondary to a significant interruption of arterial blood flow. Technical difficulty and increased catheter/artery size ratios increase the risk of femoral artery thrombosis. Arterial spasm may initially mimic femoral thrombosis but usually resolves within 4–6 h.

Incidence: The incidence of femoral artery thrombosis after CC is approximately 40%,[302,303] with younger children (*ie*, those < 10 years of age) having an increased incidence compared to older children.[302,303] Arterial complications following CC are six times more likely to occur when balloon angiography or valvotomy is performed. Patient size, patient hemodynamic status, operator technique, larger catheter size and total time of arterial cannulation act together to create the risk for arterial thrombosis.[304]

Outcomes: Outcomes related to TEs following CC include short-term and long-term consequences. Short-term consequences of CC related thrombosis include threatened limb viability, and the morbidity associated with anticoagulant or thrombolytic therapy. Long-term consequences of femoral artery thrombosis likely reflect the effectiveness of the treatment provided and include leg-length discrepancies, muscle wasting, claudication, and loss of arterial access, which is important for children who require multiple CCs in the future.[305] Symptomatic ischemia may occur at times when the child experiences rapid growth, as occurs in the first year of life and during puberty.[305]

Late complications of femoral artery catheterization can be clinically important. In a study by Taylor et al,[306] 58 children who were < 5 years old at the time of catheterization 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. The mean ankle/brachial index in the catheterized limbs was 0.79, and leg growth retardation was present in 8% of children.[306] Celermajer et al[307] reports > 30% of previously catheterized children and adolescents present with vascular access problems at subsequent catheterizations due to an occluded vessel, a stenosed vessel, or scar tissue. The practical implications of difficult access include prolonged access time, prolonged total catheter duration, and significant discomfort for patients studied under local anesthesia. Hurwitz et al[308] evaluated 48 children in whom recatheterization was performed 6 months to 9 years following the initial CC. Complete occlusion of the femoral artery was present in 4 of 48 patients (8%), with extensive hypogastric collateralization reconstituting the femoral artery approximately 3 to 4 cm below the inguinal ligament.[308]

Evidence for Prophylaxis: Five prospective trials have examined the value of prophylaxis to prevent femoral artery thrombosis[302,303,309–311] (Table 15). Freed et al[302] demonstrated that prophylactic anticoagulation therapy with aspirin does not significantly reduce the incidence of femoral artery thrombosis. However, anticoagulation therapy with 100 to 150 U/kg unfractionated heparin (UFH) reduces the incidence from 40 to 8%. Although a more recent small randomized trial has suggested that a 50 U/kg bolus of heparin may be as efficacious as 100 U/kg when given immediately after arterial puncture, this study was underpowered, and a bolus of 50 U/kg cannot not be recommended as optimal prophylaxis at this time.[311] Importantly, recent advances in interventional catheterization have resulted in the use of larger catheters and sheaths, which may increase the risk of thrombosis. Further heparin boluses or a constant infusion are frequently used in prolonged procedures (*ie*, > 60 min), especially during interventional catheterizations, however, the benefits of this practice are not known.

Recommendations

1.19.1. For neonates and children requiring CC via an artery, we recommend administration of IV UFH prophylaxis (Grade 1A)**.**
1.19.2. We recommend the use of UFH doses of 100 to 150 U/kg as a bolus (Grade 1B)**. We suggest further doses of UFH rather than no further therapy in prolonged procedures** (Grade 2B)**.**
1.19.3. We recommend against the use of aspirin therapy for prophylaxis for CC (Grade 1B)**.**

1.20 Therapy of Femoral Artery Thrombosis

Femoral artery thrombosis is most commonly seen in children as an iatrogenic complication of cardiac catheterization. Descriptions of treatment of femoral artery thrombosis in neonates or older children with thrombolytic therapy, anticoagulation, thrombectomy or observations consist exclusively of case series

Table 14—*Studies Reporting Anticoagulation in Mechanical Prosthetic Heart Valves in Children: Clinical Description and Results (Section 1.17.2)**

Study/yr	Position/Valve Type	Patients, No.	Thromboembolic Events, No.	Hemorrhagic Events, No.	Deaths, No.	Anticoagulation	Comments
Khitin et al[270]/2006	St. Jude Aortic valve, n = 27 Mitral valve n = 40 Both n = 5	72 (age ≤ 20 yr)	Warfarin, n = 4 (1.3/100 patient-yr) Cerebral embolism: Warfarin, n = 3 (1/100 patient-yr) Aspirin/dipyridomole, n = 2 (2/100 patient-yr)	Warfarin, n = 7 2.4/patient-yr, 4 fatal	Warfarin, n = 2 (0.2/patient-yr) Aspirin/ dipyridamole, n = 2 (0.2/ patient-yr)	Warfarin, n = 53 Aspirin/dipyridamole, n = 19	
Reiss et al[518]/2006	St. Jude, Carbomedics Aortic valve, n = 5 Mitral valve n = 15 Pulmonary valve, n = 32 Tricuspid valve, n = 7 Multiple n = 9	68 Age 5 mo-61 yr (mean 21 yr) 19 age < 18 yr	3 pulmonary valve thrombosis (1 with INR 1.4, 2 with INR 2.5–3.5)	Not reported	Not reported	Dicoumarol, n = 19 (age < 18 yr)	
Kojori et al[279]/2004	104 with 137 valve replacements St. Jude 37% Bjork 25% Carbomedics 20% Shiley 10% Other 8%	104 with 137 valve replacements	2 TIA, n = 3	6 (5%)	1 vitral valve replacement, 18 deaths 2 mitral valve replacements, 9 deaths	No stated regimen Warfarin Dipyridamole Aspirin; No anticoagulation	
Alexiou et al[275]/2001	Carbomedics, St. Jude, On-X, Bjork Shiley Mitral valve, n = 44 Aortic valve, n = 7	44 Age 2 mo-16 yr Mean 6.8 yr	2 1 mitral valve thrombosis 1 TE with INR 4.2	2 (after dental extraction)	6 (14% perioperative, 4 late)	Warfarin 2.5–3.0 Warfarin (intensity and regimen unknown)	
Caldarone et al[263]/2001	Mitral valves; St. Jude, Carbomedics, Bjork Shiley, tissue valves, 2%	139 with 176 valve placements	TE 3% Stroke 2%	Not reported	Not reported		
Gunther et al[519]/2000	Mechanical, n = 29 Bioprosthetic, n = 6	35	2 1 valve thrombosis to death, mechanical valve 1.6/100 patient-yr	1 (death, ICH mechanical valve; INR subtherapeutic) 0.8%/100 patient-yr	Hospital mortality: 17.1% Late deaths: n = 7 (20%)	Phenprocoumon, INR 2.5–3.5	
Alexiou et al[520]/2000	Aortic valves	56	Valve thrombosis, n = 1 Stroke, n = 1 (all stopped warfarin)	Not reported	Operative mortality: n = 3 (5.3%)	Warfarin 3–3.5	
van Doorn et al[521]/2000	Mechanical valves Bjork Shiley St. Jude Carbomedics	54 with 56 valve replacements	1	6 (1 ICH on warfarin)	1 ICH	Warfarin 2.5–3.5 or aspirin plus dipyridamole	
Yoshimura et al[522]/1999	Mitral valve, n = 30 Others, n = 26	56	6 10 mitral valve thrombotic events	4	None reported	Warfarin ± aspirin or dipyridamole Thrombotest range 15–30%	
Mazzitelle et al[523]/1998	Mechanical valve, n = 30 Aortic valve, n = 46	76	2 (6.6%)	1 (3.3%)	Not reported	Warfarin	
Bradley et al[276]/1997	St. Jude Aortic valve, mitral valve, and tricuspid valve, n = 3	64 Age ≤ 18 yr	Not reported	Not reported	Not reported	Warfarin or aspirin	32 of 64 were not given treatment until ≥ 1986
Champsaur et al[278]/1997	Mitral valve Aortic vs Bjork Shiley, n = 14 St. Jude, n = 40	54 Age 1–17 yr	0.3%/ patient-yr 1 TE-related death	0.3%/patient-yr 1 GI hemorrhage-related death	Overall 13% 6 late deaths 2 left ventricular dysfunction 2 valve related 1 hemorrhage 1 TE	Warfarin	

Table 14—*Continued*

Study/yr	Position/Valve Type	Patients, No.	Thromboembolic Events, No.	Hemorrhagic Events, No.	Deaths, No.	Anticoagulation	Comments
Bradley et al[277]/1985	Bjork Shiley, St. Jude mechanical valves Mitral valve, n = 22	28 children (age ≤ 19 yr; mean 7.9 yr); 30 valve replacements	No warfarin: 2/10 (20%) 12/100 patient-yr Life threatening	5/20 (25%) Warfarin; 22/100 patient-yr (not life threatening)	Not reported	Warfarin or aspirin/ dipyridamole or nothing	
LeBlanc et al[138]/1993	Bjork Shiley, St. Jude Aortic valve, n = 11	20 (age 11–213 mo; median 85 mo)	1; 1.7%/patient-yr (no valve thrombosis)	4; 6.8% patient-yr	No early/late/deaths	Warfarin for 3 mo Target INR 2–3 then aspirin 10 mg/k/d and dipyridamole 3 mg/kg/d	
Abid et al[269]/1992	Aortic valve; various types	64 Age < 16 yr	5 with ineffective anticoagulation (1.3/ 100 patient-yr) 4 TE 1 valve thrombosis	1 Patient receiving warfarin	8 (2.5%) 1 valve thrombosis	Warfarin, n = 40 Aspirin/dipyridamole, n = 15	
Solymar[137]/1991	Heterografts n = 48 Mechanical valves n = 175 Aortic n = 55 Mitral valve n = 95 Multiple n = 26	186	19 1 mitral valve thrombosis	2 major	22 total deaths 1 thromboembolic death	Warfarin Aspirin	91% aortic valve 82% mitral valve 60% multiple valves
Harada et al[524]/1990	Mitral valve, n = 28 Aortic valve, n = 15 Mitral valve plus tricuspid valve, n = 1 Tricuspid valve, n = 3	50 Age 4 mo–15 yr	1 2 valve thrombosis, patients receiving warfarin	Not reported	Late deaths, n = 4 1 valve thrombosis	Warfarin or aspirin	
Kadoba et al[264]/1990	Mitral valves: Shiley, n = 12 St. Jude, n = 7 Dura-mater, n = 5 Porcine, n = 1	25 Age < 1 yr	1 Valve thrombosis; treatment cryoprecipitate for increased prothrombin time	1 Increased prothrombin time	5 of 6 tissue valve death	Warfarin	
Antunes et al[525]/1989	Various mitral	352 Age < 20 yr	1.0%/patient-yr valve thrombosis TE 1.3%/patient-yr	5 All fatal 0.4%/patient-yr	5 (6.3%)	Warfarin	
Rao et al[280]/1989	Aortic valve, n = 32 Mitral valve, n = 71 Both, n = 20	130 Age 1–19 yr	Aortic valve: aspirin/dipyridamole, 2.5% (2.5/100 patient-yr) None: 5% (5.0/100 patient-yr) Mitral valve: warfarin, 4% (2% severe) Aspirin/dipyridamole, 3% (2 fatal) None, 11%	Warfarin, 4%	Not reported	Warfarin or aspirin/ dipyridamole or none	
Sade et al[526]/1988	St. Jude Aortic valve, mechanical valve, and both	48	1 mitral valve thrombosis (death) Rest of TE events not reported	No bleeding events reported	Not reported	No anticoagulation	
Robbins et al[272]/1988	Mitral valve, n = 60 Aortic valve, n = 36 Combination valves, n = 13 Tricuspid valve, n = 8	94 Age 3 mo-19 yr 49 tissue 68 mechanical	6 Mechanical valves with no anticoagulation 3 no anticoagulation or antiplatelet 1 aspirin	1 (GI) on warfarin 5 on aspirin	12% perioperative 11 in patients with mechanical valves and no anticoagulation 2 valve thromboses 1 cerebral VTE	Aspirin/dipyridamole or warfarin	

Table 14—*Continued*

Study/yr	Position/Valve Type	Patients, No.	Thromboembolic Events, No.	Hemorrhagic Events, No.	Deaths, No.	Anticoagulation	Comments
Cornish et al[527]/1987	Mitral valve, n = 66 Aortic valve, n = 8 Aortic valve and mitral valve n = 9	81 Age 3–15 yr	Not reported	Not reported	Early mortality 3.7%	Warfarin or aspirin or none	
El Makhlouf et al[136]/1987	Starr-Edwards Aortic, tricuspid, mitral Mostly mechanical	273 Age 2–16 yr 62 with > 1 valve	24 Mitral valve thrombosis; 2.7/100 patient-yr 5 of 8 tricuspid valves were thrombosed TE on aspirin 20 mg/kg/d plus dipyridamole 5 mg/kg/d (2.3/100 patient-yr On warfarin (2.3/100 patient-yr)	None reported	4.7% perioperative	Aspirin 20 mg/k/d plus dipyridamole 5 mg/k/d or warfarin	No difference between aspirin and warfarin
McGrath et al[528]/1987	St. Jude Aortic, mitral valves	30 Age 4–20 yr	7 (24.1%); 1 hemiparesis; 1 valve thrombosis and death; 5 TIAs	Not reported	Early deaths, n = 1, 3.3% Late deaths, n = 5, 17.2%	Aspirin or dipyridamole	
Schaffer et al[271]/1987	Aortic, n = 19 Mitral, n = 14	33 Age 5 mo-17 yr Mean 9.5 yr	4 suboptimal anticoagulation (warfarin, n = 3; sulfinpyrazone, n = 1) 1 valve thrombosis	None reported	Deaths, n = 7, mitral valve	Warfarin With/without sulfinpyrazone With/without dipyridamole With/without aspirin	
Stewart et al[282]/1987	Star Edwards Shiley Lilliheigh caster Aortic, n = 12 Mitral valve, n = 14 Pulmonary valve, n = 1 Tricuspid valve, n = 1 Double, n = 2	30 Age 6–17 yr	2.3/100 patient-yr; 5 (3 stopped warfarin)	5 (1 major, fatal) 4 minor (3 preventable) 2.3/100 patient-yr	1 mitral valve	Warfarin, regimen and intensity of therapy unknown	
Borkon et al[273]/1986	Mitral valve, n = 17 Aortic valve, n = 16 Pulmonary valve, n = 1	34 Age 3 wk-17 yr	1 (TE in patient receiving warfarin 1 valve thrombosis in patient receiving aspirin	1 (patient receiving anticoagulation)	1 valve thrombosis in patient receiving aspirin; 6 late deaths	Warfarin, aspirin	
Milano et al[265]/1986	Thromboembolic events Aortic valve, n = 53 Mitral valve, n = 90 Aorta and mitral valve, n = 23 Bioprosthetic valve, n = 84 Mechanical valve, n = 71 Bioprosthetic and mechanical, n = 11	166 Age < 15 yr	Bioprosthetic valve, 0.6%/patient-yr Mechanical valve, 1.4%/patient-yr	Not reported	Early mortality overall 9%	Warfarin for mechanical valve Warfarin for 3 mo for bioprosthetic valve	
Verrier et al[274]/1986	Aortic valve	51 Age 1–23 yr Mean 12.9 yr	1 TIA	4 (5.9%) 3 minor nosebleeds 1 GI bleed	2	45 aspirin 6 aspirin and dipyridamole (5 changed to warfarin)	
Woods et al[529]/1986	Various Aortic valve Mitral valve	31 Age 5 mo-16 yr	1.8%/patient-yr	0.9%/patient-yr	Not reported	Acenocoumarol or aspirin/dipyridamole	

Table 14—*Continued*

Study/yr	Position/Valve Type	Patients, No.	Thromboembolic Events, No.	Hemorrhagic Events, No.	Deaths, No.	Anticoagulation	Comments
Schaff et al[530]/1984	Stan Edwards Aortic valve, n = 19 Mitral valve, n = 24 Both, n = 1 Tricuspid valve, n = 6	50 Age 6 mo-18 yr Mean 10.4 yr	TE: major, n = 7; TIA, n = 5 (50% n = 6 no warfarin) Late TE (> 30 d): aortic valve; 5.3/100 patient-yr; mitral valve, 2/100 patient-yr	7 3 major bleeds (n = 2), ICH, death 1 abdomen bleed	11 2 fatal ICH Prothrombin time 2–2.5 times normal	Warfarin	
Pass et al[531]/1984	Mitral valve, n = 12 Aortic valve, n = 14 Tricuspid valve, n = 2 Pulmonary valve, n = 3 Pulmonary conduit, n = 1 Mitral valve and aortic valve, n = 2	34 Age 9 mo-21 yr	2 1 portal valve thrombosis 1 myocardial infarction	None	3 operative 1 early	Not specified	
Williams et al[532]/1981	n = 92 Mitral valve Aortic valve	Mechanical valve, n = 54 Tissue valve, n = 57	2 1 mechanical 1 tissue	1	None reported	Warfarin and dipyridamole Tissue valve, aspirin for 3 mo	
Human et al[533]/1982	Various mitral valves	56 (age 2–12 yr)	3%/patient-yr	Not reported	Not reported	Not specified	
Donahoo and Gardner[534]/1982	St. Jude Mitral valve, n = 7 Aortic valve, n = 7	14 (age 4 mo-17 yr)	Not reported	None	None	Warfarin or aspirin	
Weinstein et al[267]/1982	Mechanical valve, n = 11 Tissue valve, n = 7 (27 valve replacements) Mix of tissue and mechanical Bjork-Shiley, Beall	24 27 with valve replacements Age 1–18 yr Mean 12.2 yr	None reported with aspirin	None reported with aspirin	1 operative death 2 late deaths	Aspirin or aspirin plus dipyridamole or warfarin	
Spevak et al[266]/1986	Mechanical Bjork, Shiley, St. Jude Tissue valves, 20% (n = 14) Mitral valve, n = 49 Tricuspid valve, n = 13 Aortic valve, n = 6	63 70 valve replacement (age < 5 yr) Mitral valve, n = 49 Aortic valve, n = 6 Tricuspid valve, n = 13 Multiple, n = 1	2 1 mechanical valve in patient receiving anticoagulation 1 tissue 1.6/100 patient-yr	1 Star Edwards in patient receiving anticoagulation 0.8/100 patient-yr	17	Warfarin, intensity and regimen unspecified	

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 15—*Studies Reporting Outcomes of Anticoagulant Primary Prophylaxis for Pediatric Patients Undergoing CC Procedures: Clinical Description and Results (Section 1.19.1)**

Study/yr	Patients, No.	Therapy	Received Treatment, No.	Thromboembolic Events, No.	Hemorrhagic Events, No.	Comments
Roschitz et al[535]/2003	65	UFH 100 U/kg/h or Enoxaparin 1.16 mg/kg	40 25	1	No major bleeds	
Ruud et al[536]/2002	50 (age 8 mo–16 yr; median 34 mo)	UFH 75 U/kg then q2h	50 (venous and arterial access, n = 24)	No events	Not reported	All patients > 7 kg body weight
Vitiello et al[538]/1998	4,952 (age 1 d–20 yr; median 2.9 yr)	UFH 150 U/kg then 75 U/k if duration of CC > 2 h	4,952	165 with decrease pulses after CC	Not reported	Decrease in pulse volume was surrogate for thrombosis
Saxena et al[311]/1997	366 (age 17 d–11 yr; mean 39.5 mo)	UFH 50 U/kg/h vs UFH 100 U/kg/h	183 183	9.8% 9.3%	No events	
Vielhaber et al[538]/1996	75 (neonate–6 yr)	Intermittent UFH flush 10 U/mL Additional UFH 300–400 U/kg/d for 24 h	75 6	2	Not reported	
Burrows et al[539]/1990	64 (age 5 d–15.4 yr; mean 6.4 yr)	UFH 150 U/kg Additional 150 U/kg if CC duration > 2 h	64	18	Not reported	Decrease in pulse volume that improved with lytic therapy or required thrombectomy
Ino et al[304]/1988	526 infants and children	UFH 150 U/kg/h if decreased pulses 2 h later the UFH 20 U/kg/h for 48 h	526	45 (8.6%)	No major bleed Groin site bleeds, n = 4	Decrease in pulse volume was surrogate for thrombosis
Girod et al[309]/1982	1,316 (age 1 d–16 yr)	(1) UFH 100 U/kg (2) UFH 100 U/kg, then 75 U/kg/h, then 100 U, then 50 U/kg/h if decreased pulses (3) UFH 100 U/kg, then 45 min into catheterization 75 U/kg/h infusion, 20 U/kg/h if decreased pulses (n = 241)	694 381 241	11 (0.8%) arterial thromboses	No events	
Rao et al[310]/1981	116 (age 4 mo–20 yr; 75% > 5 yr)	UFH 1,000 U/mL (100 U/kg/h) vs Placebo	58 58	Not reported	Not reported	Plethysmography index to diagnosis of thrombosis
Freed et al[302]/1974	161 (age 1–34 yr; median 11 yr; 77 < 10 yr)	UFH 100 U/kg vs Placebo	40 37	3/40 (8%) 15/37 (40%) 7/15 required embolectomy	No. of events not reported; however, hemorrhage equal across groups	All thrombotic events occurred in children age < 10 yr
Freed et al[303]/1974	95	Aspirin 15 mg/kg for 5 doses vs Placebo	37 58	Thrombosis in 22% Thrombosis in 24%	None reported	

*The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

without comparison groups.[152,200,201,202,304,312–320] 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 approximately 70% of thromboses will resolve with UFH alone, without exposing children to the risks associated with thrombolytic therapy, embolectomy, and/or surgical reconstruction.[152] LMWH is classically not used initially, because if resolution does not occur with UFH and there is the need to progress to either thrombolysis or surgery, than the irreversibility of LMWH becomes problematic. However, a report has suggested LMWH may be a safe alternative in this situation.[81] If < 4 h has passed since the cardiac catheter-related UFH bolus was given, than UFH may be commenced as a continuous infusion without further bolus.

Recommendations

1.20.1. For pediatric patients with a femoral artery thrombosis, we recommend therapeutic doses of IV UFH (Grade 1B)**. We suggest treatment for at least 5 to 7 days** (Grade 2C)**.**
1.20.2. We recommend administration of thrombolytic therapy for pediatric patients 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 (Grade 1B)**.**
1.20.3. For children with femoral artery thrombosis, we suggest surgical intervention when there is a contraindication to thrombolytic therapy and organ or limb death is imminent (Grade 2C)**.**
1.20.4. We suggest for children in whom thrombolysis or surgery is not required, conversion to LMWH to complete 5 to 7 days of treatment (Grade 2C)**.**

1.21 Peripheral Arterial Catheter Thrombosis in Neonates and Children

Prophylaxis: The majority of studies concerning anticoagulant prophylaxis for peripheral artery catheters have examined interventions to prolong catheter patency as distinct from avoiding occlusive arterial thrombosis.[321–323] Butt et al,[321] in an RCT, compared UFH infusion flow rates of 2 mL/h and 1 mL/h in 319 patients and reported that there was no significant difference with respect to duration of catheter patency. However, increasing the concentration of UFH from 1 to 5 U/mL (n = 154) significantly prolonged catheter patency. Sellden et al,[322] in a consecutive cohort study, assessed intermittent vs continuous flushing (5 U/mL) with UFH containing solutions in 338 patients < 1 year of age with radial arterial catheters. Catheters were removed due to malfunction in 76% of patients receiving intermittent flushes compared to 52% of those receiving continuous infusions of UFH. In a RCT, Rais-Bahrami et al,[323] in an RCT, evaluated premature peripheral arterial catheter removal in 60 newborns catheters. Patency of peripheral arterial catheters was prolonged in infants receiving UFH normal saline flushes compared to UFH dextrose flushes. Heulitt et al,[324] in a blinded RCT, compared solutions containing or not containing papaverine in 239 children, ages 3 weeks to 18 years. Ninety-three percent of patients with catheters receiving papaverine supplemented solutions were patent as compared to 78% of catheters without papaverine supplementation.

Treatment: The majority of reports of treatment for peripheral artery catheter thrombosis in neonates and children are isolated case reports. Tarry et al[325] identified 44 cases of peripheral arterial TEs secondary to catheterizations in children with nephrotic syndrome. Of these patients, TEs were caused by vessel trauma secondary to attempted blood sampling in 9 cases (20%).[325] One case series has proposed an algorithm to assist in determining the role of surgery vs thrombolysis and anticoagulation.[163]

Recommendations

1.21.1. For pediatric patients with peripheral arterial catheters *in situ*, we recommend UFH through the catheter, preferably by continuous infusion (5 U/mL at I mL/h) [Grade 1A]**.**
1.21.2. For children with a peripheral arterial catheter-related TE, we suggest immediate removal of the catheter (Grade 1B)**. We suggest UFH anticoagulation with or without thrombolysis, or surgical thrombectomy** (Grade 2C)**.**

1.22 Neonatal Aortic Thrombosis: UAC Related

Background: Owing to its size and easy accessibility, the umbilical artery is very commonly used for catheterization during the neonatal period in both term and preterm infants. The incidence of clinically symptomatic thrombosis secondary to the use of umbilical venous catheters (UACs) has been estimated at between 1% and 3%.[326–328] This figure likely underestimates the incidence of silent events as demonstrated in studies using sequential imaging and from autopsy data, where the incidence appears much higher.[329,330] The incidence may be higher with longer catheter duration.[330]

The clinical consequences of UAC-related thrombosis depend on the extent of the thrombosis but

include lower-limb ischemia,[326,328,331] congestive cardiac failure, impaired renal function, and hypertension.[332] Embolic events are also reported and UAC thrombosis has been linked to the development of NEC.[333,334]

No recent studies have reported outcomes from UAC-related thrombosis. In one older series of 20 cases, classified as mild, moderate, or severe depending on the extent of the thrombosis, 5 of 20 patients with severe thrombosis died.[28] In those who do survive these events, long-term sequelae include persistent renovascular hypertension and lower-limb growth abnormalities.[335]

Evidence: Clinicians have employed a number of strategies to reduce the frequency of catheter occlusion and other TE related to UAC placement (Table 20). These include the use of heparin either as an intermittent flush or as a continuous low-dose infusion, variation in catheter design and materials, and differences in the location of the catheter tip. Although many of these issues remain controversial, most units now use some type of heparin infusion to maintain catheter patency.

Six RCTs have addressed the use of low-dose heparin infusions in neonates with UACs,[336–341] which was the subject of a systematic review by Barrington.[342] Five studies compared the use of UFH in the UAC infusate with or without additional UFH in flush solutions vs no UFH, while one study compared the use of UFH in the infusate vs UFH in the flush solution. Various end points were assessed in these studies including catheter patency, aortic occlusion, other ischemic events, coagulation abnormalities, intraventricular hemorrhage (IVH), and hypertension. Objective imaging was used to assess the incidence of thrombosis in two studies.[337,339]

The reduced incidence of catheter occlusion was consistent between studies (five studies used a dose of 1 U/mL UFH, and one study used 0.25 U/mL[340]) with a typical RR of 0.20 (95% CI, 0.11–0.35). This effect was not observed when UFH was administered only in the flush solution.[338]

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[343] reported the use of full systemic UFH vs low-dose UFH in a small 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.[343]

The association between the use of UFH and the occurrence of IVH in preterm neonates remains controversial. In Barrington's review,[342] 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 of IVH. This contrasts with other published data.[344,345] Lesko et al[344] 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; CI, 1.4–11). In addition, the median birth weight was lower in the UFH group who also had a higher incidence of concomitant illnesses, which may have influenced the results.[344] Malloy and Cutter[345] 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, which could potentially bias the results. Another concern is that the studies described were all performed >10 years ago, and since then the nature of the neonatal population requiring UACs has changed considerably, with increased survival of very premature infants. In this scenario, the safety of UFH prophylaxis with respect to IVH remains uncertain. This issue therefore remains incompletely resolved and will require further well-designed studies in those subgroups of neonates considered at highest risk of IVH.

The management of UAC-related thrombosis is controversial, and there are no comparative data that help define optimal therapy. The published literature consists of case reports that describe the use of various treatment modalities in individual cases. Therapeutic options, which have been reported, include the use of anticoagulation with heparin or LMWH, the use of thrombolytic therapy, and surgical thrombectomy.[318,331,332,346–351] It is clear that while these events present difficult management decisions, major aortic thrombosis is a potentially life-threatening event that requires prompt diagnosis and treatment.

Recommendations

1.22.1. To maintain UAC patency, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25 to 1 U/mL) [Grade 2A]**.**

1.22.2. For neonates with UAC-related thrombosis, we suggest therapy with UFH or LMWH for at least 10 days (Grade 2C)**.**

1.22.3. For neonates with UAC-related thrombosis, we recommend UAC removal (Grade 1B)**.**

Table 16—*Studies Reporting the Use of UFH for the Prevention of UAC-Associated Thrombosis: Clinical Description and Results (Section 1.22)**

Study/yr	Type of Publication	Interventions	Participants	Outcomes	Follow-up	Results
Barrington[342]/ 2006	Systematic review Cochrane review	Heparin infusion via UAC Heparin flushes Placebo	Newborn infants with UACs; both term and preterm infants Results from 6 RCTs	Catheter occlusion Aortic thrombosis Death IVH Hypertension Clinical ischemic events	Variable	The infusion of low-dose heparin improves catheter patency but has not been shown to prevent aortic thrombosis. The lowest dose of heparin that has been shown to be beneficial is 0.25 U/mL. Low-dose heparin administered in this way has not been shown to increase the incidence of IVH
Ankola and Atakent[340]/ 1993	RCT	Low-concentration heparin via UAC Heparin concentration 0.25 U/mL vs controls	30 term and preterm infants	Catheter occlusion, IVH, NEC, clinical ischemia, sepsis	8 d	UAC occlusion 2/15 heparin group; 11/15 in control group ($p = 0.001$); no difference in incidence of IVH
Bosque and Weaver[338]/1986	RCT	Heparin in infusate 1 U/mL Heparin in flush solution 1 U/mL	47 term and preterm infants	Catheter occlusion Ischemic complications Prothrombin time and aPTT	Not available	Reduced catheter occlusion with heparin in infusate; no prolongation of prothrombin time/ APTT; no difference in ischemic events
Chang et al[341]/ 1997	RCT	Heparin in infusate 1 U/mL Placebo	113 preterm infants < 31-wk gestation	IVH Coagulation parameters Prothrombin time aPTT Fibrinogen Antithrombin	7 d	IVH heparin group 35.8%; no-heparin group 31.5% No difference in coagulation parameters
David et al[337]/ 1981	RCT	Heparin 1 U/mL in infusate and flush No heparin	50 term and preterm infants	Clinical ischemia Aortic thrombosis Clotting studies Hematuria	24–72 h	Catheter occlusion reduced in heparin group: 13% vs 58% ($p < 0.005$); no difference in aortic thrombosis; no coagulation abnormalities

Table 16—*Continued*

Study/yr	Type of Publication	Interventions	Participants	Outcomes	Follow-up	Results
Horgan et al[339]/ 1987	RCT	Heparin via UAC 1 U/mL in infusate	111 infants	Frequency of catheter occlusion Aortic thrombosis by US following catheter removal Coagulation parameters Hypertension	Variable	16/34 thrombi heparin group vs 18/34 in control group; No. of occluded catheters was greater in the no-heparin group ($p < 0.05$); hypertension was greater in the no-heparin group
Rajani et al[336]/ 1979	RCT	Heparin 1 U/mL vs placebo	62 term and preterm infants	Clinical ischemia Catheter occlusion	7 d	Half-life of catheter function 7 d in heparin group vs just over 2 d in the no-heparin group ($p < 0.01$) UAC occlusion 4/32 in heparin group vs 19/30 in the no-heparin group ($p < 0.01$) No difference in coagulation parameters or ischemic events
Malloy and Cutter[345]/1995	Cohort study, retrospective	Heparin, variable exposure	862 very low-body-weight neonates	IVH	6 d	IVH more frequent in those exposed to a higher concentration of heparin: 83.5 U/kg/d vs 59.4 U/kg/d ($p < 0.001$)
Lesko et al[344]/ 1986	Retrospective, case-control study	Heparin exposure	Neonates with body weight < 2,000 g 66 cases with IVH 254 controls	IVH	Variable	Fourfold-increased risk of IVH in those receiving heparin OR, 3.9 (1.4–11)

*US = ultrasound. The methodologic quality description portion of this table can be found in the online verion of this article as a data supplement.

Table 17—*Studies Reporting Influence of High or Low Position for UAC on Frequency of UAC-Associated Thrombosis: Summary Evidence Profile (Section 1.23)**

Study/yr	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Barrington[352]/2006	Systematic review Cochrane review	Newborn infants both term and preterm with UACs 5 RCTs and nonrandomized study	UAC position: high or low	Ischemic events Aortic thrombosis IVH Mortality NEC Hypertension Hematuria	Variable and not always well defined in individual studies	High-placed catheters are associated with fewer vascular complications with no increase in adverse events; clinical ischemia less common with high catheters (RR 0.53, 95% CI 0.44–0.63) IVH not affected (1 trial) Death (5 trials) no significant difference (RR 1.11, 95% CI 0.88–1.4); NEC (RR 1.34, 95% CI 0.79–2.25) Duration of catheter usage (1 trial) improved with high catheters Hypertension, hematuria no difference Aortic thrombosis lower incidence with high catheters
Harris and Little[353]/1978	Nonrandomized study Alternate assignment	36 term and preterm infants	UAC position	Not stated but reports on ischemic events, NEC, and death.	Not stated; variable	Reduced incidence of ischemic events with high catheters Deaths NEC no difference
Kempley et al[357]/1993	RCT	308 term and preterm infants	UAC position	NEC Ischemic events Hypertension Hematuria Duration of catheter usability	Variable until hospital discharge	Reduced incidence of ischemic events with high catheters Longer catheter placement with high catheters No difference in mortality, NEC, hypertension, or hematuria
Mokrohisky et al[354]/1978	RCT	73 term and preterm infants	UAC position	Ischemic events Hypertension NEC Sepsis Aortic thrombosis (aortography at catheter removal) Hematuria	Not stated	Higher incidence of ischemic events with low catheters: 31/40 vs 13/33 ($p < 0.005$)
Stork et al[356]/1984	RCT (abstract only)	182 term and preterm infants	UAC position	Ischemic events Hypertension NEC	At least 30 d	Reduced ischemic events with high catheters.
Umbilical Artery Catheter Trial Study Group[358]/1992	RCT	970 preterm infants, body weight 500–1,500 g	UAC position	IVH Death Ischemic events Sepsis Seizures NEC	5 d, 120 d or discharge from hospital	Reduced clinical ischemic events; no significant differences in other parameters
Wesstrom et al[355]/1979	RCT	62 infants	UAC position	Aortic thrombosis by angiography or at autopsy	Variable	Reduced incidence of aortic thrombosis with high catheters (RR, 0.31, 95% CI, 0.11–0.86)

*See Table 20 for expansion of abbreviations.

Table 18—*Studies Reporting Anticoagulation for Sinovenous Thrombosis in Children: Clinical Description and Results (Section 1.29.1)***

Study/yr	Treatment	Patients, No.	Follow-up, yr	Thromboembolic Events, No.	Major Hemorrhage	Clinical Outcome/Radiologic Recanalization
deVeber et al[540]/1994, deVeber et al[396]/1998		150 14 received anticoagulation			Significant bleeding did not occur for any of the children receiving heparin	Mortality 16% in untreated, 14% in treated; poor neurologic outcome in 22% untreated, 0% in treated; the 2 deaths in children receiving anticoagulants were not due to bleeding nor extension of their cerebral venous thrombosis but to the severity of the underlying diagnosis
Uziel et al[397]/1995	Warfarin target INR 2–3 initially, then 1.5–2	3	18 mo, 10 mo, and 20 mo	None	1 who already had hemorrhage and severe thrombocytopenia had new hemorrhage requiring craniotomy and drainage	Good neurologic outcome in all 3
deVeber et al[396]/1998	Warfarin target INR 2–3	30	Median 1 yr (1 mo to 3.2 yr)	3 deaths (none anticoagulated) 2 recurrent CSVT, both anticoagulated (1 SLE on low-dose warfarin after LMWH 1 renal disease off anticoagulant treatment)	1 small hemorrhage into previously bland infarct in standard heparin group (asymptomatic)	Recanalization in majority of those rescanned regardless of treatment (17/19 anticoagulated; 3/4 not anticoagulated)
Holzmann et al[398]/1999		15 8 received anticoagulation				No deaths, minimal morbidity
Lancon et al[541]/1999	None	12		Not reported	None	Full recovery in 11/12; 1 with intractable status had residual hemiparesis
Lanthier et al[443]/2000	None	5		Recurrent CSVT in 1/5 with Crohn disease		
deVeber et al[26]/2001		160 85 received anticoagulation	Mean 1.6 yr (0.05–5.2 yr)	Recurrent thrombosis in 19/143 followed: 12 cerebral, 7 systemic in 5/61 (8%) neonates and 14/82 (17%) nonneonates	None died or had neurologic complications secondary to hemorrhage	Outcome: mortality, 12/143 (8%); neurologic morbidity, 54/143 (38%); recurrence not related to treatment
Carvalho et al[375]/2001	None	31	Median 5 yr (1 mo to 12 yr)	No data	5/19 neonates had hemorrhage on initial imaging; 1/12 older children had hemorrhagic conversion infarct	4 (2 neonates) died, none of CSVT (1 sepsis, 2 brain tumor, 1 leukemia); 27 survivors followed up: 11 normal outcome, 16 residual sequelae

Table 18—*Continued*

Study/yr	Treatment	Patients, No.	Follow-up, yr	Thromboembolic Events, No.	Major Hemorrhage	Clinical Outcome/Radiologic Recanalization
Kao et al[542]/2002	Thrombolysis or UFH or LMWH short term, LMWH, warfarin or aspirin subsequently	4		2 had peripheral venous thrombosis while not receiving antiplatelet or anticoagulant	No hemorrhage	Good neurologic outcome in all 4
Heller et al[373]/2003	LMWH: anti Xa at 2–4 h after dose 0.4 to 0.6 IU;' UFH: APTT onefold to twofold	205 49 excluded	Patency assessed using magnetic resonance at 6 mo	Data published in Kenet et al[403]/2007	Data published in Kenet et al[403]/2007	5 deaths, none anticoagulated Complete patency in 51/119 (43%), partial patency in 49/119 (41%), no patency in 19 (16%); no effect of anticoagulation on patency
Johnson et al[399]/2003	Warfarin target INR 2–3	17 15 received treatment	?	No recurrence or progression of thrombus on imaging	1 hemorrhage in tPA	No deaths, 16 no sequelae, 1 with learning disability who was anticoagulated had had surgery for empyema Of 15 patients rescanned (13 anticoagulated), 9 complete resolution, 5 partial
Barnes et al[386]/2004	Warfarin INR 2–3	16 10 received treatment	8 d to 5 yr	No recurrences	No hemorrhages reported	1 death following craniosynostosis surgery; 8/14 normal; 5 also had complete or partial recanalization, all of whom were anticoagulated; 2/3 normal also anticoagulated
De Schryver et al[400]/2004			Median 2 yr 6 mo (4 mo to 7 yr 4 mo)	No recurrences reported	No hemorrhages reported	3 (18%) died short term, 2 died later of malignancy, none anticoagulated; all 5 anticoagulated survived with normal intelligence quotient, but one had difficulty with writing; 5 survivors who were not anticoagulated also had normal intelligence quotient, but 1 had cognitive inefficiency and behavior problems

Table 18—*Continued*

Study/yr	Treatment	Patients, No.	Follow-up, yr	Thromboembolic Events, No.	Major Hemorrhage	Clinical Outcome/Radiologic Recanalization
Kenet et al[376]/2004	Warfarin target INR 2–3	46 38 (4 < 1 mo old, 32 > 1 mo old) 11 received long-term treatment	Median 4.1 yr	No recurrence of CSVT 1 DVT later	1 hemorrhage in a neonate treated with anticoagulation	Older children: 2 died not anticoagulated; neonates: 1 died after hemorrhage in the context of anticoagulation; older children: 8 sequelae; neonates: 2 mild sequelae
Sébire et al[387]/2005	Warfarin target INR 2–3	42 18 treated	Median 1 yr (6 mo to 10 yr)	2 recurrent SVT (1 congenital nephrotic initially anticoagulated, 1 ALL not anticoagulated) 3 systemic thrombosis	No hemorrhages in 8 presenting without hemorrhage No extension of hemorrhage in the 6 presenting with hemorrhage initially 1 fatal hemorrhage in anticoagulated patient with recurrent SVT and congenital nephrotic syndrome	5 (12%) died, 3 short term, 1 after recurrence, 1 with sequelae; 11 (26%) no neurologic or cognitive difficulties, 14 cognitive difficulties, 14 pseudotumour cerebri Survival with no cognitive sequelae associated with anticoagulation (OR, 3.64, 95% CI, 0.98–13.4; p = 0.05) Death less common in anticoagulated but not statistically significant (OR, 0.29; 95% CI, 0.03–2.89; p = 0.3)
Fitzgerald et al[379]/2006		42 (all < 1 mo old) 3 treated				6/29 (21%) normal development with no sequelae (1 anticoagulated); other 2 anticoagulated unavailable for follow-up
Bonduel et al[401]/2006	Warfarin target INR 2–3	38 (all > 1 mo old) 26 without hemorrhage LMWH, all oral anticoagulation 3 mo	Median 3.8 yr (3 mo–11.5 yr)	No recurrences on cessation of oral anticoagulation	No major hemorrhagic complications	7 deaths due to underlying condition, none secondary to CVT
Schobess et al[78]/2006	LMWH AntiXa at 2–4h 0.6–1.0	29			1 subdural bleed in patient receiving twice-daily LMWH	
Fluss et al[402]/2006		21	Mean 2.5 yr	Not reported but usually initial presentation or within 6 mo of presentation with steroid sensitive or dependent nephrotic syndrome	No hemorrhage reported	1 squint (resolved); 15 good, 1 death (PE), 1 cognitive sequelae (thalamic infarction)

Table 18—*Continued*

Study/yr	Treatment	Patients, No.	Follow-up, yr	Thromboembolic Events, No.	Major Hemorrhage	Clinical Outcome/Radiologic Recanalization
Kenet et al[403]/2007	Variable: UFH, LMWH, warfarin	396 250 treated	Median 24 mo (range 0.1–84 mo)	22 (5.7%) had recurrent venous thrombosis (13 cerebral; 3.4%) at median 6 mo after first CSVT. Recurrent venous thrombosis only occurred if first CSVT was diagnosed aged > 2 yr. No effect of underlying medical condition ($p = 0.2$). No anticoagulation in clinical risk situations and in children with idiopathic CSVT ($n = 3$); significantly associated with higher recurrence ($p < 0.001$). Anticoagulation administered did not influence thrombosis free survival ($p = 0.54$). Only 6/22 patients (27.3%) were receiving secondary antithrombotic treatment immediately prior to recurrent VT. 2/4 children receiving prophylactic LMWH therapy showed reduced 4-h anti-factor Xa activity levels (0.1 and 0.34 IU/mL, respectively) at the time of recurrence respectively. Follow-up venography ($n = 266$ children): compared with those with complete or partial patency of the initial vascular territory involved, children with no patency at follow-up venous imaging had a shorter thrombosis-free survival. In the multivariable Cox regression, no anticoagulation prior to relapse (hazard ratio, 8.8; 95% CI: 1.4–55.2; $p = 0.02$), and persistent vascular occlusion on follow-up venous imaging following first CSVT onset (hazard ratio, 6.3; 95% CI: 1.1–37.9; $p = 0.03$) were independently associated with recurrent venous thrombosis in this cohort	Hemorrhage on initial imaging in 33 (8%), in 23 of whom anticoagulation was not administered. In anticoagulated group, 1 fatal hemorrhage in anticoagulated neonate, 1 fatal hemorrhage in patient with recurrent SVT and congenital nephrotic syndrome (same patient as Sébire et al[387]/2005), 2 bleeds from puncture sites	12 (3%) deaths as previously reported in Heller et al[373]/2003, Kenet et al[376]/2004, Sébire et al[387]/2005; only 1 of those who died was anticoagulated

*SLE = systemic lupus erythematosus; ALL = acute lymphoblastic leukemia. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 19—*Studies Reporting Anticoagulation for AIS in Children: Clinical Description and Results (Section 1.31.1)***

Study Year	Treatment	Patients, No.	Follow-up	Thromboembolic Events, No.	Major Hemorrhage, No.	Outcome	Comments
DeVivo et al[543]/1977		54		11 (21%)			Cardiac disease, n = 4; sickle-cell disease, n = 3; systemic lupus erythematosus, n = 2; not given, n = 2
Dusser et al[545]/1986		41		4 (10%)			Moyamoya, n = 3; cardiac, n = 1
Riikonen and Santavuori[440]/1994		42		11 (25%)			Migrainous infarction, n = 4; focal cerebrovascular abnormalities, n = 1; unexplained stroke, n = 2; MELAS, n = 2; other, n = 2
Mancini et al[441]/1997		35		4 (11%)			Sickle-cell disease, n = 1; homocystinuria, n = 1; Williams syndrome, n = 1; HIV infection, n = 1
Abram et al[442]/1996		41		7 (17%)			Moyamoya, n = 3; not given, n = 4
Lanthier et al[443]/2000		46; all > 1 mo old		Recurrence in 2/34 (6%) with 0 or 1 risk factor but in 5/12 (42%) with 2 or more risk factors			
deVeber et al[546]/2000		99		Not discussed	Not discussed	Antithrombotic treatment predictive of poor outcome (p = 0.04)	
Chabrier et al[444]/2000		59	Mean 30 mo	13 (22%); 1 or more recurrences, 2 mo-5 yr after first Dissection (1/12, 8% despite anticoagulation) TCA (4/15, 27% despite aspirin) Cardiac (1/7 aspirin) Systemic disease (3/8) Moyamoya (3/4) Except in TCA, new strokes occur up to 5 yr after the first event		No information on deaths	Not clear whether treatment reduced risk of recurrence

Table 19—*Continued*

Study Year	Treatment	Patients, No.	Follow-up	Thromboembolic Events, No.	Major Hemorrhage, No.	Outcome	Comments
De Schryver et al[445]/2000		37	Mean 7.1 yr (median 7 y 93 mo to 20 yr)	2 strokes, 8 TIAs, 9 seizures	None	4 deaths, mean 4.5 yr; all of underlying disease (no deaths associated with recurrence)	Not clear whether there is overlap between outcomes (*eg*: some of those with seizures also had TIAs and/or died)
Sträter et al[463]/2001		135; 49 aspirin, 86 LMWH	Mean 36 mo (8–48 mo)	13 recurrent strokes, 4 in aspirin, 9 in LMWH (enoxaparin, n = 7; dalteparin, n = 2) No difference between aspirin and LMWH study arms (OR, 1.3; 95% CI, 0.4–4.5; p = 0.76)	None	3/13 died after recurrence	
Burak et al[79]/2003	AntiXa not done	27	3–60 mo (mean 17 mo)	None documented	1 hemorrhagic conversion	2 with internal carotid artery clot had partial (n = 1) or complete (n = 1) recanalization; no progression thrombus	
Bowen et al[547]/2005		8; treatment			For LMWH: no major hemorrhage, 1 bleeding at puncture site, 1 epistaxis	6 (22%) normal, 9 (33%) mild impairment, 12 (44%) moderate/severe	
Steinlin et al[446]/2004		20; 18 with follow-up; no treatment	Mean 7 yr (1–15 yr)	3/18 (17%) recurred: 2 moyamoya, 1 polyarteritis		2/20 (10%) died; 10/16 of survivors followed up had hemisyndrome, but all survivors had some change dominance; 3 visual field defect; 13/16 neuropsychiatric	
Barnes et al[386]/2004		95; 28 treatment	1.6 yr (11 d-7.2 yr)	3 (3%) known to have recurred	None	14 died, 15 neurologically normal; no effect of antiplatelet/anticoagulation on outcome	Did not examine effect of treatment on recurrence risk
Chung and Wong[447]/2004		36	Median 8.7 yr (2- 12.4 yr)	4 (11%) recurred: 1 MELAS, 3 moyamoya	Treated?	5 died, 3 short term after hemorrhagic transformation	

Table 19—*Continued*

Study Year	Treatment	Patients, No.	Follow-up	Thromboembolic Events, No.	Major Hemorrhage, No.	Outcome	Comments
Brankovic-Sreckovic et al[426]/2004		36	Median 5 yr 5 mo (1–9 yr)	5 (14%), median 6 mo (5 d to 18 mo); 1 moyamoya, 1 homocystinuria, 3 cardiac embolism; all given aspirin 2–3 mg/kg after recurrence with no further recurrence; 2 cardiac: clinically silent stroke at time of presentation		Death after recurrence in patient with homocystinuria: 7 (19%) No residual deficit	
Salih et al[421]/2006		95/104 follow-up	Mean 40 m Median 33 m	6/72 (8%); older children recurred (4 moyamoya, 2 of whom had sickle-cell disease; 1 MELAS, 1 SWS); no neonate recurred		5/95 died during follow-up 6 of 90 (7%) survivors had no residual deficit	
Herguner et al[548]/2005		39	Mean 39 ± 24 mo (4–96 mo)	2 recurred: 1 with HOCM and protein S deficiency, 1 with nephritic syndrome			MRA in only 5, no results reported; many had underlying conditions associated with venous thrombosis
Aydinli et al[549]/2006		57	Mean 27 ± 33 mo (6–108 mo)	3 (5%), all in the untreated group		1 died of stroke complications	Not all had vascular imaging; few details in recurrences
Bonduel et al[401]/2006		112; all received treatment	92 follow-ups for median 4.8 yr (5 mo to 11.8 yr)	None receiving warfarin recurred; 4/84 (5%) on aspirin thrombotic progression and recurrence, then warfarin with no further recurrence	None	6 died short term, 2 (2%) of thrombosis and 4 from underlying disease 63 (68%) neurologic sequelae	
Soman et al[480]/2006		17; all received treatment	Mean 1.69 yr (1 mo-3 yr)	None	2 subdural hemorrhages (both also on aspirin, both had marked cerebral atrophy: 1 moyamoya, 1 progeria vasculopathy)		

Table 19—*Continued*

Study Year	Treatment	Patients, No.	Follow-up	Thromboembolic Events, No.	Major Hemorrhage, No.	Outcome	Comments
Ganesan et al[448]/2006		171		After adjusting for presence of vasculopathy, trend for reduction in risk of recurrence for aspirin (hazard ratio, 0.55; 95% CI, 0.26–1.16; p = 0.11) but not for anticoagulation (hazard ratio, 1.06; 95% CI, 0.45–2.59; p = 0.89)	Not documented	13 (6%) died, 2 of uncal herniation, 1 after hemorrhagic transformation, 1 short term of other causes, 4 at the time of clinical recurrence, and 5 later after censoring at the time of recurrence; no data on outcome	
Fullerton et al[422]/ 2007	32 aspirin 11 anticoagulation 6 both 46 none	92/97		4 TIAs, plus 15 recurrent strokes (11 within 6 mo, 2 within 6–12 mo, 2 > 6 mo) Treatment: 3/32 (9%) on aspirin, 3/11 (27%) anticoagulated, 0/6 on both, 9/46 (18%) on neither Treatment did not predict recurrence (p = 0.42, log-rank test) 52 had vascular imaging: 24 normal (no recurrence), 6 occlusion (no recurrence), 22 abnormal (2/3 had recurrence within 5 yr): 20 stenosis, 7 moyamoya, 2 vasculitis, 1 dissection	14 ischemic, 1 hemorrhagic	No data on outcome	

*HOCM = hypertrophic obstructive cardiomyopathy; TCA = transient cerebral arteriopathy; MELAS = mitochondrial myopathy encephalopathy lactic acidosis and stroke syndrome; MRA = magnetic resonance arteriography; SWS = Sturge Weber syndrome. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

Table 20—*Studies Reporting AIS Prevention Strategies in Children With Sickle-Cell Anemia: Clinical Description and Results (Section 1.31.3)**

Study/yr	Intervention/Control	Inclusion/Exclusion	Trt-target Hb, g/dL	Trt-target HbS%	Patients, No.	Follow-up	Thromboembolic Events, No.	Comments
Portnoy and Herion[451]/1972	None						20%	
Wood[453]/1978	None				86		60%	Stroke not defined
Moohr et al[455]/1982	None, n = 14 Treatment, n = 14, 2–3 wk to Hb > 13 and HbS < 10% Stop treatment, n = 9 (2 had second strokes after 2–48 mo)		> 13	< 10	17 + 12		13 (92%) by 48 mo; 6 died, 1 (noncompliant) 2–48 mo (p = 0.001, Gehan) 2 had second stroke when off treatment: 2 mo, 3 mo; the rest were followed up 9–44 mo	Stroke defined as clinical acute hemiplegia No parenchymal or structural imaging
Balkaran et al[456]/1992	None				13		6 (47%) recurrent event	
Sarnaik et al[550]/1979	Transfusion	Sickle-cell disease and stroke, 12 of whom had had recurrence			27	3 yr (1–9 yr)	25 no further events; 1 brief TIA at HbS 48%; 1 recurrent stroke 26 wk after last treatment	
Wilimas et al[454]/1980	Transfusion, HbS < 20% for 1–2 yr, 10 then stopped			< 20	12; arteriography normal in 2, abnormal in 10		7/10 patients who stopped transfusion had recurrent stroke; Arteriography did not improve in any	Small numbers
Russell et al[457]/1984	4 patients not transfused; remainder: if arteriography abnormal, transfusion at 3–4 wk interval: Hb > 8–10 g/dL, HbS < 30%		> 8–10	< 30	34 SS, 1 SC		3/4 patients with multiple arteries affected and not transfused had recurrence; Transfusion to HbS < 30% reduced recurrence from 90 to 10% in patients with multiple arteries abnormal	Well-characterized patients Intervention clear End point mixed No repeat imaging Not generalizable beyond patients with multiple vessel abnormalities

Table 20—*Continued*

Study/yr	Intervention/Control	Inclusion/Exclusion	Trt-target Hb, g/dL	Trt-target HbS%	Patients, No.	Follow-up	Thromboembolic Events, No.	Comments
Wang et al[551]/1991	Transfusion HbS < 30% for 5–12y (median 9.5y); then stop.			< 30	10		5/10 recurrent stroke 3 mild ischemic same territory 2 massive hemorrhage, 1 C/L 1/10 died 3/10 declined further treatment	Small numbers All cardiovascular disease developing moyamoya
Cohen[552]/1992	Transfusion to HbS 50%			< 50	15		2 hemorrhages but at HbS 30% No recurrent infarcts	No vascular imaging
de Montalambert et al[553]/1993	Transfusion in 9; no transfusion in 10				19		No recurrence in 10 not transfused	Selection bias
Rana et al[554]/1997	9 transfusion every 3–6 wk to HbS < 30% for median 6 yr (1.5–16 yr), then stopped except in emergency; 3 never transfused			< 30			None > 80.75 yr old Hydroxyurea started in 6 patients for other indications; median, 4 yr (3/12 to 17 yr); later none	Patient treatment HU and transfusion for chest crisis, pain, anemia, surgery No vascular imaging Small series
Pegelow et al[555]/1995	SS, sickle B thal^{+}, 1 sickle B thal^{0} all transfused				57		Recurrent stroke, 4.2/100 patient-yr; 8 recurrent strokes (2 hemorrhage, both HbS < 30%, 6 infarcts, 5/6 HbS > 30%); recurrent TIA in 13: 6 HbS > 30%	Clinical definition adhered to Comparison with historical cohorts Vascular imaging not mandatory
Dobson et al[556]/2002	Transfusion to HbS < 30% for 2.2–20.4 yr			< 30			41% had recurrent strokes or TIA Recurrence more common in moyamoya	Clinical definition Vascular imaging
Scothorn et al[557]/2002	Transfusion				137		31/137 (23%) had at least 1 recurrent stroke; mean time to recurrence: 4 yr; recurrence 2.2/100 patient-yr; after 2 yr, recurrence continued only in those with no antecedent event	Clinical definition Vascular imaging not reported Retrospective HbS at time of stroke not available for all but at varying times after first stroke

Table 20—*Continued*

Study/yr	Intervention/Control	Inclusion/Exclusion	Trt-target Hb, g/dL	Trt-target HbS%	Patients, No.	Follow-up	Thromboembolic Events, No.	Comments
Hulbert et al[558]/2006	Transfusion				137		Patients receiving simple transfusion short term were 5 times (1.3–18.6) more likely to have a recurrent stroke than those who had exchange transfusion short term; patients receiving exchange transfusion long term were 0.61 times (0.42–0.88) less likely to have a recurrent stroke than those who had simple transfusion long term	Comparison of centers with all simple or all exchange geographic effects Retrospective Exchange increased as a proportion with time, other recent changes (*eg*, intensive care)
Ware et al[559]/1999	Hydroxyurea				25		3/16 (19%) patients had another stroke receiving hydroxyurea, mainly early before maximum HbS increase; 1 patient who was noncompliant with hydroxyurea as well as blood, had stroke 4 mo after stopping	Cohort Relatively short-term follow-up No vascular imaging Some patients did not have vasculopathy so had low risk of another stroke
Sumoza et al[560]/2002	Hydroxyurea				5		None had recurrent event over 42–112 mo	Cohort Small numbers No vascular imaging Arterial infarcts or white matter abnormality Venous infarcts
Ware et al[561]/2004	Hydroxyurea				35		Recurrence 3.6 per 100 patient-yr if blood transfusions overlapped until hydroxyurea dose adequate	

Table 20—*Continued*

Study/yr	Intervention/Control	Inclusion/Exclusion	Trt-target Hb, g/dL	Trt-target HbS%	Patients, No.	Follow-up	Thromboembolic Events, No.	Comments
Vernet et al[475]/1996	EDAS				4		No recurrence in MCA territories initially revascularized over 1.5 yr; recurrence in posterior territory	1 case Revascularization did not stop progression of disease
Mendelowitsch et al[476]/1997	EC-IC bypass						Reduction in glutamate and tissue acidosis; clinical improvement	1 case No long-term follow-up
Schmugge et al[477]/2001	EC-IC bypass; hydroxyurea 30 mg/kg/d						No recurrent events over 28 mo; vasculopathy stable	1 case
Fryer et al[478]/2003	EDAS				6	Mean 33 mo (28–43 mo)	1/6 had a further event ipsilateral to the EDAS 2 wk later	Small numbers No control group
Vermylen et al[472]/1998	HLA-identical stem-cell treatment				50		93% survival, 82% disease free	
Bernaudin[473]/1999	Bone marrow transplant from HLA-identical siblings						91% survival; 85% disease free; 1/16 (6%) recurrent stroke	
Walters et al[474]/2000	Stem-cell transplant, phenytoin, control of hypertension, magnesium supplements if low, Hb 9–11, platelets > 50,000				50 (48 SS)	57.9 mo (38–95 mo)	94% survival; 84% disease free; no new clinical strokes; MRI stable or improved in all	Short follow-up 1 died of cerebral hemorrhage, and 2 GVHD 9/43 (20%) had seizures soon after bone marrow treatment

*Trt-target = transfusion target; EDAS = encephaloduroarteriosynangiosis; EC-IC = extracerebral-intracerebral; Hb = hemoglobin; HbS = sickle hemoglobin; HLA = histocompatability locus antigen; MCA = middle cerebral artery; GVHD = graft vs host disease; SS = homozygous sickle-cell disease.

Table 21—*Studies Reporting AIS Prevention Strategies in Children With Sickle-Cell Anemia: Clinical Description and Results (Section 1.31.4)

Study/yr	Design	Inclusion/Exclusion	Patients, No.	Intervention/Control	End Point	Effectively Blinded Assessment of Outcome
Portnoy and Herion[451]/1972	Cohort			None	Recurrence	
Wood[453]/1978	Cohort		86	None	Recurrence, stroke	
Sarnaik et al[550]/1979	Cohort	Sickle-cell disease, stroke	27	Blood transfusion	Recurrence, stroke	No
Wilimas et al[454]/1980	Cohort		12; arteriography normal in 2, and abnormal in 10	Transfusion HbS < 20% for 1–2 yr, 10 then stopped	Recurrent stroke; improvement in arteriography	
Moohr et al[455]/1982	Cohort		17 + 12	None, n = 14; treatment, n = 14, 2–3 wk to Hb > 13 and HbS < 10%; stop treatment, n = 9 (2 had second strokes) after 2–48 mo	Recurrence, stroke	
Balkaran et al[456]/1992	Cohort		13	None	Recurrence	
Russell et al[457]/1984	Cohort	First stroke, age 18 mo–18 yr; arteriography abnormal, multiple stenosis/occlusion	34 SS, 1SC	4 patients not transfused; remainder: if arteriography abnormal, transfusion at 3–4 wk intervals: Hb > 8–10 g/dL, HbS < 30%	Recurrent "episode"; stroke; RIND; TIA	
Wang et al[551]/1991	Cohort	All cerebrovascular disease; 5 unilateral	10	Transfusion HbS < 30% for 5–12 yr (median 9.5 yr), then stop	Recurrent events	
Cohen[552]/1992	Cohort	Transfused to HbS < 30% for stroke for at least 4 yr	15	Transfusion to HbS 50%	Recurrent events	
de Montalambert et al[553]/1993	Cohort		19	Transfusion in 9; no transfusion in 10	Recurrent stroke	
Rana et al[554]/1997	Cohort	Infarct on CT in 8	12; 9 treatment	9 treatment every 3–6 wk to HbS < 30% for median 6 yr (1.5–16 yr), then stopped except in emergency; 3 never transfused	Recurrent events	
Pegelow et al[555]/1995	Multicenter cohort	Transfused patients, first stroke age 20 mo to 24 yr	57 SS, 2 SB^+, 1 SB^0	All treatment	Recurrent stroke with new infarct/hemorrhage; recurrent TIA	
Dobson et al[556]/2002	Single-center cohort	SS with stroke; age < 18 yr; 1980–1999		Transfusion to HbS < 30% for 2.2–20.4 yr	Recurrent CVA; stroke > 24 h, with/without imaging; TIA < 24 h, no imaging	
Scothorn et al[557]/2002	Multicenter cohort	First stroke 1.4–14 yr; all SS; stroke defined clinically and with imaging	137	All treatment	Recurrent stroke: acute neurologic syndrome; symptoms and signs > 24 h	

Table 21—*Continued*

Study/yr	Design	Inclusion/Exclusion	Patients, No.	Intervention/Control	End Point	Effectively Blinded Assessment of Outcome
Ware et al[559]/1999	Cohort	Transfused for stroke for at least 2 yr but problems: 2 allommunized, 4 autoantibodies, 1 stroke on treatment (n = 1), 11 ferritin, 5 noncompliant with blood treatment and/or chelation	25	Hydoxyurea 15 mg/kg/d escalated as tolerated up to maximum 30 mg/kg/d for 3–52 mo (median 22 mo)	Recurrent stroke	
Sumoza et al[560]/2002	Cohort	1 TIA, 4 stroke; treatment: hydroxyurea; 2 after second stroke; 3 first stroke (no treatment)	5	Hydroxyurea: 40 mg/kg/d in 4 patients, 30 mg/kg/d in 1 patient	Recurrent stroke or TIA	
Vernet et al[475]/1996		HbSS, moyamoya and multiple strokes	1	EDAS in 4 (initially MCA bilaterally, then posterior bilaterally after recurrence there)	Recurrent clinical events	
Mendelowitsch et al[476]/1997		HbSS and moyamoya	1	EC-IC bypass	Recurrent clinical events, glutamate (microdialysis)	
Schmugge et al[477]/2001		HbSD (Jehovah's witness) and multiple strokes	1	EC-IC bypass Hydroxyurea 30 mg/kg/d	Recurrent clinical events Progression vasculopathy on TCD	
Fryer et al[478]/2003	Cohort	Patients with sickle-cell disease and moyamoya	6	EDAS	Recurrent clinical event	
Vermylen et al[472]/1998	Cohort		50	HLA-identical stem-cell treaatment (bone marrow, n = 48; cord blood, n = 2)	Survival; disease-free survival	
Bernaudin[473]/1999	Cohort			Bone marrow transplant from HLA-identical siblings	Survival, absence of sickle-cell disease; recurrent stroke	
Walters et al[474]/2000	Cohort		50 (48 SS)	Stem-cell transplant c Px phenytoin, control of hypertension, Mg2+ supps if low, Hb 9–11, platelets > 50,000	Clinical stroke; progression of silent infarction on MRI	

*CVA = cerebrovascular accident; RIND = reversible ischemic neurologic deficit; see Table 26 for expansion of other abbreviations.

1.22.4 For neonates with UAC-related thrombosis with potentially life-, limb-, or organ-threatening symptoms, we suggest thrombolysis with tPa. When thrombolysis is contraindicated, we suggest surgical thrombectomy (Grade 2C)**.**

1.23 UAC-Related Thrombosis: Effect of Catheter Location

Background: There are two options for the positioning of a UAC tip, which are routinely described as high or low. The high position is at the level of the T6-T9 thoracic vertebral bodies. In this position, the catheter tip is placed above the celiac axis, superior mesenteric artery, and the renal arterie,s and is therefore essentially lies above the diaphragm. The low position is at the level of the L3-L4 lumbar vertebral bodies, and the position is therefore below these major vessels but above the aortic bifurcation. It has been controversial to what extent the position of the catheter tip influences complications related to UAC placement, including the development of thrombotic problems.

Evidence: A review that included five RCTs and one additional nonrandomized study has addressed differences in outcomes between high-UAC and low-UAC placement in both term and preterm infants.[352] This review[353–357] (Table 17) reported outcomes varied to some extent between studies but included clinical ischemic events, aortic thrombosis, duration of catheter placement, IVH, mortality, NEC, hypertension, and hematuria.

Clinical ischemic events were significantly less common with high catheter position (RR, 0.53; 95% CI, 0.44–0.63). Two studies reported the incidence of aortic thrombosis following catheter removal as defined by angiography.[354,355] Although Wesstom et al[355] noted a lower incidence of aortic thrombosis with high-placed catheters (RR, 0.31; 95% CI, 0.11–0.86), this effect was not observed by Mokrohisky et al[354] (RR, 1.17; 95% CI, 0.94–1.44). However, not all infants in the latter study underwent angiography. Duration of catheter patency was only reported in one study and was lower in the high catheter group, which is potentially in keeping with the lower incidence of ischemic events.[357] No differences were observed in mortality or in the incidence of IVH, NEC, or hypertension.[353–358]

The results of these studies certainly appear to favor the use of high UAC placement in terms of the potential reduction in ischemic events. However, four of six of these studies were published prior to 1985, and may not altogether reflect current neonatal intensive care populations and treatment practices. In addition, despite the randomized nature of these studies, a number of methodologic problems with their design and analysis can be identified that could bias results.

Recommendation

1.23 We suggest UAC placement in a high position rather than a low position (Grade 2B)**.**

1.24 Neonatal Aortic Thrombosis: Spontaneous

Background: Non–UAC-associated, or spontaneous aortic thrombosis, is a rare event. While some cases appear to be idiopathic, others have been associated with putative risk factors. Reported clinical risk factors include dehydration, polycythaemia, and viral infections.[359–361] In addition, a number of cases have been reported in association with underlying prothrombotic defects, particularly type 1 antithrombin deficiency and the presence of antiphospholipid antibodies of maternal origin.[350,362–365] Many published cases have evidence of extensive thrombosis involving either the abdominal or thoracic aorta, the latter sometimes mimicking coarctation at presentation.[366] The outcome of these events is variable, but overall mortality appears to be relatively high.

Evidence: As with UAC-related aortic thrombosis, optimal therapy cannot be defined from existing data. Options which have been used and are considered appropriate include anticoagulation, thrombolytic therapy, and surgery.[359,365–367] Treatment should be individualized based of the extent of thrombosis and the urgency of the clinical situation, taking into account potential contraindications to specific treatment options, particularly the risk of bleeding associated with the use of anticoagulant and thrombolytic agents. The management of spontaneous aortic thrombosis should be the same as those for UAC-related TE**.**

1.25 Primary Prophylaxis for Venous Access Related to Hemodialysis

CVLs and fistulas are frequently used to provide venous access for children during hemodialysis. There are two RCTs that address thromboprophylaxis for CVLs, but none are specific to hemodialysis patients.[8,313] Results of the studies were discussed above, and none showed efficacy of therapy compared to no therapy. Pediatric hemodialysis patients may be at increased risk from CVL-related DVT due to the usually large-bore catheters used, and the fluid shifts associated with intermittent dialysis. This patient population re-

quires specific study to determine the role of primary thromboprophylaxis.

Recommendation

1.25 In patients undergoing hemodialysis, we suggest against routine use of VKAs or LMWH for prevention of thrombosis related to CVLs or fistulas (Grade 2C)**.**

1.26 Use of UFH or LMWH for Hemodialysis

Hemodialysis is one of the treatment choices for children with chronic renal failure until renal transplant is available. There are substantial data in adults with respect to the benefit of using either UFH or LMWH to maintain circuit patency during hemodialysis. There are no studies in children.[368]

Recommendation

1.26 We suggest the use of UFH or LMWH in hemodialysis (Grade 2C)**.**

1.27 Kawasaki Disease

During the acute phase, Kawasaki disease may cause medium-vessel and large-vessel arteritis, arterial aneurysms, valvulitis, and myocarditis. 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.[369] Kawasaki disease is the leading cause of acquired heart disease in children in North America. 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 have coronary aneurysms is aimed at preventing myocardial ischemia or infarction.[369]

Initial Treatment: In patients with Kawasaki disease, aspirin is initially given in high doses (80 to 100 mg/kg/d during the acute phase, for up to 14 days) as an antiinflammatory agent, then in lower doses as an antiplatelet agent (3 to 5 mg/kg/d for 6 to 8 weeks) to prevent coronary aneurysm thrombosis and subsequent infarction (the major cause of death in patients with Kawasaki disease).[369] Because concomitant use of ibuprofen or other nonsteroidal antiinflammatory drugs may interfere with the effectiveness of aspirin, these agents should be avoided.[370]

Based on a large multicenter RCT, high-dose IV gamma globulin plus aspirin is significantly better compared to aspirin alone to reduce the prevalence of coronary artery abnormalities when administered early in the course of Kawasaki syndrome. Seven weeks after initiating therapy, coronary artery abnormalities were present in 14 of 79 children (18%) in the aspirin group, compared to only 3 of 79 (4%) in the gamma globulin plus aspirin group ($p = 0.005$).[371] Methylprednisolone in the acute phase has been shown not to be beneficial in a recent well-designed RCT.[372]

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.[141] These findings suggest that treatment with abciximab may promote vascular remodeling in this population and warrants further study.

Prevention of Thrombosis in Patients With Coronary Artery Disease: Because no prospective data exist to guide clinicians in choosing an optimal regimen for the prevention of thrombosis in Kawasaki disease patients 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.[369] 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.[369]

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.[369] 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.[369] Some physicians substitute a therapeutic dose of LMWH for warfarin.[369]

Treatment of Coronary Artery Thrombosis: Because no studies have been performed in children, the treatment of infants and children with coronary thrombosis is derived from studies in adults with acute coronary syndromes.[369]

Recommendations

1.27.1. In children with Kawasaki disease, we recommend aspirin in high doses (80 to 100 mg/kg/d during the short-term phase, for up to 14 days) as an antiinflammatory agent, then in

lower doses (1 to 5 mg/kg/d for 6 to 8 weeks) as an antiplatelet agent (Grade 1B).

1.27.2. In children with Kawasaki disease, we suggest against concomitant use of ibuprofen or other nonsteroidal antiinflammatory drugs during aspirin therapy (Grade 2C).

1.27.3. In children with Kawasaki disease, we recommend IV gamma globulin (2 g/kg, single dose) within 10 days of the onset of symptoms (Grade 1A).

1.27.4. In children with giant coronary aneurysms following Kawasaki disease, we suggest warfarin (target INR, 2.5; INR range, 2.0 to 3.0) in addition to therapy with low-dose aspirin be given as primary thromboprophylaxis (Grade 2C).

1.28 Neonatal Sinovenous Thrombosis

Background: The venous drainage of the brain occurs through a network of cerebral sinuses and veins. The walls of the cerebral sinuses are dural sleeves that attach along cranial suture lines. Cerebral sinuses lack valves. Cortical and deep cerebral veins carry blood from the brain into the sinuses, and blood flows out from there via the jugular veins. In cerebral sinovenous thrombosis (CSVT), "outflow" obstruction causes venous hypertension within the brain tissue, leading to generalized or focal cerebral edema and elevated tissue hydrostatic pressure. When regional tissue pressure exceeds arterial inflow pressure, zones of infarction, which may be hemorrhagic, ensue. Thrombosis within the superior sagittal sinus or obstruction of its outflow compromises cerebrospinal fluid absorption through the arachnoid granulations resulting in diffuse cerebral swelling, communicating hydrocephalus, and chronic pseudotumor cerebri (benign intracranial hypertension).

The incidence of CSVT in neonates is at least 2.6/100,000.[373] Neonates comprise 17 to 85% of pediatric CSVT patients.[26,373–376] Premature and term neonates are affected,[374] and there is a slight excess of boys. The incidence is almost certainly underestimated in neonates. Seizures and lethargy are frequent, and focal neurologic deficits are rare.[377,378] Venous infarcts are present in $> 50\%$, of which the majority are hemorrhagic.[26,379] 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 ($p = 0.03$).[380]

In neonates, the pathogenesis of CSVT includes mechanical distortion of the venous sinuses underlying the suture lines as the cranial bones overlap during birth.[26,377] At least half have of neonates have perinatal complications including diffuse hypoxic injury and others.[26,379] Genetic thrombophilias are also risk factors. Postnatal risk factors include meningitis, dehydration, congenital heart disease, and extracorporeal membrane oxygenation. Multiple maternal, neonatal, perinatal, or prothrombotic factors are present in over half of neonates with CSVT.[380]

Reported outcomes after neonatal CSVT include death in 7% and neurologic impairments in 36 to 79% of survivors.[26,379] Adverse neurologic outcomes include cognitive and motor deficits and in 20 to 40%, and epilepsy.[375] The presence of infarcts at diagnosis and perinatal complications predict worse outcome.[381,382]

While overt recurrent CSVT is rare in neonates, propagation of the initial thrombus after diagnosis of CVT is a concern. A cohort study reported asymptomatic propagation in the first week after diagnosis in 11 of 44 neonates (25%) treated without anticoagulation.[383]

Treatment includes anticoagulation, usually with LMWH in the absence of hemorrhage, although this is controversial. The optimal dose and duration of anticoagulant treatment are not known. However, neonates clearly 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.[383] Therefore, one approach is to assess for recanalization at 6 weeks and if complete stop anticoagulants, or if incomplete continue for an additional 6 weeks (3 months of anticoagulation) then stop. Early neurosurgical intervention may be necessary for even mild ventriculomegaly due to obstructive hydrocephalus. In neonatal CSVT, the brain is already experiencing elevated tissue pressure from venous obstruction and in combination with expanding ventricles cerebral perfusion may be compromised.

Evidence: There are no randomized trials; however, data on the safety of anticoagulation in neonates with CSVT are available.[26,373,379] Just over one third of neonates in the series of deVeber et al[26] received antithrombotic therapy, and no fatal complications of treatment were observed. In a consecutive cohort treatment safety study utilizing standardized protocols for anticoagulation of neonatal CSVT, bleeding occurred in 3 of 37 treated neonates (8%) but was not fatal in any.[383]

Recommendations

1.28.1. For neonates with CSVT without significant ICH, we suggest anticoagulation, initially

with UFH, or LMWH and subsequently with LMWH or VKA for a minimum of 6 weeks, and no longer than 3 months (Grade 2C).

1.28.2. For children with CSVT with significant hemorrhage, we suggest radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus propagation is noted (Grade 2C).

1.29 Childhood CSVT

Background: The estimated incidence of pediatric CSVT is 0.6 per 100,000 children per year, with > 40% occurring in neonates.[26] This remains a minimum estimate because there is difficulty in making the diagnosis. In contrast to arterial ischemic stroke (AIS), the clinical manifestations of CSVT may develop very gradually over days or weeks. Most infants and children present only with seizures, headaches, or altered mental status; however, focal neurologic deficits representing focal venous infarction also occur. At presentation, diffuse cerebral swelling (pseudotumor cerebri) is common[384]; and hydrocephalus, either communicating or obstructive, related to IVH, may overshadow the clinical picture.

Radiographic diagnosis of CSVT requires imaging of the thrombus within cerebral sinuses and veins because nearly half of children have normal-appearing brain parenchyma and the location and characteristics of venous infarction are very nonspecific. Plain CT and MRI brain scans may show thrombus as a linear region of altered signal within venous sinus channels.[385] CT with contrast enhancement can demonstrate a filling defect in venous channels including the "empty delta" sign.[26,385] However even contrast CT scans still frequently misses the diagnosis of CSVT.[26,377,386] Usually dedicated imaging of the cerebral venous system is required, including magnetic resonance venography or CT venography.[374,386,387] Since time-of-flight magnetic resonance venography is prone to flow artifacts, in equivocal cases high-resolution CT venography or digital subtraction angiography may be necessary.

Clinical outcomes after pediatric CSVT include death in 9 to 29% and neurologic deficits, headaches, and seizure disorders in over half of survivors.[26,387] Among neurologic deficits, cognitive and behavioral deficits are common and motor deficits less common. Predictors of poor outcome include presentation with venous infarcts or seizures[26] and, for death, presentation with coma.[387] 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 had recurrent cerebral or systemic thrombosis.[26]

In adults, recanalization of thrombus is maximal at 4 months after diagnosis during anticoagulation therapy[388]and is correlated with improved outcome.[389] In children, recanalization as early as 2 weeks after the onset of clinical symptoms has been reported.[390] Data from 77 consecutive children with CSVT who were prospectively studied at a single Canadian center (Toronto) are becoming available.[383] Approximately one third of children have achieved recanalization at 3 months, and nearly half have done so by 6 months after diagnosis. Propagation of the thrombus in the initial 5 days after diagnosis of CSVT was observed in over one third when initial anticoagulation was withheld. Propagation was asymptomatic in half and associated with new venous infarcts in 40%. Among 50 children receiving anticoagulant treatment, new or increased ICH was observed in 3 children (5%) and was nonfatal in all.

Anticoagulant therapy is routinely provided in many centers. In children with CSVT and ICH anticoagulation is often withheld, despite an absence of evidence of risk of extension of hemorrhage. In adults with CSVT and hemorrhage, available evidence suggests that the benefit of anticoagulation still outweighs the risk.[391–393] Treatment also 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.

Evidence: There are currently no randomized trials in the children (Table 18). Four randomized placebo-controlled trials of heparin in adults with CSVT have shown a trend or statistically significant benefit for heparin.[391,392,394,395] A Cochrane meta-analysis including results from the two highest-quality trials[391,392] found a nonstatistically significant benefit for heparin in preventing death or dependency (RR, 0.46; 95% CI, 0.16–1.31). In a *post hoc* sensitivity analysis including data from the Nagaraja and Maiti trials (Nagaraja 1995; Maiti 1997), the pooled RR for death was 0.33 (95% CI, 0.14–0.78), a highly significant benefit. The review concluded that anticoagulant treatment should probably be provided.

For pediatric CSVT, data supporting anticoagulant treatment include literature analysis, nonrandomized treatment studies, and safety studies. A pooled combined outcome data from 150 cases of pediatric CSVT published between 1980 and 1996 reported that among 136 who were not anticoagulated, the frequency of death was 16% and of poor neurologic outcome in 22% (combined poor outcome 36.5%). Among 14 treated children, the mortality rate was 14% and poor neurologic outcome zero (combined poor outcome 14%).[396] In the series of Sébire et

al[387], survival with no cognitive sequelae was associated with anticoagulation (OR, 3.64; 95% CI, 0.98–13.4; p = 0.05); death was less common in anticoagulated patients, but this was not statistically significant (OR, 0.29, 95% CI, 0.03–2.89; p = 0.3). Safety studies are available for anticoagulation in pediatric CSVT. In a prospective cohort study of anticoagulant therapy in 30 children with CSVT from 1992 to 1996, the mortality rate was 3/8 in untreated cildren compared to 0/22 in treated children. Single-center and small multicenter series in children[26,78,373,376,386,387,396–403] have shown that IV unfractionated and subcutaneous LMWH can be used safely in children, provided that there is close attention to detail, particularly in terms of monitoring aPPT for UFH or anti-FXa levels for LMWH. Hemorrhage is uncommon in anticoagulated patients in all series, may be treated with craniotomy and drainage, and is rarely fatal.

In a recent study[403] 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 recurrence ($p < 0.001$). 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 = 0.54).

Evidence regarding thrombolysis,[404–407] mechanical dissolution of clots, thrombectomy,[408] and surgical decompression[409,410] is confined to case reports[411] 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.[404–406] A nonrandomized study comparing UK thrombolysis with heparin in adults suggested better functional outcome for the thrombolyzed patients but higher risk of hemorrhage.[407]

Follow-up: As pseudotumor cerebri,[384,387] with its associated risk of visual failure undetected by the patient or parent, and otitic hydrocephalus have been reported after CSVT, there is a good case for neurology and/or ophthalmology follow-up in the first year. Persistent headache, nausea, or vomiting (particularly if nocturnal or early morning) mandate further neuroimaging to exclude hydrocephalus, which may need shunting. Pseudotumour cerebri may respond to treatment with steroids or acetazolamide or may require lumboperitoneal shunting. Cognitive and neurologic sequelae have also been reported and may require rehabilitation and longer term therapy.[382,400,412] Occasionally, patients with cryptogenic CSVT later manifest symptoms of an underlying disease, such as Behçet disease, so patients should be encouraged to report back if they have concerns after discharge. Nonrecanalization may be associated with a higher risk of recurrence[403] so repeat MRI and magnetic resonance venography may be justified.

Recommendations

1.29.1. 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)**.**

1.29.2. We suggest that if after 3 months of therapy there is incomplete radiologic recanalization of CSVT or ongoing symptoms, administration of a further 3 months of anticoagulation (Grade 2C)**.**

1.29.3. For children with CSVT with significant hemorrhage, we suggest radiologic monitoring of the thrombosis at 5 to 7 days. If thrombus propagation is noted at that time, we suggest anticoagulation (Grade 2C)**.**

1.29.4. We suggest children with CSVT in the context of a potentially recurrent risk factors (*eg*, nephrotic syndrome, L asparaginase therapy) should receive prophylactic anticoagulation at times of risk factor recurrence (Grade 2C)**.**

1.29.5. We suggest thrombolysis thrombectomy or surgical decompression only in children with severe CSVT, for whom there is no improvement with initial UFH therapy (Grade 2C)**.**

1.30 Neonatal AIS

Background: The diagnosis of neonatal AIS is very challenging. Patients present with seizures or lethargy. Focal clinical signs including hemiparesis are rare due to the immaturity of the brain. For radiographic diagnosis, cranial ultrasound may miss stroke. CT scan findings may be negative in small infarcts or within the initial 24 h. MRI with diffusion-weighted imaging is immediately diagnostic for AIS.[413]

The incidence of acute neonatal AIS is 1 in 4,000 live births.[414] Among children birth to age 18 years with AIS, over one fourth are neonates. It is evident that many more neonates have AIS, but the diagnosis is missed. A form of perinatal stroke with delayed diagnosis has been referred to as *presumed perinatal AIS*.[415] Such infants are neurologically "normal" in the first month of life, demonstrate early hand preference or other signs of hemiparesis typically

between 4 to 12 months of age, and have a CT scan showing a remote lesion consistent with prenatal or perinatal AIS.

Overt risk factors for may be evident, including congenital heart disease, meningitis, polycythemia, *in utero* cocaine exposure, or catheterization. However, frequently neonatal AIS occurs in a well-appearing infant with a normal pregnancy or labor history or only relatively minor complications. Embolization from the placenta via the patent foramen ovale is a likely mechanism, and prothrombotic disorders may be risk factors,[416,417] although this is controversial. Independent associations with neonatal AIS include primiparity, preeclampsia, intrauterine growth restriction, infertility, and chorioamnionitis.[418] The rate of neonatal AIS increased dramatically when multiple risk factors are present.

In a term infant with AIS, the typical distribution is the middle cerebral artery, more commonly left than right, and small artery infarcts can also occur. Hemorrhagic conversion is well recognized.

Outcomes: Neurologic deficits or epilepsy occur in 50 to 75% of survivors; sensorimotor deficits are most common.[415] Long-term follow-up is critical because later deficits with brain maturation often emerge. Radiographic features that predict development of later hemiparesis include concomitant involvement of hemisphere, posterior limb of the internal capsule, and basal ganglia (lenticulostriate vessels) irrespective of the size of the infarct, and involvement of cerebral peduncles seen on early diffusion weighted MRI imaging.[419]

Evidence: Recurrent stroke is very rare after AIS in the neonatal period.[420–422]

Recommendations

1.30.1. In the absence of a documented ongoing cardioembolic source, we recommend against anticoagulation or aspirin therapy for neonates with a first AIS (Grade 1B)**.**
1.30.2. In neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C)**.**

1.31 Childhood AIS

Background: The diagnosis of AIS in pediatric patients is complex. First, acute focal neurologic signs in childhood can be symptomatic of nonischemic pathologies including migraine and post-seizure Todd paresis that mimic stroke.[423] Second, radiographic findings of acute AIS can be delayed or missed on a CT scan and are also nonspecific. Focal regions of edema on CT or signal change on MRI due to venous infarction in CSVT, watershed or borderzone ischemia, reversible posterior leukoencephalopathy, and demyelinating lesions may mimic AIS.[423–425] Third, silent infarction (with no clinical symptoms) occurs in children with congenital heart disease and in up to 25% of children with sickle-cell anemia with MRI.[426,427]

Reported incidence rates for AIS vary between 2 to 13/100,000 children per year.[428–430] AIS peaks in the first year boys are at increased risk.[429] Mechanisms include cardiogenic embolism, cerebral vasculopathy, and *in situ* thrombosis. The conditions underlying these three mechanisms for stroke differ markedly in children compared with adults and 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. Congenital heart disease and related interventions (surgery or catheterization) can send cardiac embolism to cerebral arteries, or venous thrombi can reach cerebral arteries by "paradoxical embolism" through intracardiac defects. 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.[431] Dissection of craniocervical arteries underlies approximately 7% of childhood AIS.[432] 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. Recurrent sequential infarcts, some silent, are often 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. Hematologic and prothrombotic conditions include sickle-cell anemia, iron deficiency anemia,[424,433] hyperhomocysteinemia,[434–437] and elevated lipoprotein(a)[438] and inherited prothrombotic disorders.[438,439] Children with sickle-cell anemia can have stroke related to occlusion of small cerebral arteries or via the development of moyamoya.

Outcomes from childhood AIS include death in 5% and permanent cognitive or motor disability in 30 to 80%. Thus, although survival rates are significantly better than in adult stroke, children 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.

The overall risk of a recurrent AIS and TIA is 10 to 35%.[386,421,422,426,440–448] The recurrence risk increases in the presence of multiple stroke risk factors,[443] vasculopathy,[422,448,449] and genetic thrombophilia.[448] Children with vascular stenosis or moyamoya have a risk of recurrence as high as 66%.[422,448,450] Recurrence risk is greatest in the initial weeks and months following index AIS but persists for at least several years.[422,448] 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.[448] In sickle-cell anemia, reinfarction occurs in 7.06/100 patient-years.[427] In children with sickle-cell anemia receiving no treatment, recurrence is as high as 92%.[451–459]

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. The results of adult stroke trials testing antithrombotic treatments cannot be directly extrapolated to children due to different mechanisms for thrombus formation in adults with atherosclerosis (favoring platelet activation). Additionally immaturities in the child's coagulation system likely confer differing risks and benefits for antithrombotic agents in children compared with adults. Children with acute AIS are usually treated with initial heparin or LMWH for suspected or established conditions that theoretically favor fibrin clot formation, including cardiogenic embolism and acute arterial dissection. Alternatively antiplatelet treatment, typically aspirin, is provided. For children with moyamoya, direct and indirect revascularization procedures to bypass the stenotic and occluded arteries are available to increase regional cerebral blood flow in and reduce the risk of recurrence.[460,461] In cerebral vasculitis, immunosuppressive agents may be required.[462]

Evidence: To date, no RCTs of antithrombotic therapy have been conducted in children with stroke (Tables 19–21). Primary prevention of pediatric AIS is a feasible option only in children with conditions placing them at very high risk for AIS, including sickle-cell disease or congenital heart disease (*eg*, those who have undergone the Fontan procedure). Antiplatelet, anticoagulantm 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. One study assessing 135 consecutive children with AIS selected by physician preference for aspirin (5 mg/kg/d) or low-dose LMWH therapy reported no major complications and a 10% risk of recurrent stroke during therapy.[463] In another cohort study of 110 children with AIS, all children with cardiac conditions received warfarin and the remainder received aspirin; no major hemorrhagic complications occurred.[401]

In children with cerebral arterial dissection underlying AIS, the risk of recurrent strokes is approximately 12%.[432,464,465] Recurrence appears to be reduced by antithrombotic treatment[464] but is still observed during anticoagulation[432,464,465] or antiplatelet treatment.[464] In adults with cerebral artery dissection, a Cochrane metaanalysis of 327 pooled patients reported no significant difference for initial or recurrent stroke during anticoagulant treatment (5/414) vs antiplatelet treatment (6/157). The frequency of major hemorrhage was 0.5% during anticoagulation.[466] Subsequently data from a large dissection trial, the "SPONTADS" study,[467] has been published showing recurrent stroke in 2/71 receiving anticoagulation and 1/23 receiving aspirin treatment. If data from the 105 SPONTADS patients are added to those pooled in the Cochrane analysis, there is a strong trend showing benefit of anticoagulant therapy (7/485 stroke receiving treatment) over antiplatelet therapy (7/180 stroke receiving treatment; Fisher exact test, $p = 0.066$; RR, 1.88; 95% CI, 1.097–3.226).

Children with sickle-cell anemia and transcranial Doppler (TCD) velocities > 200 cm/s have a 40% risk of stroke over the next 3 years[468]; an RCT found significant reduction in risk by blood transfusion every 6 weeks to decrease seerum hemoglobin percentage to $< 30\%$ (STOP trial[469]). Patients should receive regular transfusions indefinitely because the risk of overt stroke or reversion to high-risk TCD increases when blood transfusions stop (STOP2[470]). Hydroxyurea may also reduce stroke risk in children with TCD velocities > 200 cm/s.[471] Overt stroke is twice as common in children with silent or covert infarction in the context of sickle-cell anemia,[427] and an RCT of blood transfusion to prevent progression of silent infarction in this group will report around 2012. Bone marrow transplantation[472–474] and revascularization for moyamoya[475–478] are additional options for selected patients; however, no RCTs have been completed for these therapies. For children with moyamoya, whether related to sickle-cell anemia or not, the safety of revascularization surgery was recently assessed.[479] Within 30 days of 271 craniotomies for pial synangiosis, 11 episodes of stroke (7.7% per patient; 4% per surgically treated hemisphere), and 3 severe TIAs were observed; however, long-term recurrent stroke was rare.

When aspirin therapy fails or is not tolerated in children with AIS, clopidogrel is frequently used. Risks of combination therapy with aspirin plus clopidogrel, however, were recently highlighted by a study of 17 children received clopidogrel (9 alone, 8 concurrent with aspirin) of whom 2 had subdural hemorrhages (both also on aspirin, both had marked cerebral atrophy: 1 moyamoya, 1 progeria vasculopathy).[480]

There are no data addressing the safety or efficacy of tPA in children with AIS, and the literature associating outcomes with this treatment consists solely of isolated case reports. A recent study reported tPA in children with cerebrovascular hospital discharge diagnostic codes at a frequency of 1.6%.[481] Although rarely feasible, older children with acute AIS may received a diagnosis within the time window for this treatment. There is no evidence to support tPA use in pediatric AIS, and tPA should not be used outside of the criteria for safe use established by RCTs in adults with stroke, which includes < 3 h from onset of symptoms for IV tPA and < 6 h from onset for intraarterial tPA.

Recommendations

1.31.1. For children with non–sickle-cell disease-related acute AIS, we recommend UFH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes have been excluded (Grade 1B)**.**

1.31.2. We recommend, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis (1 to 5 mg/kg/d) for a minimum of 2 years (Grade 1B)**.**

1.31.3. We suggest for AIS secondary to dissection or cardioembolic causes, anticoagulant therapy with LMWH or VKAs for at least 6 weeks, with ongoing treatment dependent on radiologic assessment (Grade 2C)**.**

1.31.4. We recommend against the use of thrombolysis (tPA) for AIS in children, outside of specific research protocols (Grade 1B)**.**

1.31.5. We recommend, for children with sickle-cell disease and AIS, IV hydration and exchange transfusion to reduce sickle hemoglobin levels to at least < 30% of total hemoglobin (Grade 1B)**.**

1.31.6. For children with sickle-cell disease and AIS, after initial exchange transfusion we recommend a long-term transfusion program (Grade 1B)**.**

1.31.7. In children with sickle-cell anemia who have transcranial Doppler velocities > 200 cm/s on screening, we recommend regular blood transfusion, which should be continued indefinitely (Grade 1B)**.**

1.31.8. We recommend that children with moyamoya be referred to an appropriate center for consideration of revascularization (Grade 1B)**.**

1.31.9. For children receiving aspirin who have recurrent AIS or TIAs, we suggest changing to clopidogrel or anticoagulant (LMWH or VKA) therapy (Grade 2C)**.**

1.32 Purpura Fulminans

Although rare, the most commonly reported homozygote prothrombotic disorder presenting during the newborn period is protein C deficiency. Homozygote protein S deficiency is even less common.[482–495] All patients presenting in the newborn period had undetectable levels of protein C (or protein S), whereas children with delayed presentation had detectable levels ranging between 0.05 and 0.20 U/mL.

The classical clinical presentation of homozygous protein C/protein S deficiency consists of cerebral or ophthalmic damage (or both) that occurred *in utero*, purpura fulminans within hours or days of birth and, on rare occasions, large-vessel thrombosis. 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.[496–498] The skin lesions start as small, ecchymotic sites 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. They also occur at pressure points, at sites of previous punctures, and at previously affected sites. Affected infants also have disseminated intravascular coagulation-related secondary hemorrhagic complications.

The diagnosis of infants with homozygous protein C/protein S deficiency is based on the appropriate clinical picture, a protein C/protein S level that is usually undetectable, heterozygous state 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 U/mL.

Initial Treatment: The diagnosis of homozygous protein C/protein S deficiency is usually unanticipated and made at the time of the clinical presentation. 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.[499]

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.[492] Plasma levels of protein S (which is entirely bound to C4b) were 23% at 2 h and 14% at 24 h, with an approximate half-life of 36 h.[500,501]

Doses of protein C concentrate have ranged from 20 to 60 U/kg. In one study, a dose of 60 U/kg resulted in peak protein C levels of > 0.60 U/mL.[492]

Replacement therapy should be continued until all of 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.

Long-term Therapy: 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. To avoid skin necrosis, when oral anticoagulation therapy is initiated, replacement therapy should be continued until the INR is therapeutic. The therapeutic range for the INR can be individualized to some extent but is usually between 2.5 and 4.5. 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.[492]

1.32.1. For neonates with homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of FFP q12h or protein C concentrate, when available, at 20 to 60 U/kg until the clinical lesions resolve (Grade 1B)**.**

1.32.2. We suggest long-term treatment with VKAs (Grade 2C)**, LMWH** (Grade 2C)**, protein C replacement** (Grade 1B)**, or liver transplantation** (Grade 2C)**.**

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References

1 Andrew M, Marzinotto V, Brooker LA, et al. Oral anticoagulation therapy in pediatric patients: a prospective study. Thromb Haemost 1994; 71:265–269
2 Monagle P, Michelson AD, Bovill E, et al. Antithrombotic therapy in children. Chest 2001; 119(suppl):344S–370S
3 Michelson AD, Bovill E, Monagle P, et al. Antithrombotic therapy in children. Chest 1998; 114(suppl):748S–769S
4 Ignjatovic V, Furmedge J, Newall F, et al. Age-related differences in heparin response. Thromb Res 2006; 118: 741–745
5 Ignjatovic V, Summerhayes R, Than J, et al. Therapeutic range for unfractionated heparin therapy: age-related differences in response in children. J Thromb Haemost 2006; 4:2280–2282
6 Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 1995; 108(suppl):506S–522S
7 Mitchell L, Abshire T, Hanna K, et al. Supranormalizing antithrombin levels are safe in children with acute lyphoblastic leukaemia treated with L-asparaginase: results of the PARKAA study. Blood 1999; 94:27a
8 Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. Thromb Res 2003; 109:101–108
9 Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. Thromb Res 2003; 109:85–92
10 Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood 1994; 83:1251–1257
11 Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. Pediatrics 1995; 96:939–943
12 Nowak-Gottl U, von Kries R, Gobel U. Neonatal symptomatic thromboembolism in Germany: two year survey. Arch Dis Child Fetal Neonatal Ed 1997; 76:F163–F167
13 van Ommen CH, Heijboer H, Buller HR, et al. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr 2001; 139:676–681
14 Gibson B, Chalmers E, Bolton-Maggs P, et al. Thrombembolism in childhood: a prospective 2 year BPSU study in the United Kingdom. Thromb Haemost 2003; 1(suppl 1):OC422
15 Massicotte MP, Dix D, Monagle P, et al. Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications. J Pediatr 1998; 133:770–776
16 Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. Pediatr Res 2000; 47:763–766

17 Kuhle S, Massicotte P, Chan A, et al. A case series of 72 neonates with renal vein thrombosis: data from the 1-800-NO-CLOTS Registry. Thromb Haemost 2004; 92:729–733
18 White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107:I4–I8
19 Newall F, Wallace T, Crock C, et al. Venous thromboembolic disease: a single-centre case series study. J Paediatr Child Health 2006; 42:803–807
20 Nowak-Gottl U, Heinecke A, von Kries R, et al. Thrombotic events revisited in children with acute lymphoblastic leukemia: impact of concomitant Escherichia coli asparaginase/prednisone administration. Thromb Res 2001; 103:165–172
21 Mitchell LG, Andrew M, Hanna K, et al. A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. Cancer 2003; 97:508–516
22 Monagle P, Barnes C, Ignjatovic V, et al. Developmental haemostasis: impact for clinical haemostasis laboratories. Thromb Haemost 2006; 95:362–372
23 Hibbert J, Howlett DC, Greenwood KL, et al. The ultrasound appearances of neonatal renal vein thrombosis. Br J Radiol 1997; 70:1191–1194
24 Cremin BJ, Davey H, Oleszczuk-Raszke K. Neonatal renal venous thrombosis: sequential ultrasonic appearances. Clin Radiol 1991; 44:52–55
25 Wright NB, Blanch G, Walkinshaw S, et al. Antenatal and neonatal renal vein thrombosis: new ultrasonic features with high frequency transducers. Pediatr Radiol 1996; 26:686–689
26 deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. N Engl J Med 2001; 345:417–423
27 Schmidt B, Andrew M. Neonatal thrombotic disease: prevention, diagnosis, and treatment. J Pediatr 1988; 113:407–410
28 Vailas GN, Brouillette RT, Scott JP, et al. Neonatal aortic thrombosis: recent experience. J Pediatr 1986; 109:101–108
29 Patronas NJ, Duda EE, Mirfakhraee M, et al. Superior sagittal sinus thrombosis diagnosed by computed tomography. Surg Neurol 1981; 15:11–14
30 Govaert P, Voet D, Achten E, et al. Noninvasive diagnosis of superior sagittal sinus thrombosis in a neonate. Am J Perinatol 1992; 9:201–204
31 Wiznitzer M, Masaryk TJ. Cerebrovascular abnormalities in pediatric stroke: assessment using parenchymal and angiographic magnetic resonance imaging. Ann Neurol 1991; 29:585–589
32 Krishnamoorthy KS, Soman TB, Takeoka M, et al. Diffusion-weighted imaging in neonatal cerebral infarction: clinical utility and follow-up. J Child Neurol 2000; 15:592–602
33 Male C, Chait P, Ginsberg JS, et al. Comparison of venography and ultrasound for the diagnosis of asymptomatic deep vein thrombosis in the upper body in children: results of the PARKAA study; prophylactic antithrombin replacement in kids with ALL treated with asparaginase. Thromb Haemost 2002; 87:593–598
34 Chait P, Dinyari M, Massicotte MP. The sensitivity and specificity of lineograms and ultrasound compared to venography for the diagnosis of central venous line related thrombosis in symptomatic children: the LUV study. Thromb Haemost 2001; 86(suppl):697
35 Shankar KR, Abernethy LJ, Das KS, et al. Magnetic resonance venography in assessing venous patency after multiple venous catheters. J Pediatr Surg 2002; 37:175–179
36 Stumper O, Sutherland GR, Geuskens R, et al. Transesophageal echocardiography in evaluation and management after a Fontan procedure. J Am Coll Cardiol 1991; 17:1152–1160
37 Fyfe DA, Kline CH, Sade RM, et al. Transesophageal echocardiography detects thrombus formation not identified by transthoracic echocardiography after the Fontan operation. J Am Coll Cardiol 1991; 18:1733–1737
38 Balling G, Vogt M, Kaemmerer H, et al. Intracardiac thrombus formation after the Fontan operation. J Thorac Cardiovasc Surg 2000; 119:745–752
39 Streif W, Monagle P, South M, et al. Spontaneous arterial thrombosis in children. J Pediatr 1999; 134:110–112
40 Dalen K, Day DL, Ascher NL, et al. Imaging of vascular complications after hepatic transplantation. AJR Am J Roentgenol 1988; 150:1285–1290
41 Kirchhof K, Jansen O, Sartor K. [CT angiography of the cerebral veins]. Rofo 1996; 165:232–237
42 Ozsvath RR, Casey SO, Lustrin ES, et al. Cerebral venography: comparison of CT and MR projection venography. AJR Am J Roentgenol 1997; 169:1699–1707
43 Hagen T, Bartylla K, Waziri A, et al. [Value of CT-angiography in diagnosis of cerebral sinus and venous thromboses]. Radiologe 1996; 36:859–866
44 Tsao PN, Lee WT, Peng SF, et al. Power Doppler ultrasound imaging in neonatal cerebral venous sinus thrombosis. Pediatr Neurol 1999; 21:652–655
45 van Ommen C, Monagle P, Peters M, et al. Pulmonary embolism in childhood. In: van Beek E, Oudkerk M, ten Cate JW, eds. Pulmonary embolism: epidemiology, diagnosis, and treatment. Oxford, UK: Blackwell Scientific, 1999
46 Newall F, Barnes C, Ignjatovic V, et al. Heparin-induced thrombocytopenia in children. J Paediatr Child Health 2003; 39:289–292
47 Hirsh J. Heparin. N Engl J Med 1991; 324:1565–1574
48 Ignjatovic V, Summerhayes R, Gan A, et al. Monitoring unfractionated heparin (UFH) therapy: which anti Factor Xa assay is appropriate? Thromb Res 2007; 120:347–351
49 Andrew M, Marzinotto V, Massicotte P, et al. Heparin therapy in pediatric patients: a prospective cohort study. Pediatr Res 1994; 35:78–83
50 Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. Ann Intern Med 1993; 119:874–881
51 Andrew M, deVeber G. Pediatric thromboembolism and stroke protocols. Hamilton, BC: Decker, 1997
52 McDonald MM, Jacobson LJ, Hay WW Jr, et al. Heparin clearance in the newborn. Pediatr Res 1981; 15:1015–1018
53 Turner Gomes S, Nitschmann E, Benson L, et al. Heparin is cleared faster in children with congenital heart disease than adults. J Am Coll Cardiol 1993;21:59a
54 Andrew M, Ofosu F, Schmidt B, et al. Heparin clearance and ex vivo recovery in newborn piglets and adult pigs. Thromb Res 1988; 52:517–527
55 Cruickshank MK, Levine MN, Hirsh J, et al. A standard heparin nomogram for the management of heparin therapy. Arch Intern Med 1991; 151:333–337
56 Kuhle S, Eulmesekian P, Kavanagh B, et al. A clinically significant incidence of bleeding in critically ill children receiving therapeutic doses of unfractionated heparin: a prospective cohort study. Haematologica 2007; 92:244–247
57 Avioli LV. Heparin-induced osteopenia: an appraisal. Adv Exp Med Biol 1975; 52:375–387
58 Schuster J, Meier-Ruge W, Egli F. [Pathology of osteopathy following heparin therapy]. Dtsch Med Wochenschr 1969; 94:2334–2338
59 Murphy MS, John PR, Mayer AD, et al. Heparin therapy and bone fractures. Lancet 1992; 340:1098

60 Sackler JP, Liu L. Heparin-induced osteoporosis. Br J Radiol 1973; 46:548–550
61 Severin T, Sutor AH. Heparin-induced thrombocytopenia in pediatrics. Semin Thromb Hemost 2001; 27:293–299
62 Potter C, Gill JC, Scott JP, et al. Heparin-induced thrombocytopenia in a child. J Pediatr 1992; 121:135–138
63 Klement D, Rammos S, von Kries R, et al. Heparin as a cause of thrombus progression: heparin-associated thrombocytopenia is an important differential diagnosis in paediatric patients even with normal platelet counts. Eur J Pediatr 1996; 155:11–14
64 Murdoch IA, Beattie RM, Silver DM. Heparin-induced thrombocytopenia in children. Acta Paediatr 1993; 82:495–497
65 Magnani HN. Heparin-induced thrombocytopenia (HIT): an overview of 230 patients treated with orgaran (Org 10172). Thromb Haemost 1993; 70:554–561
66 Spadone D. Heparin induced thrombocytopenia in the newborn. J Vasc Surg 1996; 15:306–312
67 Schmugge M, Risch L, Huber AR, et al. Heparin-induced thrombocytopenia-associated thrombosis in pediatric intensive care patients. Pediatrics 2002; 109:E10
68 Boshkov L, Ibsen L, Kirby A, et al. Heparin-induced thrombocytopenia (HIT) in neonates and very young children undergoing congenital cardiac surgery: a likely underrecognized complication with significant morbidity and mortality; report of 4 sequential cases. J Thromb Haemost 2003; 1(suppl 1):1494a
69 Etches W, Stang L, Conradi A. Incidence of heparin-induced thrombocytopenia in a pediatric intensive care population. Blood 2003; 102(suppl):536a
70 Klenner AF, Fusch C, Rakow A, et al. Benefit and risk of heparin for maintaining peripheral venous catheters in neonates: a placebo-controlled trial. J Pediatr 2003; 143: 741–745
71 Saxon BR, Black MD, Edgell D, et al. Pediatric heparin-induced thrombocytopenia: management with Danaparoid (orgaran). Ann Thorac Surg 1999; 68:1076–1078
72 Severin T, Zieger B, Sutor AH. Anticoagulation with recombinant hirudin and danaparoid sodium in pediatric patients. Semin Thromb Hemost 2002; 28:447–454
73 Risch L, Fischer JE, Herklotz R, et al. Heparin-induced thrombocytopenia in paediatrics: clinical characteristics, therapy and outcomes. Intensive Care Med 2004; 30:1615–1624
74 Klenner A. Heparin-induced thrombocytopenia in children. In: Warkentin T, Greinacher A, eds. Heparin-induced thrombocytopenia. 3rd ed. New York, NY: Marcel Dekker, 2004; 553–571
75 Hirsh J, Warkentin TE, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 1998;114(suppl):489S–510S
76 Dunaway KK, Gal P, Ransom JL. Use of enoxaparin in a preterm infant. Ann Pharmacother 2000; 34:1410–1413
77 Streif W, Goebel G, Chan AK, et al. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. Arch Dis Child Fetal Neonatal Ed 2003; 88:F365–F370
78 Schobess R, During C, Bidlingmaier C, et al. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open-label pilot study of once-daily versus twice-daily enoxaparin administration. Haematologica 2006; 91:1701–1704
79 Burak CR, Bowen MD, Barron TF. The use of enoxaparin in children with acute, nonhemorrhagic ischemic stroke. Pediatr Neurol 2003; 29:295–298
80 Elhasid R, Lanir N, Sharon R, et al. Prophylactic therapy with enoxaparin during L-asparaginase treatment in children with acute lymphoblastic leukemia. Blood Coagul Fibrinolysis 2001; 12:367–370
81 Bontadelli J, Moeller A, Schmugge M, et al. Use of enoxaparin in the treatment of catheter-related arterial thrombosis in infants with congenital heart disease. Cardiol Young 2006; 16:27
82 Dix D, Charpentier K, Sparling C, et al. Determining of trough anti-factor Xa levels in pediatric patients on low molecular weight heparin (LMWH). J Pediatr Hematol Oncol 1998; 20(suppl)
83 Dix D, Andrew M, Marzinotto V, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. J Pediatr 2000; 136:439–445
84 Revel-Vilk S, Sharathkumar A, Massicotte P, et al. Natural history of arterial and venous thrombosis in children treated with low molecular weight heparin: a longitudinal study by ultrasound. J Thromb Haemost 2004; 2:42–46
85 Chan AK, Berry LR, Monagle PT, et al. Decreased concentrations of heparinoids are required to inhibit thrombin generation in plasma from newborns and children compared to plasma from adults due to reduced thrombin potential. Thromb Haemost 2002; 87:606–613
86 Massicotte MP, Adams M, Leaker M, et al. A normogram to establish therapeutic levels of low molecular weight heparin (LMWH), clivarine in children requiring treatment for venous thromboembolism (VTE). Thromb Haemost 1997; 78(suppl):282
87 Nohe N, Flemmer A, Rumler R, et al. The low molecular weight heparin dalteparin for prophylaxis and therapy of thrombosis in childhood: a report on 48 cases. Eur J Pediatr 1999; 158(suppl 3):S134–S139
88 Kuhle S, Massicotte MP, Andrew M, et al. A dose-finding study of Tinzaparin in pediatric patients. Blood 2002;100: 279a
89 Massicotte P, Adams M, Marzinotto V, et al. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. J Pediatr 1996; 128:313–318
90 Crowther MA, Berry LR, Monagle PT, et al. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. Br J Haematol 2002; 116:178–186
91 Massonnet-Castel S, Pelissier E, Bara L, et al. Partial reversal of low molecular weight heparin (PK 10169) anti-Xa activity by protamine sulfate: *in vitro* and *in vivo* study during cardiac surgery with extracorporeal circulation. Haemostasis 1986; 16:139–146
92 Harenberg J, Wurzner B, Zimmermann R, et al. Bioavailability and antagonization of the low molecular weight heparin CY 216 in man. Thromb Res 1986; 44:549–554
93 van Ryn-McKenna J, Cai L, Ofosu FA, et al. Neutralization of enoxaparine-induced bleeding by protamine sulfate. Thromb Haemost 1990; 63:271–274
94 Thomas DP. Does low molecular weight heparin cause less bleeding? Thromb Haemost 1997; 78:1422–1425
95 Haroon Y, Shearer MJ, Rahim S, et al. The content of phylloquinone (vitamin K1) in human milk, cows' milk and infant formula foods determined by high-performance liquid chromatography. J Nutr 1982; 112:1105–1117
96 von Kries R, Shearer M, McCarthy PT, et al. Vitamin K1 content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K1 supplements given to the mother. Pediatr Res 1987; 22:513–517
97 Bonduel MM. Oral anticoagulation therapy in children. Thromb Res 2006; 118:85–94
98 Massicotte P, Leaker M, Marzinotto V, et al. Enhanced

thrombin regulation during warfarin therapy in children compared to adults. Thromb Haemost 1998; 80:570–574
99 Streif W, Andrew M, Marzinotto V, et al. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. Blood 1999; 94:3007–3014
100 Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1998; 114(suppl):445S–469S
101 Newall F, Savoia H, Campbell J, et al. Anticoagulation clinics for children achieve improved warfarin management. Thromb Res 2004; 114:5–9
102 Massicotte P, Marzinotto V, Vegh P, et al. Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor. J Pediatr 1995; 127:389–394
103 Nowatzke WL, Landt M, Smith C, et al. Whole blood international normalization ratio measurements in children using near-patient monitors. J Pediatr Hematol Oncol 2003; 25:33–37
104 Marzinotto V, Monagle P, Chan A, et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. Pediatr Cardiol 2000; 21:347–352
105 Newall F, Monagle P, Johnston L. Home INR monitoring of oral anticoagulant therapy in children using the CoaguChek S point-of-care monitor and a robust education program. Thromb Res 2006; 118:587–593
106 Newall F, Campbell J, Savoia H, et al. Incidence of major bleeding in a large paediatric cohort of patients requiring warfarin therapy. J Thromb Haemost 2005; 3:OR357
107 Taybi H, Capitanio MA. Tracheobronchial calcification: an observation in three children after mitral valve replacement and warfarin sodium therapy. Radiology 1990; 176:728–730
108 Ries M, Klinge J, Rauch R. Erfahrungen mit der antikoagulatientherapie bei 10 patienten an der Univ Kinderklinik Erlangen. In: Sutor AH, ed. Thrombosen im Kindersalter. Basel, Switzerland: Editiones Roche, 1992
109 Massicotte P, Julian J, Webber C, et al. Osteoporosis: a potential complication of long term warfarin therapy. Thromb Haemost 1999; 80(suppl):1333a
110 Barnes C, Newall F, Ignjatovic V, et al. Reduced bone density in children on long-term warfarin. Pediatr Res 2005; 57:578–581
111 Bolton-Maggs P, Brook L. The use of vitamin K for reversal of over-warfarinization in children. Br J Haematol 2002; 118:924
112 Wilhelm MJ, Schmid C, Kececioglu D, et al. Cardiopulmonary bypass in patients with heparin-induced thrombocytopenia using Org 10172. Ann Thorac Surg 1996; 61:920–924
113 Rajasekhar D, Kestin AS, Bednarek FJ, et al. Neonatal platelets are less reactive than adult platelets to physiological agonists in whole blood. Thromb Haemost 1994; 72:957–963
114 Rajasekhar D, Barnard MR, Bednarek FJ, et al. Platelet hyporeactivity in very low birth weight neonates. Thromb Haemost 1997; 77:1002–1007
115 Ts'ao CH, Green D, Schultz K. Function and ultrastructure of platelets of neonates: enhanced ristocetin aggregation of neonatal platelets. Br J Haematol 1976; 32:225–233
116 Katz JA, Moake JL, McPherson PD, et al. Relationship between human development and disappearance of unusually large von Willebrand factor multimers from plasma. Blood 1989; 73:1851–1858
117 Weinstein MJ, Blanchard R, Moake JL, et al. Fetal and neonatal von Willebrand factor (vWF) is unusually large and similar to the vWF in patients with thrombotic thrombocytopenic purpura. Br J Haematol 1989; 72:68–72
118 Andrew M, Vegh P, Johnston M, et al. Maturation of the hemostatic system during childhood. Blood 1992; 80:1998–2005
119 Sanders JM, Holtkamp CA, Buchanan GR. The bleeding time may be longer in children than in adults. Am J Pediatr Hematol Oncol 1990; 12:314–318
120 Aversa LA, Vazquez A, Penalver JA, et al. Bleeding time in normal children. J Pediatr Hematol Oncol 1995; 17:25–28
121 Kundu SK, Heilmann EJ, Sio R, et al. Characterization of an in vitro platelet function analyzer, PFA-100. Clin Appl Thromb/Hemost 1996; 2:241–249
122 Carcao MD, Blanchette VS, Dean JA, et al. The Platelet Function Analyzer (PFA-100): a novel *in-vitro* system for evaluation of primary haemostasis in children. Br J Haematol 1998; 101:70–73
123 Israels SJ, Cheang T, McMillan-Ward EM, et al. Evaluation of primary hemostasis in neonates with a new *in vitro* platelet function analyzer. J Pediatr 2001; 138:116–119
124 Roschitz B, Sudi K, Kostenberger M, et al. Shorter PFA-100 closure times in neonates than in adults: role of red cells, white cells, platelets and von Willebrand factor. Acta Paediatr 2001; 90:664–670
125 Homoncik M, Jilma B, Hergovich N, et al. Monitoring of aspirin (ASA) pharmacodynamics with the platelet function analyzer PFA-100. Thromb Haemost 2000; 83:316–321
126 Israels SJ, Michelson AD. Antiplatelet therapy in children. Thromb Res 2006; 118:75–83
127 Done AK, Yaffe SJ, Clayton JM. Aspirin dosage for infants and children. J Pediatr 1979; 95:617–625
128 Michelson AD. Platelet function testing in cardiovascular diseases. Circulation 2004; 110:e489–e493
129 Israels S, Rand M, Michelson A. Neonatal platelet function. Semin Thromb Hemost 2003; 29:363–371
130 Porter JD, Robinson PH, Glasgow JF, et al. Trends in the incidence of Reye's syndrome and the use of aspirin. Arch Dis Child 1990; 65:826–829
131 Remington PL, Shabino CL, McGee H, et al. Reye syndrome and juvenile rheumatoid arthritis in Michigan. Am J Dis Child 1985; 139:870–872
132 Starko KM, Ray CG, Dominguez LB, et al. Reye's syndrome and salicylate use. Pediatrics 1980; 66:859–864
133 Halpin TJ, Holtzhauer FJ, Campbell RJ, et al. Reye's syndrome and medication use. JAMA 1982; 248:687–691
134 Young RS, Torretti D, Williams RH, et al. Reye's syndrome associated with long-term aspirin therapy. JAMA 1984; 251:754–756
135 Baum J. Aspirin in the treatment of juvenile arthritis. Am J Med 1983; 74:10–15
136 el Makhlouf A, Friedli B, Oberhansli I, et al. Prosthetic heart valve replacement in children: results and follow-up of 273 patients. J Thorac Cardiovasc Surg 1987; 93:80–85
137 Solymar L, Rao PS, Mardini MK, et al. Prosthetic valves in children and adolescents. Am Heart J 1991; 121:557–568
138 LeBlanc JG, Sett SS, Vince DJ. Antiplatelet therapy in children with left-sided mechanical prostheses. Eur J Cardiothorac Surg 1993; 7:211–215
139 Li J, Berezny K, Yow E, et al. Optimal dose of clopidogrel for platelet inhibition in children: primary results of the PICOLO trial [abstract]. Circulation. 2006; 114:II450
140 Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. Circulation 1995; 92:2373–2380
141 Williams RV, Wilke VM, Tani LY, et al. Does Abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease? Pediatrics 2002; 109:E4
142 Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. Blood 1987; 70:165–172
143 Andrew M, Paes B, Johnston M. Development of the

hemostatic system in the neonate and young infant. Am J Pediatr Hematol Oncol 1990; 12:95–104
144 Reverdiau-Moalic P, Gruel Y, Delahousse B, et al. Comparative study of the fibrinolytic system in human fetuses and in pregnant women. Thromb Res 1991; 61:489–499
145 Corrigan JJ Jr, Sleeth JJ, Jeter M, et al. Newborn's fibrinolytic mechanism: components and plasmin generation. Am J Hematol 1989; 32:273–278
146 Andrew M, Brooker L, Leaker M, et al. Fibrin clot lysis by thrombolytic agents is impaired in newborns due to a low plasminogen concentration. Thromb Haemost 1992; 68: 325–330
147 Leaker M, Massicotte MP, Brooker LA, et al. Thrombolytic therapy in pediatric patients: a comprehensive review of the literature. Thromb Haemost 1996; 76:132–134
148 Important drug warning regarding the use of Abbokinase (urokinase). Rockville, MD: US Food and Drug Administration, Center for Drug Evaluation and Research, 1999; 208–1448
149 Gupta AA, Leaker M, Andrew M, et al. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. J Pediatr 2001; 139:682–688
150 Albisetti M. Thrombolytic therapy in children. Thromb Res 2006; 118:95–105
151 Newall F, Browne M, Savoia H, et al. Assessing the outcome of systemic tissue plasminogen activator for the management of venous and arterial thrombosis in paediatrics. J Pediatr Hematol Oncol 2007; 29:269–273
152 Zenz W, Muntean W, Beitzke A, et al. Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. Br Heart J 1993; 70:382–385
153 Bovill EG, Becker R, Tracy RP. Monitoring thrombolytic therapy. Prog Cardiovasc Dis 1992; 34:279–294
154 Wever ML, Liem KD, Geven WB, et al. Urokinase therapy in neonates with catheter related central venous thrombosis. Thromb Haemost 1995; 73:180–185
155 Gore JM, Sloan M, Price TR, et al. Intracerebral hemorrhage, cerebral infarction, and subdural hematoma after acute myocardial infarction and thrombolytic therapy in the Thrombolysis in Myocardial Infarction Study: Thrombolysis in Myocardial Infarction, Phase II, pilot and clinical trial. Circulation 1991; 83:448–459
156 Monagle P, Phelan E, Downie P, et al. Local thrombolytic therapy in children. Thromb Haemost 1997; 78(suppl):504
157 Kaufman SL, Martin LG, Gilarsky BP, et al. Urokinase thrombolysis using a multiple side hole multilumen infusion catheter. Cardiovasc Intervent Radiol 1991; 14:334–337
158 Zenz W, Arlt F, Sodia S, et al. Intracerebral hemorrhage during fibrinolytic therapy in children: a review of the literature of the last thirty years. Semin Thromb Hemost 1997; 23:321–332
159 Farnoux C, Camard O, Pinquier D, et al. Recombinant tissue-type plasminogen activator therapy of thrombosis in 16 neonates. J Pediatr 1998; 133:137–140
160 Khong PL, John PR. Technical aspects of insertion and removal of an inferior vena cava IVC filter for prophylactic treatment of pulmonary embolus. Pediatr Radiol 1997; 27:239–241
161 McBride WJ, Gadowski GR, Keller MS, et al. Pulmonary embolism in pediatric trauma patients. J Trauma 1994; 37:913–915
162 Williams S, Chait P, Temple M, et al. Vena cava filters in children: review of a single centre clinical experience over 17 years. Thromb Haemost 2003; 1:OC439
163 Coombs CJ, Richardson PW, Dowling GJ, et al. Brachial artery thrombosis in infants: an algorithm for limb salvage. Plast Reconstr Surg 2006; 117:1481–1488
164 Martinez-Ibanez V, Sanchez de Toledo J, De Diego M, et al. Wilms' tumours with intracaval involvement. Med Pediatr Oncol 1996; 26:268–271
165 Sarigul A, Farsak B, Koramaz I, et al. Postoperative graft thrombosis in Fontan procedure. Turk J Pediatr 2000; 42:80–83
166 Kokov LS, Korostelev AN, Grinko AN, et al. Recanalization and thrombectomy of internal anastomosis in a patient with tetralogy of Fallot using the AngioJet rheolytic catheter. Catheter Cardiovasc Interv 2001; 53:504–507
167 Ries M, Zenker M, Girisch M, et al. Percutaneous endovascular catheter aspiration thrombectomy of severe superior vena cava syndrome. Arch Dis Child Fetal Neonatal Ed 2002; 87:F64–F66
168 Lodge AJ, Jaggers J, Adams D, et al. Vascular control for resection of suprahepatic intracaval Wilms' tumor: technical considerations. J Pediatr Surg 2000; 35:1836–1837
169 David M, Andrew M. Venous thromboembolic complications in children. J Pediatr 1993; 123:337–346
170 Andrew M, Monagle P, Brooker LA. Epidemiology of venous thromboembolic events. In: Thromboembolic complications during infancy and childhood. Hamilton, BC: Decker, 2000
171 Tanke RB, van Megen R, Daniels O. Thrombus detection on central venous catheters in the neonatal intensive care unit. Angiology 1994; 45:477–480
172 Roy M, Turner Gomes S, Gill G. Incidence and diagnosis of neonatal thrombosis associated with umbilical venous catheters. Thromb Haemost 1997; 78:724
173 Vos LJ, Potocky V, Broker FH, et al. Splenic vein thrombosis with oesophageal varices: a late complication of umbilical vein catheterization. Ann Surg 1974; 180:152–156
174 Obladen M, Ernst D, Feist D, et al. Portal hypertension in children following neonatal umbilical disorders. J Perinat Med 1975; 3:101–104
175 van Ommen CH, Peters M. Venous thromboembolic disease in childhood. Semin Thromb Hemost 2003; 29:391–404
176 Nuss R, Hays T, Manco-Johnson M. Childhood thrombosis. Pediatrics 1995; 96:291–294
177 Andrew M, Marzinotto V, Pencharz P, et al. A cross-sectional study of catheter-related thrombosis in children receiving total parenteral nutrition at home. J Pediatr 1995; 126:358–363
178 Randolph AG, Cook DJ, Gonzales CA, et al. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. Chest 1998; 113:165–171
179 Krafte-Jacobs B, Sivit CJ, Mejia R, et al. Catheter-related thrombosis in critically ill children: comparison of catheters with and without heparin bonding. J Pediatr 1995; 126: 50–54
180 Derish MT, Smith DW, Frankel LR. Venous catheter thrombus formation and pulmonary embolism in children. Pediatr Pulmonol 1995; 20:349–354
181 Kuhle S, Koloshuk B, Marzinotto V, et al. A cross-sectional study evaluating post-thrombotic syndrome in children. Thromb Res 2003; 111:227–233
182 Wang M, Hays T, Balasa V, et al. Low-dose tissue plasminogen activator thrombolysis in children. J Pediatr Hematol Oncol 2003; 25:379–386
183 Schermer E, Streif W, Genser N, et al. [Thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) in 13 children: a case series]. Wien Klin Wochenschr 2000; 112: 927–933
184 Levy M, Benson LN, Burrows PE, et al. Tissue plasminogen

activator for the treatment of thromboembolism in infants and children. J Pediatr 1991; 118:467–472
185 Knofler R, Dinger J, Kabus M, et al. Thrombolytic therapy in children: clinical experiences with recombinant tissue-plasminogen activator. Semin Thromb Hemost 2001; 27: 169–174
186 Ryan CA, Andrew M. Failure of thrombolytic therapy in four children with extensive thromboses. Am J Dis Child 1992; 146:187–193
187 Mathur M, Desai N, Sharma J, et al. Management of a large organized intraatrial catheter-tip thrombus in a child with acquired immunodeficiency syndrome using escalating tissue plasminogen activator infusions. Pediatr Crit Care Med 2005; 6:79–82
188 Cesaro S, Paris M, Corro R, et al. Successful treatment of a catheter-related right atrial thrombosis with recombinant tissue plasminogen activator and heparin. Support Care Cancer 2002; 10:253–255
189 Levitas A, Zucker N, Zalzstein E, et al. Successful treatment of infective endocarditis with recombinant tissue plasminogen activator. J Pediatr 2003; 143:649–652
190 Martinez-Tallo E, Campo F, Delgado M, et al. Thrombus in right atrium in two infants successfully treated with tissue plasminogen activator. Pediatr Emerg Care 1997; 13:37–39
191 Manco-Johnson MJ, Grabowski EF, Hellgreen M, et al. Recommendations for tPA thrombolysis in children: on behalf of the Scientific Subcommittee on Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. Thromb Haemost 2002; 88:157–158
192 Albisetti M, Schmugge M, Haas R, et al. Arterial thromboembolic complications in critically ill children. J Crit Care 2005; 20:296–300
193 Van Overmeire B, Van Reempts PJ, Van Acker KJ. Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. Arch Dis Child 1992; 67:443–445
194 Manco-Johnson MJ, Nuss R, Hays T, et al. Combined thrombolytic and anticoagulant therapy for venous thrombosis in children. J Pediatr 2000; 136:446–453
195 De Blanche LE, Schmitz ML, Johnson CE, et al. Successful surgical management of a neonate with a saddle pulmonary embolus. Ann Thorac Surg 2004; 78:e1–2
196 Putnam JB Jr, Lemmer JH Jr, Rocchini AP, et al. Embolectomy for acute pulmonary artery occlusion following Fontan procedure. Ann Thorac Surg 1988; 45:335–336
197 Uflacker R. Interventional therapy for pulmonary embolism. J Vasc Interv Radiol 2001; 12:147–164
198 Poon WL, Luk SH, Yam KY, et al. Mechanical thrombectomy in inferior vena cava thrombosis after caval filter placement: a report of three cases. Cardiovasc Intervent Radiol 2002; 25:440–443
199 Vincent RN, Dinkins J, Dobbs MC. Mechanical thrombectomy using the AngioJect in a child with congenital heart disease. Catheter Cardiovasc Interv 2004; 61:253–255
200 Kobayashi T, Shinohara M, Tomomasa T, et al. Percutaneous hydrodynamic thrombectomy for femoral arterial thrombosis after arterial catheterization. Pediatr Cardiol 2003; 24:409–411
201 Gorich J, Rilinger N, Sokiranski R, et al. Mechanical thrombolysis of acute occlusion of both the superficial and the deep femoral arteries using a thrombectomy device. AJR Am J Roentgenol 1998; 170:1177–1180
202 Mack RM, Hartmann JR, Sauvage LR. Iliofemoral venous thrombectomy in a child with a coagulation abnormality. J Pediatr 1966; 68:374–380
203 Cook A, Shackford S, Osler T, et al. Use of vena cava filters in pediatric trauma patients: data from the National Trauma Data Bank. J Trauma 2005; 59:1114–1120
204 Reed RA, Teitelbaum GP, Stanley P, et al. The use of inferior vena cava filters in pediatric patients for pulmonary embolus prophylaxis. Cardiovasc Intervent Radiol 1996; 19:401–405
205 Haider EA, Rosen JC, Torres C, et al. Serial repositioning of a Gunther tulip retrievable inferior vena cava filter in a pediatric patient. Pediatr Radiol 2005; 35:1135–1138
206 Inoue Y, Kato M, Ohsuka T, et al. Successful treatment of a child with inferior vena cava thrombosis using a temporary inferior vena cava filter. Pediatr Cardiol 2002; 23:74–76
207 Cahn MD, Rohrer MJ, Martella MB, et al. Long-term follow-up of Greenfield inferior vena cava filter placement in children. J Vasc Surg 2001; 34:820–825
208 Anton N, Chait P, Chan A, et al. Vena caval filters in children: preliminary safety and efficacy data. Thromb Haemost 2001; 82(suppl):2227
209 Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146–153
210 Wiernikowski JT, Athale UH. Thromboembolic complications in children with cancer. Thromb Res 2006; 118:137–152
211 Orsino A, Schneider R, DeVeber G, et al. Childhood acute myelomonocytic leukemia (AML-M4) presenting as catastrophic antiphospholipid antibody syndrome. J Pediatr Hematol Oncol 2004; 26:327–330
212 Ruud E, Holmstrom H, De Lange C, et al. Low-dose warfarin for the prevention of central line-associated thromboses in children with malignancies: a randomized, controlled study. Acta Paediatr 2006; 95:1053–1059
213 Nowak-Gottl U, Munchow N, Klippel U, et al. The course of fibrinolytic proteins in children with malignant bone tumours. Eur J Pediatr 1999; 158(suppl 3):S151–S153
214 Male C, Foulon D, Hoogendoorn H, et al. Predictive value of persistent versus transient antiphospholipid antibody subtypes for the risk of thrombotic events in pediatric patients with systemic lupus erythematosus. Blood 2005; 106:4152–4158
215 Duncan BW, Adzick NS, Longaker MT, et al. *In utero* arterial embolism from renal vein thrombosis with successful postnatal thrombolytic therapy. J Pediatr Surg 1991; 26:741–743
216 Zigman A, Yazbeck S, Emil S, et al. Renal vein thrombosis: a 10-year review. J Pediatr Surg 2000; 35:1540–1542
217 Mocan H, Beattie TJ, Murphy AV. Renal venous thrombosis in infancy: long-term follow-up. Pediatr Nephrol 1991; 5:45–49
218 Ricci MA, Lloyd DA. Renal venous thrombosis in infants and children. Arch Surg 1990; 125:1195–1199
219 Nuss R, Hays T, Manco-Johnson M. Efficacy and safety of heparin anticoagulation for neonatal renal vein thrombosis. Am J Pediatr Hematol Oncol 1994; 16:127–131
220 Ryan JA Jr, Abel RM, Abbott WM, et al. Catheter complications in total parenteral nutrition: a prospective study of 200 consecutive patients. N Engl J Med 1974; 290:757–761
221 Mollitt DL, Golladay ES. Complications of TPN catheter-induced vena caval thrombosis in children less than one year of age. J Pediatr Surg 1983; 18:462–467
222 Wakefield A, Cohen Z, Craig M, et al. Thrombogenicity of total parenteral nutrition solutions: I. Effect on induction of monocyte/macrophage procoagulant activity. Gastroenterology 1989; 97:1210–1219
223 Wakefield A, Cohen Z, Rosenthal A, et al. Thrombogenicity of total parenteral nutrition solutions: II: Effect on induction

of endothelial cell procoagulant activity. Gastroenterology 1989; 97:1220–1228
224 Moukarzel A, Azancot-Benisty A, Brun P, et al. M-mode and two-dimensional echocardiography in the routine follow-up of central venous catheters in children receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr 1991; 15:551–555
225 Dollery CM, Sullivan ID, Bauraind O, et al. Thrombosis and embolism in long-term central venous access for parenteral nutrition. Lancet 1994; 344:1043–1045
226 Newall F, Barnes C, Savoia H, et al. Warfarin therapy in children who require long-term total parenteral nutrition. Pediatrics 2003; 112:e386
227 de Neef M, Heijboer H, van Woensel JB, et al. The efficacy of heparinization in prolonging patency of arterial and central venous catheters in children: a randomized double-blind trial. Pediatr Hematol Oncol 2002; 19:553–560
228 Smith S, Dawson S, Hennessey R, et al. Maintenance of the patency of indwelling central venous catheters: is heparin necessary? Am J Pediatr Hematol Oncol 1991; 13:141–143
229 Svoboda P, Barton RP, Barbarash OL, et al. Recombinant urokinase is safe and effective in restoring patency to occluded central venous access devices: a multiple-center, international trial. Crit Care Med 2004; 32:1990–1996
230 Fisher AA, Deffenbaugh C, Poole RL, et al. The use of alteplase for restoring patency to occluded central venous access devices in infants and children. J Infus Nurs 2004; 27:171–174
231 Haire WD, Deitcher SR, Mullane KM, et al. Recombinant urokinase for restoration of patency in occluded central venous access devices: a double-blind, placebo-controlled trial. Thromb Haemost 2004; 92:575–582
232 Choi M, Massicotte MP, Marzinotto V, et al. The use of alteplase to restore patency of central venous lines in pediatric patients: a cohort study. J Pediatr 2001; 139:152–156
233 Wells WJ, Yu RJ, Batra AS, et al. Obstruction in modified Blalock shunts: a quantitative analysis with clinical correlation. Ann Thorac Surg 2005; 79:2072–2076
234 Fenton KN, Siewers RD, Rebovich B, et al. Interim mortality in infants with systemic-to-pulmonary artery shunts. Ann Thorac Surg 2003;76:152–156; discussion 156–157
235 Al Jubair KA, Al Fagih MR, Al Jarallah AS, et al. Results of 546 Blalock-Taussig shunts performed in 478 patients. Cardiol Young 1998; 8:486–490
236 Motz R, Wessel A, Ruschewski W, et al. Reduced frequency of occlusion of aorto-pulmonary shunts in infants receiving aspirin. Cardiol Young 1999; 9:474–477
237 Tam VK, Murphy K, Parks WJ, et al. Saphenous vein homograft: a superior conduit for the systemic arterial shunt in the Norwood operation. Ann Thorac Surg 2001; 71:1537–1540
238 Bartram U, Grunenfelder J, Van Praagh R. Causes of death after the modified Norwood procedure: a study of 122 postmortem cases. Ann Thorac Surg 1997; 64:1795–1802
239 Graham EM, Shakir H, Atz AM, et al. Neoaortic root modification for late thrombosis after Norwood palliation. Ann Thorac Surg 2006; 82:e29–e30
240 Brennan TV, Rodefeld MD, Tacy TA, et al. Late thrombosis of the native aortic root after Norwood reconstruction for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2001; 121:580–582
241 Fraisse A, Chetaille P, Kreitmann B, et al. [Short and medium-term results of the Norwood intervention (first stage)]. Arch Mal Coeur Vaiss 2001; 94:457–463
242 Bove EL, Lloyd TR. Staged reconstruction for hypoplastic left heart syndrome: contemporary results. Ann Surg 1996; 224:387–394; discussion 394–385
243 van Son JA, Black MD, Devoe K, et al. Organized thrombus in left main coronary artery in hypoplastic left heart syndrome. Ann Thorac Surg 1995; 60:462–463
244 Pennington DG, Nouri S, Ho J, et al. Glenn shunt: long-term results and current role in congenital heart operations. Ann Thorac Surg 1981; 31:532–539
245 Kopf GS, Laks H, Stansel HC, et al. Thirty-year follow-up of superior vena cava-pulmonary artery (Glenn) shunts. J Thorac Cardiovasc Surg 1990; 100:662–670; discussion 670–671
246 Koutlas TC, Harrison JK, Bashore TM, et al. Late conduit occlusion after modified Fontan procedure with classic Glenn shunt. Ann Thorac Surg 1996; 62:258–261; discussion 261–262
247 Monagle P, Cochrane A, McCrindle B, et al. Thromboembolic complications after fontan procedures: the role of prophylactic anticoagulation. J Thorac Cardiovasc Surg 1998; 115:493–498
248 Monagle P, Karl TR. Thromboembolic problems after the Fontan operation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2002; 5:36–47
249 Kaulitz R, Ziemer G, Rauch R, et al. Prophylaxis of thromboembolic complications after the Fontan operation (total cavopulmonary anastomosis). J Thorac Cardiovasc Surg 2005; 129:569–575
250 Seipelt RG, Franke A, Vazquez-Jimenez JF, et al. Thromboembolic complications after Fontan procedures: comparison of different therapeutic approaches. Ann Thorac Surg 2002; 74:556–562
251 Zahn EM, Lima VC, Benson LN, et al. Use of endovascular stents to increase pulmonary blood flow in pulmonary atresia with ventricular septal defect. Am J Cardiol 1992; 70:411–412
252 Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003; 348:1639–1646
253 Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003; 348:1647–1655
254 Arola A, Jokinen E, Ruuskanen O, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents: a nationwide study in Finland. Am J Epidemiol 1997; 146:385–393
255 Malcic I, Jelusic M, Kniewald H, et al. Epidemiology of cardiomyopathies in children and adolescents: a retrospective study over the last 10 years. Cardiol Young 2002; 12:253–259
256 Nield LE, McCrindle BW, Bohn DJ, et al. Outcomes for children with cardiomyopathy awaiting transplantation. Cardiol Young 2000; 10:358–366
257 Hsu DT, Addonizio LJ, Hordof AJ, et al. Acute pulmonary embolism in pediatric patients awaiting heart transplantation. J Am Coll Cardiol 1991; 17:1621–1625
258 Baker DW, Wright RF. Management of heart failure: IV. Anticoagulation for patients with heart failure due to left ventricular systolic dysfunction. JAMA 1994; 272:1614–1618
259 Badesh DAS, Ahearn G, Barst R, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence based clinical practice guidelines. Chest 2004;126(suppl):35S–62S
260 Barst R. Recent advances in the treatment of pediatric pulmonary arterial hypertension. Pediatr Clin North Am 1999; 46:331–345
261 Rosenzweig EB, Barst RJ. Idiopathic pulmonary arterial hypertension in children. Curr Opin Pediatr 2005; 17:372–380
262 Yankah AC, Alexi-Meskhishvili V, Weng Y, et al. Performance of aortic and pulmonary homografts in the right

ventricular outflow tract in children. J Heart Valve Dis 1995; 4:392–395
263 Caldarone CA, Raghuveer G, Hills CB, et al. Long-term survival after mitral valve replacement in children aged < 5 years: a multi-institutional study. Circulation 2001; 104: I143–I147
264 Kadoba K, Jonas RA, Mayer JE, et al. Mitral valve replacement in the first year of life. J Thorac Cardiovasc Surg 1990; 100:762–768
265 Milano A, Vouhe PR, Baillot-Vernant F, et al. Late results after left-sided cardiac valve replacement in children. J Thorac Cardiovasc Surg 1986; 92:218–225
266 Spevak PJ, Freed MD, Castaneda AR, et al. Valve replacement in children less than 5 years of age. J Am Coll Cardiol 1986; 8:901–908
267 Weinstein GS, Mavroudis C, Ebert PA. Preliminary experience with aspirin for anticoagulation in children with prosthetic cardiac valves. Ann Thorac Surg 1982; 33:549–553
268 Serra AJ, McNicholas KW, Olivier HF Jr, et al. The choice of anticoagulation in pediatric patients with the St. Jude Medical valve prostheses. J Cardiovasc Surg (Torino) 1987; 28:588–591
269 Abid F, Abid A, Fekih M, et al. Aortic valve replacement in children under 16 years of age with congenital or rheumatic valvular disease: a study of 64 cases. J Cardiovasc Surg (Torino) 1992; 33:265–271
270 Khitin LM, Sade RM, Bradley SM, et al. Prevention of thrombosis and embolism in children and adolescents with mechanical valve prostheses: warfarin versus antiplatelet agents. J Heart Valve Dis 2006; 15:394–399; discussion 399
271 Schaffer MS, Clarke DR, Campbell DN, et al. The St. Jude Medical cardiac valve in infants and children: role of anticoagulant therapy. J Am Coll Cardiol 1987; 9:235–239
272 Robbins RC, Bowman FO Jr, Malm JR. Cardiac valve replacement in children: a twenty-year series. Ann Thorac Surg 1988; 45:56–61
273 Borkon AM, Soule L, Reitz BA, et al. Five year follow-up after valve replacement with the St. Jude Medical valve in infants and children. Circulation 1986; 74:I110–I115
274 Verrier ED, Tranbaugh RF, Soifer SJ, et al. Aspirin anticoagulation in children with mechanical aortic valves. J Thorac Cardiovasc Surg 1986; 92:1013–1020
275 Alexiou C, Galogavrou M, Chen Q, et al. Mitral valve replacement with mechanical prostheses in children: improved operative risk and survival. Eur J Cardiothorac Surg 2001; 20:105–113
276 Bradley SM, Sade RM, Crawford FA Jr, et al. Anticoagulation in children with mechanical valve prostheses. Ann Thorac Surg 1997; 64:30–34; discussion 35–36
277 Bradley L, Midgley F, Watson D, et al. Anticoagulation therapy in children with mechanical prosthetic cardiac valves. Am J Cardiol 1985; 56:533–535
278 Champsaur G, Robin J, Tronc F, et al. Mechanical valve in aortic position is a valid option in children and adolescents. Eur J Cardiothorac Surg 1997; 11:117–122
279 Kojori F, Chen R, Caldarone CA, et al. Outcomes of mitral valve replacement in children: a competing-risks analysis. J Thorac Cardiovasc Surg 2004; 128:703–709
280 Rao PS, Solymar L, Mardini MK, et al. Anticoagulant therapy in children with prosthetic valves. Ann Thorac Surg 1989; 47:589–592
281 Schaff HV, Danielson GK. Current status of valve replacement in children. Cardiovasc Clin 1986; 16:427–436
282 Stewart S, Cianciotta D, Alexson C, et al. The long-term risk of warfarin sodium therapy and the incidence of thromboembolism in children after prosthetic cardiac valve replacement. J Thorac Cardiovasc Surg 1987; 93:551–554
283 Williams JB, Karp RB, Kirklin JW, et al. Considerations in selection and management of patients undergoing valve replacement with glutaraldehyde-fixed porcine bioprotheses. Ann Thorac Surg 1980; 30:247–258
284 Arabia FA, Tsau PH, Smith RG, et al. Pediatric bridge to heart transplantation: application of the Berlin Heart, Medos and Thoratec ventricular assist devices. J Heart Lung Transplant 2006; 25:16–21
285 Blume ED, Naftel DC, Bastardi HJ, et al. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multi-institutional study. Circulation 2006; 113:2313–2319
286 Duncan BW, Bohn DJ, Atz AM, et al. Mechanical circulatory support for the treatment of children with acute fulminant myocarditis. J Thorac Cardiovasc Surg 2001; 122:440–448
287 Hetzer R, Alexi-Meskishvili V, Weng Y, et al. Mechanical cardiac support in the young with the Berlin Heart EXCOR pulsatile ventricular assist device: 15 years' experience. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2006; 99–108
288 Hetzer R, Loebe M, Potapov EV, et al. Circulatory support with pneumatic paracorporeal ventricular assist device in infants and children. Ann Thorac Surg 1998; 66:1498–1506
289 Kaczmarek I, Sachweh J, Groetzner J, et al. Mechanical circulatory support in pediatric patients with the MEDOS assist device. ASAIO J 2005; 51:498–500
290 Levi D, Marelli D, Plunkett M, et al. Use of assist devices and ECMO to bridge pediatric patients with cardiomyopathy to transplantation. J Heart Lung Transplant 2002; 21:760–770
291 Minami K, Knyphausen E, Suzuki R, et al. Mechanical ventricular circulatory support in children: Bad Oeynhausen experience. Ann Thorac Cardiovasc Surg 2005; 11:307–312
292 Reinhartz O, Hill JD, Al-Khaldi A, et al. Thoratec ventricular assist devices in pediatric patients: update on clinical results. ASAIO J 2005; 51:501–503
293 Reinhartz O, Keith FM, El-Banayosy A, et al. Multicenter experience with the thoratec ventricular assist device in children and adolescents. J Heart Lung Transplant 2001; 20:439–448
294 Schmid C, Debus V, Gogarten W, et al. Pediatric assist with the Medos and Excor systems in small children. ASAIO J 2006; 52:505–508
295 Schmid C, Tjan T, Etz C, et al. The excor device: revival of an old system with excellent results. Thorac Cardiovasc Surg 2006; 54:393–399
296 Sharma MS, Webber SA, Morell VO, et al. Ventricular assist device support in children and adolescents as a bridge to heart transplantation. Ann Thorac Surg 2006; 82:926–932
297 Stiller B, Weng Y, Hubler M, et al. Pneumatic pulsatile ventricular assist devices in children under 1 year of age. Eur J Cardiothorac Surg 2005; 28:234–239
298 Undar A, McKenzie ED, McGarry MC, et al. Outcomes of congenital heart surgery patients after extracorporeal life support at Texas Children's Hospital. Artif Organs 2004; 28:963–966
299 Fraser CD Jr, Carberry KE, Owens WR, et al. Preliminary experience with the MicroMed DeBakey pediatric ventricular assist device. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2006:109–114
300 Morales DL, Dibardino DJ, McKenzie ED, et al. Lessons learned from the first application of the DeBakey VAD Child: an intracorporeal ventricular assist device for children. J Heart Lung Transplant 2005; 24:331–337
301 Studer MA, Kennedy CE, Dreyer WJ, et al. An alternative treatment strategy for pump thrombus in the DeBakey VAD

Child: use of clopidogrel as a thrombolytic agent. J Heart Lung Transplant 2006; 25:857–861
302 Freed MD, Keane JF, Rosenthal A. The use of heparinization to prevent arterial thrombosis after percutaneous cardiac catheterization in children. Circulation 1974; 50:565–569
303 Freed MD, Rosenthal A, Fyler D. Attempts to reduce arterial thrombosis after cardiac catheterization in children: use of percutaneous technique and aspirin. Am Heart J 1974; 87:283–286
304 Ino T, Benson LN, Freedom RM, et al. Thrombolytic therapy for femoral artery thrombosis after pediatric cardiac catheterization. Am Heart J 1988; 115:633–639
305 Kern IB. Management of children with chronic femoral artery obstruction. J Pediatr Surg 1977; 12:83–90
306 Taylor LM Jr, Troutman R, Feliciano P, et al. Late complications after femoral artery catheterization in children less than five years of age. J Vasc Surg 1990; 11:297–304; discussion 304–306
307 Celermajer DS, Robinson JT, Taylor JF. Vascular access in previously catheterised children and adolescents: a prospective study of 131 consecutive cases. Br Heart J 1993; 70:554–557
308 Hurwitz RA, Franken EA Jr, Girod DA, et al. Angiographic determination of arterial patency after percutaneous catheterization in infants and small children. Circulation 1977; 56:102–105
309 Girod DA, Hurwitz RA, Caldwell RL. Heparinization for prevention of thrombosis following pediatric percutaneous arterial catheterization. Pediatr Cardiol 1982; 3:175–180
310 Rao PS, Thapar MK, Rogers JH Jr, et al. Effect of intraarterial injection of heparin on the complications of percutaneous arterial catheterization in infants and children. Cathet Cardiovasc Diagn 1981; 7:235–246
311 Saxena A, Gupta R, Kumar RK, et al. Predictors of arterial thrombosis after diagnostic cardiac catheterization in infants and children randomized to two heparin dosages. Cathet Cardiovasc Diagn 1997; 41:400–403
312 Brus F, Witsenburg M, Hofhuis WJ, et al. Streptokinase treatment for femoral artery thrombosis after arterial cardiac catheterisation in infants and children. Br Heart J 1990; 63:291–294
313 Carlson KM, Rutledge JM, Parker BR, et al. Use of tissue plasminogen activator for femoral artery thrombosis following transcatheter coil occlusion of patent ductus arteriosus. Pediatr Cardiol 2005; 26:83–86
314 Harrison BM, Wood CB. Spontaneous femoral artery thrombosis and intermittent claudication in childhood nephrotic syndrome. Arch Dis Child 1972; 47:836–837
315 Kothari SS, Kumar RK, Varma S, et al. Thrombolytic therapy in infants for femoral artery thrombosis following cardiac catheterisation. Indian Heart J 1996; 48:246–248
316 Ries M, Singer H, Hofbeck M, et al. Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. Br Heart J 1994; 72:403
317 Friedman J, Fabre J, Netscher D, et al. Treatment of acute neonatal vascular injuries: the utility of multiple interventions. J Pediatr Surg 1999; 34:940–945
318 Giacoia GP. High-dose urokinase therapy in newborn infants with major vessel thrombosis. Clin Pediatr (Phila) 1993; 32:231–237
319 Wessel DL, Keane JF, Fellows KE, et al. Fibrinolytic therapy for femoral arterial thrombosis after cardiac catheterization in infants and children. Am J Cardiol 1986; 58:347–351
320 Lincoln JC, Deverall PB. The treatment of arterial thrombosis in infants and children by balloon catheters. J Pediatr Surg 1969; 4:359–362
321 Butt W, Shann F, McDonnell G, et al. Effect of heparin concentration and infusion rate on the patency of arterial catheters. Crit Care Med 1987; 15:230–232
322 Sellden H, Nilsson K, Larsson LE, et al. Radial arterial catheters in children and neonates: a prospective study. Crit Care Med 1987; 15:1106–1109
323 Rais-Bahrami K, Karna P, Dolanski EA. Effect of fluids on life span of peripheral arterial lines. Am J Perinatol 1990; 7:122–124
324 Heulitt MJ, Farrington EA, O'Shea TM, et al. Double-blind, randomized, controlled trial of papaverine-containing infusions to prevent failure of arterial catheters in pediatric patients. Crit Care Med 1993; 21:825–829
325 Tarry WC, Moser AJ, Makhoul RG. Peripheral arterial thrombosis in the nephrotic syndrome. Surgery 1993; 114: 618–623
326 Alpert J, O'Donnell JA, Parsonnet V, et al. Clinically recognized limb ischemia in the neonate after umbilical artery catheterization. Am J Surg 1980; 140:413–418
327 O'Neill JA Jr, Neblett WW III, Born ML. Management of major thromboembolic complications of umbilical artery catheters. J Pediatr Surg 1981; 16:972–978
328 Stringel G, Mercer S, Richler M, et al. Catheterization of the umbilical artery in neonates: surgical implications. Can J Surg 1985; 28:143–146
329 Joseph R, Chong A, Teh M, et al. Thrombotic complication of umbilical arterial catheterization and its sequelae. Ann Acad Med Singapore 1985; 14:576–582
330 Boo NY, Wong NC, Zulkifli SS, et al. Risk factors associated with umbilical vascular catheter-associated thrombosis in newborn infants. J Paediatr Child Health 1999; 35:460–465
331 Klinger G, Hellmann J, Daneman A. Severe aortic thrombosis in the neonate: successful treatment with low-molecular-weight heparin; two case reports and review of the literature. Am J Perinatol 2000; 17:151–158
332 Krueger TC, Neblett WW, O'Neill JA, et al. Management of aortic thrombosis secondary to umbilical artery catheters in neonates. J Pediatr Surg 1985; 20:328–332
333 Joshi VV, Draper DA, Bates RD, III. Neonatal necrotizing enterocolitis: occurrence secondary to thrombosis of abdominal aorta following umbilical arterial catheterization. Arch Pathol 1975; 99:540–543
334 Rand T, Weninger M, Kohlhauser C, et al. Effects of umbilical arterial catheterization on mesenteric hemodynamics. Pediatr Radiol 1996; 26:435–438
335 Seibert JJ, Northington FJ, Miers JF, et al. Aortic thrombosis after umbilical artery catheterization in neonates: prevalence of complications on long-term follow-up. AJR Am J Roentgenol 1991; 156:567–569
336 Rajani K, Goetzman BW, Wennberg RP, et al. Effect of heparinization of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. Pediatrics 1979; 63:552–556
337 David RJ, Merten DF, Anderson JC, et al. Prevention of umbilical artery catheter clots with heparinized infusates. Dev Pharmacol Ther 1981; 2:117–126
338 Bosque E, Weaver L. Continuous versus intermittent heparin infusion of umbilical artery catheters in the newborn infant. J Pediatr 1986; 108:141–143
339 Horgan MJ, Bartoletti A, Polansky S, et al. Effect of heparin infusates in umbilical arterial catheters on frequency of thrombotic complications. J Pediatr 1987; 111:774–778
340 Ankola PA, Atakent YS. Effect of adding heparin in very low concentration to the infusate to prolong the patency of umbilical artery catheters. Am J Perinatol 1993; 10:229–232

341 Chang GY, Lueder FL, DiMichele DM, et al. Heparin and the risk of intraventricular hemorrhage in premature infants. J Pediatr 1997; 131:362–366
342 Barrington K. Umbilical artery catheters in the newborn: effects of heparin. Cochrane Database Syst Rev 2006; CD000507
343 McDonald M, Johnson M, Rumack C, et al. Heparin prevention of catheter related thrombosis. Pediatr Res 1984; 18(suppl)
344 Lesko SM, Mitchell AA, Epstein MF, et al. Heparin use as a risk factor for intraventricular hemorrhage in low-birth-weight infants. N Engl J Med 1986; 314:1156–1160
345 Malloy MH, Cutter GR. The association of heparin exposure with intraventricular hemorrhage among very low birth weight infants. J Perinatol 1995; 15:185–191
346 Colburn MD, Gelabert HA, Quinones-Baldrich W. Neonatal aortic thrombosis. Surgery 1992; 111:21–28
347 Ahluwalia JS, Kelsall AW, Diederich S, et al. Successful treatment of aortic thrombosis after umbilical catheterization with tissue plasminogen activator. Acta Paediatr 1994; 83:1215–1217
348 Kothari SS, Varma S, Wasir HS. Thrombolytic therapy in infants and children. Am Heart J 1994; 127:651–657
349 Kawahira Y, Kishimoto H, Lio M, et al. Spontaneous aortic thrombosis in a neonate with multiple thrombi in the main branches of the abdominal aorta. Cardiovasc Surg 1995; 3:219–221
350 Sanchez J, Velasco F, Alvarez R, et al. Aortic thrombosis in a neonate with hereditary antithrombin III deficiency: successful outcome with thrombolytic and replacement treatment. Acta Paediatr 1996; 85:245–247
351 Torkington J, Hitchcock R, Wilkinson K, et al. Successful use of recombinant tissue plasminogen activator in the treatment of aortic thrombosis in a premature neonate. Eur J Vasc Endovasc Surg 1997; 13:515–516
352 Barrington K. Umbilical artery catheters in the newborn: effects of catheter tip. Cochrane Database Syst Rev 2006; 3
353 Harris MS, Little GA. Umbilical artery catheters: high, low, or no. J Perinat Med 1978; 6:15–21
354 Mokrohisky ST, Levine RL, Blumhagen JD, et al. Low positioning of umbilical-artery catheters increases associated complications in newborn infants. N Engl J Med 1978; 299:561–564
355 Wesstrom G, Finnstrom O, Stenport G. Umbilical artery catheterization in newborns: I. Thrombosis in relation to catheter type and position. Acta Paediatr Scand 1979; 68:575–581
356 Stork E, Carol W, Kleigman R, et al. Neonatal hypertension appears unrelated to aortic catheter position. Pediatr Res 1984; 18(suppl)
357 Kempley ST, Bennett S, Loftus BG, et al. Randomized trial of umbilical arterial catheter position: clinical outcome. Acta Paediatr 1993; 82:173–176
358 Umbilical Artery Catheter Trial Study Group. Relationship of intraventricular hemorrhage or death with the level of umbilical artery catheter placement: a multicenter randomized clinical trial. Pediatrics 1992; 90:881–887
359 Corrigan JJ Jr, Jeter M, Allen HD, et al. Aortic thrombosis in a neonate: failure of urokinase thrombolytic therapy. Am J Pediatr Hematol Oncol 1982; 4:243–247
360 Tugrul Kural I, Tinaztepe K, Yurdakul Y. Aortic thrombosis in the newborn infant. J Cardiovasc Surg (Torino) 1984; 25:246–248
361 Lanari M, Lazzarotto T, Papa I, et al. Neonatal aortic arch thrombosis as a result of congenital cytomegalovirus infection. Pediatrics 2001; 108:E114
362 Bjarke B, Herin P, Blomback M. Neonatal aortic thrombosis: a possible clinical manifestation of congenital antithrombin 3 deficiency. Acta Paediatr Scand 1974; 63:297–301
363 Newman RS, Spear GS, Kirschbaum N. Postmortem DNA diagnosis of factor V Leiden in a neonate with systemic thrombosis and probable antithrombin deficiency. Obstet Gynecol 1998; 92:702–705
364 Sheridan-Pereira M, Porreco RP, Hays T, et al. Neonatal aortic thrombosis associated with the lupus anticoagulant. Obstet Gynecol 1988; 71:1016–1018
365 Tuohy J, Harrison A. Prenatal transfer of anticardiolipin antibodies associated with fatal neonatal aortic thrombosis. Aust NZ J Obstet Gynaecol 2005; 45:175–176
366 Hamilton RM, Penkoske PA, Byrne P, et al. Spontaneous aortic thrombosis in a neonate presenting as coarctation. Ann Thorac Surg 1988; 45:564–565
367 Sherman GG, Munster M, Govendrageloo K, et al. Low molecular weight heparin in the successful treatment of a spontaneous aortic thrombosis in a neonate. Pediatr Hematol Oncol 2000; 17:409–413
368 Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. J Am Soc Nephrol 2004; 15:3192–3206
369 Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004; 110:2747–2771
370 Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001; 345:1809–1817
371 Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986; 315:341–347
372 Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med 2007; 356:663–675
373 Heller C, Heinecke A, Junker R, et al. Cerebral venous thrombosis in children: a multifactorial origin. Circulation 2003; 108:1362–1367
374 Medlock MD, Olivero WC, Hanigan WC, et al. Children with cerebral venous thrombosis diagnosed with magnetic resonance imaging and magnetic resonance angiography. Neurosurgery 1992; 31:870–876; discussion 876
375 Carvalho KS, Bodensteiner JB, Connolly PJ, et al. Cerebral venous thrombosis in children. J Child Neurol 2001; 16: 574–580
376 Kenet G, Waldman D, Lubetsky A, et al. Paediatric cerebral sinus vein thrombosis: a multi-center, case-controlled study. Thromb Haemost 2004; 92:713–718
377 Barron TF, Gusnard DA, Zimmerman RA, et al. Cerebral venous thrombosis in neonates and children. Pediatr Neurol 1992; 8:112–116
378 Wu YW, Miller SP, Chin K, et al. Multiple risk factors in neonatal sinovenous thrombosis. Neurology 2002; 59:438–440
379 Fitzgerald KC, Williams LS, Garg BP, et al. Cerebral sinovenous thrombosis in the neonate. Arch Neurol 2006; 63:405–409
380 Wu YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. Ann Neurol 2003; 54:123–126
381 Shevell MI, Silver K, O'Gorman AM, et al. Neonatal dural sinus thrombosis. Pediatr Neurol 1989; 5:161–165
382 deVeber GA, MacGregor D, Curtis R, et al. Neurologic outcome in survivors of childhood arterial ischemic stroke

and sinovenous thrombosis. J Child Neurol 2000; 15:316–324
383 Moharir M, Shroff M, MacGregor D, et al. Clinical and radiographic features of thrombosis propagation in neonatal and childhood cerebral sinovenous thrombosis. Ann Neurol 2006; 60(suppl):S141
384 Lin A, Foroozan R, Danesh-Meyer HV, et al. Occurrence of cerebral venous sinus thrombosis in patients with presumed idiopathic intracranial hypertension. Ophthalmology 2006; 113:2281–2284
385 Huisman TA, Holzmann D, Martin E, et al. Cerebral venous thrombosis in childhood. Eur Radiol 2001; 11:1760–1765
386 Barnes C, Newall F, Furmedge J, et al. Arterial ischaemic stroke in children. J Paediatr Child Health 2004; 40:384–387
387 Sébire G, Tabarki B, Saunders DE, et al. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. Brain 2005; 128:477–489
388 Baumgartner RW, Studer A, Arnold M, et al. Recanalisation of cerebral venous thrombosis. J Neurol Neurosurg Psychiatry 2003; 74:459–461
389 Strupp M, Covi M, Seelos K, et al. Cerebral venous thrombosis: correlation between recanalization and clinical outcome; a long-term follow-up of 40 patients. J Neurol 2002; 249:1123–1124
390 Macchi PJ, Grossman RI, Gomori JM, et al. High field MR imaging of cerebral venous thrombosis. J Comput Assist Tomogr 1986; 10:10–15
391 Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. Lancet 1991; 338: 597–600
392 de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke 1999; 30:484–488
393 Stam J, De Bruijn SF, DeVeber G. Anticoagulation for cerebral sinus thrombosis. Cochrane Database Syst Rev 2002; CD002005
394 Maiti B, Chakrabarti I. Study on cerebral venous thrombosis with special reference to efficacy of heparin. J Neurol Sci 1997; 150(suppl):S147
395 Nagaraja D, Rao B, Taly A, et al. Randomized controlled trial of heparin in puerperal cerebral venous/sinus thrombosis. Nimhans J 1995; 13:115
396 deVeber G, Monagle P, Chan A, et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurol 1998; 55:1539–1543
397 Uziel Y, Laxer RM, Blaser S, et al. Cerebral vein thrombosis in childhood systemic lupus erythematosus. J Pediatr 1995; 126:722–727
398 Holzmann D, Huisman TA, Linder TE. Lateral dural sinus thrombosis in childhood. Laryngoscope 1999; 109:645–651
399 Johnson MC, Parkerson N, Ward S, et al. Pediatric sinovenous thrombosis. J Pediatr Hematol Oncol 2003; 25:312–315
400 De Schryver EL, Blom I, Braun KP, et al. Long-term prognosis of cerebral venous sinus thrombosis in childhood. Dev Med Child Neurol 2004; 46:514–519
401 Bonduel M, Sciuccati G, Hepner M, et al. Arterial ischemic stroke and cerebral venous thrombosis in children: a 12-year Argentinean registry. Acta Haematol 2006; 115:180–185
402 Fluss J, Geary D, deVeber G. Cerebral sinovenous thrombosis and idiopathic nephrotic syndrome in childhood: report of four new cases and review of the literature. Eur J Pediatr 2006; 165:709–716
403 Kenet G, Kirkham K, Niederstadt T, et al. European collaborative paediatric database on cerebral venous thrombosis: risk factors for recurrent venous thromboembolism. Lancet Neurol 2007; 6:573–575
404 Liebetrau M, Mayer TE, Bruning R, et al. Intra-arterial thrombolysis of complete deep cerebral venous thrombosis. Neurology 2004; 63:2444–2445
405 Griesemer DA, Theodorou AA, Berg RA, et al. Local fibrinolysis in cerebral venous thrombosis. Pediatr Neurol 1994; 10:78–80
406 Soleau SW, Schmidt R, Stevens S, et al. Extensive experience with dural sinus thrombosis. Neurosurgery 2003; 52: 534–544; discussion 544
407 Wasay M, Bakshi R, Kojan S, et al. Nonrandomized comparison of local urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis. Stroke 2001; 32:2310–2317
408 Chahlavi A, Steinmetz MP, Masaryk TJ, et al. A transcranial approach for direct mechanical thrombectomy of dural sinus thrombosis: report of two cases. J Neurosurg 2004; 101:347–351
409 Stefini R, Latronico N, Cornali C, et al. Emergent decompressive craniectomy in patients with fixed dilated pupils due to cerebral venous and dural sinus thrombosis: report of three cases. Neurosurgery 1999; 45:626–629; discussion 629–630
410 Keller E, Pangalu A, Fandino J, et al. Decompressive craniectomy in severe cerebral venous and dural sinus thrombosis. Acta Neurochir Suppl 2005; 94:177–183
411 Ciccone A, Canhao P, Falcao F, et al. Thrombolysis for cerebral vein and dural sinus thrombosis. Cochrane Database Syst Rev 2004; CD003693
412 Hetherington R, Dennis M, Barnes M, et al. Functional outcome in young adults with spina bifida and hydrocephalus. Childs Nerv Syst 2006; 22:117–124
413 Raju TN, Nelson KB, Ferriero D, et al. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007; 120:609–616
414 Lynch JK, Hirtz DG, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke Workshop on Perinatal and Childhood Stroke. Pediatrics 2002; 109:116–123
415 Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. Ann Neurol 2001; 50:163–168
416 Gunther G, Junker R, Sträter R, et al. Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. Stroke 2000; 31:2437–2441
417 Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 2001; 107: 1400–1404
418 Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA 2005; 293:723–729
419 de Vries LS, van der Grond J, van Haastert IC, et al. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. Neuropediatrics 2005; 36:12–20
420 Kurnik K, Kosch A, Sträter R, et al. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. Stroke 2003; 34:2887–2892
421 Salih MA, Abdel-Gader AG, Al-Jarallah AA, et al. Outcome of stroke in Saudi children. Saudi Med J 2006; 27(suppl 1):S91–S96
422 Fullerton HJ, Wu YW, Sidney S, et al. Risk of recurrent childhood arterial ischemic stroke in a population-based

cohort: the importance of cerebrovascular imaging. Pediatrics 2007; 119:495–501
423 Shellhaas RA, Smith SE, O'Tool E, et al. Mimics of childhood stroke: characteristics of a prospective cohort. Pediatrics 2006; 118:704–709
424 Ganesan V, Prengler M, McShane MA, et al. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol 2003; 53:167–173
425 Braun KP, Kappelle LJ, Kirkham FJ, et al. Diagnostic pitfalls in paediatric ischaemic stroke. Dev Med Child Neurol 2006; 48:985–990
426 Brankovic-Sreckovic V, Milic-Rasic V, Jovic N, et al. The recurrence risk of ischemic stroke in childhood. Med Princ Pract 2004; 13:153–158
427 Pegelow CH, Macklin EA, Moser FG, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood 2002; 99:3014–3018
428 Giroud M, Lemesle M, Gouyon JB, et al. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. J Clin Epidemiol 1995; 48:1343–1348
429 Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: ethnic and gender disparities. Neurology 2003; 61:189–194
430 Zahuranec DB, Brown DL, Lisabeth LD, et al. Is it time for a large, collaborative study of pediatric stroke? Stroke 2005; 36:1825–1829
431 Sebire G. Transient cerebral arteriopathy in childhood. Lancet 2006; 368:8–10
432 Rafay MF, Armstrong D, Deveber G, et al. Craniocervical arterial dissection in children: clinical and radiographic presentation and outcome. J Child Neurol 2006; 21:8–16
433 Hartfield DS, Lowry NJ, Keene DL, et al. Iron deficiency: a cause of stroke in infants and children. Pediatr Neurol 1997; 16:50–53
434 van Beynum IM, Smeitink JA, den Heijer M, et al. Hyperhomocysteinemia: a risk factor for ischemic stroke in children. Circulation 1999; 99:2070–2072
435 Cardo E, Monros E, Colome C, et al. Children with stroke: polymorphism of the MTHFR gene, mild hyperhomocysteinemia, and vitamin status. J Child Neurol 2000; 15:295–298
436 Prengler M, Sturt N, Krywawych S, et al. Homozygous thermolabile variant of the methylenetetrahydrofolate reductase gene: a potential risk factor for hyperhomocysteinaemia, CVD, and stroke in childhood. Dev Med Child Neurol 2001; 43:220–225
437 Sirachainan N, Tapanapruksakul P, Visudtibhan A, et al. Homocysteine, MTHFR C677 T, vitamin B12, and folate levels in Thai children with ischemic stroke: a case-control study. J Pediatr Hematol Oncol 2006; 28:803–808
438 Nowak-Gottl U, Junker R, Hartmeier M, et al. Increased lipoprotein(a) is an important risk factor for venous thromboembolism in childhood. Circulation 1999; 100:743–748
439 Haywood S, Liesner R, Pindora S, et al. Thrombophilia and first arterial ischaemic stroke: a systematic review. Arch Dis Child 2005; 90:402–405
440 Riikonen R, Santavuori P. Hereditary and acquired risk factors for childhood stroke. Neuropediatrics 1994; 25:227–233
441 Mancini J, Girard N, Chabrol B, et al. Ischemic cerebrovascular disease in children: retrospective study of 35 patients. J Child Neurol 1997; 12:193–199
442 Abram HS, Knepper LE, Warty VS, et al. Natural history, prognosis, and lipid abnormalities of idiopathic ischemic childhood stroke. J Child Neurol 1996; 11:276–282
443 Lanthier S, Carmant L, David M, et al. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. Neurology 2000; 54:371–378
444 Chabrier S, Husson B, Lasjaunias P, et al. Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients. J Child Neurol 2000; 15:290–294
445 De Schryver EL, Kappelle LJ, Jennekens-Schinkel A, et al. Prognosis of ischemic stroke in childhood: a long-term follow-up study. Dev Med Child Neurol 2000; 42:313–318
446 Steinlin M, Roellin K, Schroth G. Long-term follow-up after stroke in childhood. Eur J Pediatr 2004; 163:245–250
447 Chung B, Wong V. Pediatric stroke among Hong Kong Chinese subjects. Pediatrics 2004; 114:e206–e212
448 Ganesan V, Prengler M, Wade A, et al. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation 2006; 114:2170–2177
449 Sträter R, Becker S, von Eckardstein A, et al. Prospective assessment of risk factors for recurrent stroke during childhood: a 5-year follow-up study. Lancet 2002; 360:1540–1545
450 Danchaivijitr N, Cox TC, Saunders DE, et al. Evolution of cerebral arteriopathies in childhood arterial ischemic stroke. Ann Neurol 2006; 59:620–626
451 Portnoy BA, Herion JC. Neurological manifestations in sickle-cell disease, with a review of the literature and emphasis on the prevalence of hemiplegia. Ann Intern Med 1972; 76:643–652
452 Powars D, Wilson B, Imbus C, et al. The natural history of stroke in sickle cell disease. Am J Med 1978; 65:461–471
453 Wood DH. Cerebrovascular complications of sickle cell anemia. Stroke 1978; 9:73–75
454 Wilimas J, Goff JR, Anderson HR Jr, et al. Efficacy of transfusion therapy for one to two years in patients with sickle cell disease and cerebrovascular accidents. J Pediatr 1980; 96:205–208
455 Moohr JW, Wilson H, Pang EJ. Strokes and their management in sickle cell disease. In: Fried W, ed. Comparitive clinical aspects of sickle cell disease. Amsterdam, the Netherlands: Elsevier, 1982; 101–111
456 Balkaran B, Char G, Morris JS, et al. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992; 120:360–366
457 Russell MO, Goldberg HI, Hodson A, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood 1984; 63:162–169
458 Njamnshi AK, Mbong EN, Wonkam A, et al. The epidemiology of stroke in sickle cell patients in Yaounde, Cameroon. J Neurol Sci 2006; 250:79–84
459 Fatunde OJ, Adamson FG, Ogunseyinde O, et al. Stroke in Nigerian children with sickle cell disease. Afr J Med Med Sci 2005; 34:157–160
460 Ikezaki K. Rational approach to treatment of moyamoya disease in childhood. J Child Neurol 2000; 15:350–356
461 Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. Childs Nerv Syst 2005; 21:358–364
462 Benseler SM, Silverman E, Aviv RI, et al. Primary central nervous system vasculitis in children. Arthritis Rheum 2006; 54:1291–1297
463 Sträter R, Kurnik K, Heller C, et al. Aspirin versus low-dose low-molecular-weight heparin: antithrombotic therapy in pediatric ischemic stroke patients; a prospective follow-up study. Stroke 2001; 32:2554–2558
464 Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. Neurology 2001; 57:1155–1160
465 Ganesan V, Chong WK, Cox TC, et al. Posterior circulation stroke in childhood: risk factors and recurrence. Neurology 2002; 59:1552–1556

466 Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. Cochrane Database Syst Rev 2000; Issue 4, CD000255
467 Beletsky V, Nadareishvili Z, Lynch J, et al. Cervical arterial dissection: time for a therapeutic trial? Stroke 2003; 34: 2856–2860
468 Adams RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol 1997; 42:699–704
469 Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998; 339:5–11
470 Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005; 353:2769–2778
471 Gulbis B, Haberman D, Dufour D, et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. Blood 2005; 105: 2685–2690
472 Vermylen C, Cornu G, Ferster A, et al. Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium. Bone Marrow Transplant 1998; 22:1–6
473 Bernaudin F. Results and current indications of bone marrow allograft in sickle cell disease [in French]. Pathol Biol (Paris) 1999; 47:59–64
474 Walters MC, Storb R, Patience M, et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report: multicenter investigation of bone marrow transplantation for sickle cell disease. Blood 2000; 95:1918–1924
475 Vernet O, Montes JL, O'Gorman AM, et al. Encephaloduroarterio-synangiosis in a child with sickle cell anemia and moyamoya disease. Pediatr Neurol 1996; 14:226–230
476 Mendelowitsch A, Sekhar LN, Clemente R, et al. EC-IC bypass improves chronic ischemia in a patient with moyamoya disease secondary to sickle cell disease: an in vivo microdialysis study. Neurol Res 1997; 19:66–70
477 Schmugge M, Frischknecht H, Yonekawa Y, et al. Stroke in hemoglobin (SD) sickle cell disease with moyamoya: successful hydroxyurea treatment after cerebrovascular bypass surgery. Blood 2001; 97:2165–2167
478 Fryer RH, Anderson RC, Chiriboga CA, et al. Sickle cell anemia with moyamoya disease: outcomes after EDAS procedure. Pediatr Neurol 2003; 29:124–130
479 Scott RM, Smith JL, Robertson RL, et al. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. J Neurosurg 2004; 100:142–149
480 Soman T, Rafay MF, Hune S, et al. The risks and safety of clopidogrel in pediatric arterial ischemic stroke. Stroke 2006; 37:1120–1122
481 Janjua N, Nasar A, Lynch JK, et al. Thrombolysis for ischemic stroke in children: data from the nationwide inpatient sample. Stroke 2007; 38:1850–1854
482 Pescatore P, Horellou HM, Conard J, et al. Problems of oral anticoagulation in an adult with homozygous protein C deficiency and late onset of thrombosis. Thromb Haemost 1993; 69:311–315
483 Marlar RA, Sills RH, Groncy PK, et al. Protein C survival during replacement therapy in homozygous protein C deficiency. Am J Hematol 1992; 41:24–31
484 Deguchi K, Tsukada T, Iwasaki E, et al. Late-onset homozygous protein C deficiency manifesting cerebral infarction as the first symptom at age 27. Intern Med 1992; 31:922–925
485 Yamamoto K, Matsushita T, Sugiura I, et al. Homozygous protein C deficiency: identification of a novel missense mutation that causes impaired secretion of the mutant protein C. J Lab Clin Med 1992; 119:682–689
486 Auberger K. Evaluation of a new protein-C concentrate and comparison of protein-C assays in a child with congenital protein-C deficiency. Ann Hematol 1992; 64:146–151
487 Grundy CB, Melissari E, Lindo V, et al. Late-onset homozygous protein C deficiency. Lancet 1991; 338:575–576
488 Marlar RA, Neumann A. Neonatal purpura fulminans due to homozygous protein C or protein S deficiencies. Semin Thromb Hemost 1990; 16:299–309
489 Tripodi A, Franchi F, Krachmalnicoff A, et al. Asymptomatic homozygous protein C deficiency. Acta Haematol 1990; 83:152–155
490 Petrini P, Segnestam K, Ekelund H, et al. Homozygous protein C deficiency in two siblings. Pediatr Hematol Oncol 1990; 7:165–175
491 Marlar RA, Adcock DM, Madden RM. Hereditary dysfunctional protein C molecules (type II): assay characterization and proposed classification. Thromb Haemost 1990; 63:375–379
492 Marlar RA, Montgomery RR, Broekmans AW. Report on the diagnosis and treatment of homozygous protein C deficiency: report of the Working Party on Homozygous Protein C Deficiency of the ICTH-Subcommittee on Protein C and Protein S. Thromb Haemost 1989; 61:529–531
493 Ben-Tal O, Zivelin A, Seligsohn U. The relative frequency of hereditary thrombotic disorders among 107 patients with thrombophilia in Israel. Thromb Haemost 1989; 61:50–54
494 Pung-amritt P, Poort SR, Vos HL, et al. Compound heterozygosity for one novel and one recurrent mutation in a Thai patient with severe protein S deficiency. Thromb Haemost 1999; 81:189–192
495 Burrows FA, Kelton J. Low fetal risks in pregnancies associated with idiopathic thrombocytopenic purpura do not justify obstetrical interventions. Am J Obstet Gynecol 1990; 163:1147–1150
496 Adcock DM, Brozna J, Marlar RA. Proposed classification and pathologic mechanisms of purpura fulminans and skin necrosis. Semin Thromb Hemost 1990; 16:333–340
497 Auletta MJ, Headington JT. Purpura fulminans: a cutaneous manifestation of severe protein C deficiency. Arch Dermatol 1988; 124:1387–1391
498 Adcock DM, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. Semin Thromb Hemost 1990; 16:283–292
499 Estelles A, Garcia-Plaza I, Dasi A, et al. Severe inherited "homozygous" protein C deficiency in a newborn infant. Thromb Haemost 1984; 52:53–56
500 Mahasandana C, Suvatte V, Chuansumrit A, et al. Homozygous protein S deficiency in an infant with purpura fulminans. J Pediatr 1990; 117:750–753
501 Mahasandana C, Suvatte V, Marlar RA, et al. Neonatal purpura fulminans associated with homozygous protein S deficiency. Lancet 1990; 335:61–62
502 Andrew M, Schmidt B, Mitchell L, et al. Thrombin generation in newborn plasma is critically dependent on the concentration of prothrombin. Thromb Haemost 1990; 63: 27–30
503 Andrew M, Mitchell L, Vegh P, et al. Thrombin regulation in children differs from adults in the absence and presence of heparin. Thromb Haemost 1994; 72:836–842
504 Andrew M, deVeber G. Pediatric thromboembolism and stroke protocols. Hamilton, BC: Decker, 1999
505 Goldenberg NA, Knapp-Clevenger R, Hays T, et al. Lemierre's and Lemierre's-like syndromes in children: survival

and thromboembolic outcomes. Pediatrics 2005; 116:e543–e548
506 Hofmann S, Knoefler R, Lorenz N, et al. Clinical experiences with low-molecular weight heparins in pediatric patients. Thromb Res 2001; 103:345–353
507 Punzalan RC, Hillery CA, Montgomery RR, et al. Low-molecular-weight heparin in thrombotic disease in children and adolescents. J Pediatr Hematol Oncol 2000; 22:137–142
508 Mitchell L, Andrew M, Hanna K, et al. Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia: results of the PAARKA study. Thromb Haemost 2003; 90:235–244
509 Shen V, Li X, Murdock M, et al. Recombinant tissue plasminogen activator (alteplase) for restoration of function to occluded central venous catheters in pediatric patients. J Pediatr Hematol Oncol 2003; 25:38–45
510 Terrill KR, Lemons RS, Goldsby RE. Safety, dose, and timing of reteplase in treating occluded central venous catheters in children with cancer. J Pediatr Hematol Oncol 2003; 25:864–867
511 Chesler L, Feusner JH. Use of tissue plasminogen activator (rt-PA) in young children with cancer and dysfunctional central venous catheters. J Pediatr Hematol Oncol 2002; 24:653–656
512 Jacobs BR, Haygood M, Hingl J. Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. J Pediatr 2001; 139:593–596
513 Fratino G, Mazzola C, Buffa P, et al. Mechanical complications related to indwelling central venous catheter in pediatric hematology/oncology patients. Pediatr Hematol Oncol 2001; 18:317–324
514 Ponec D, Irwin D, Haire WD, et al. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: a double-blind placebo-controlled trial; the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) efficacy trial. J Vasc Interv Radiol 2001; 12:951–955
515 Davis SN, Vermeulen L, Banton J, et al. Activity and dosage of alteplase dilution for clearing occlusions of venous-access devices. Am J Health Syst Pharm 2000; 57:1039–1045
516 Kleta R, Schleef J, Jurgens H. Tissue plasminogen activator and obstructed central venous catheters. Med Pediatr Oncol 1998; 30:376
517 Haire WD, Atkinson JB, Stephens LC, et al. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. Thromb Haemost 1994; 72:543–547
518 Reiss N, Blanz U, Breymann T, et al. Mechanical valve replacement of the systemic atrioventricular valve in children. ASAIO J 2006; 52:559–561
519 Gunther T, Mazzitelli D, Schreiber C, et al. Mitral-valve replacement in children under 6 years of age. Eur J Cardiothorac Surg 2000; 17:426–430
520 Alexiou C, McDonald A, Langley SM, et al. Aortic valve replacement in children: are mechanical prostheses a good option? Eur J Cardiothorac Surg 2000; 17:125–133
521 van Doorn C, Yates R, Tsang V, et al. Mitral valve replacement in children: mortality, morbidity, and haemodynamic status up to medium term follow up. Heart 2000; 84:636–642
522 Yoshimura N, Yamaguchi M, Oshima Y, et al. Surgery for mitral valve disease in the pediatric age group. J Thorac Cardiovasc Surg 1999; 118:99–106
523 Mazzitelli D, Guenther T, Schreiber C, et al. Aortic valve replacement in children: are we on the right track? Eur J Cardiothorac Surg 1998; 13:565–571
524 Harada Y, Imai Y, Kurosawa H, et al. Ten-year follow-up after valve replacement with the St. Jude Medical prosthesis in children. J Thorac Cardiovasc Surg 1990; 100:175–180
525 Antunes MJ, Vanderdonck KM, Sussman MJ. Mechanical valve replacement in children and teenagers. Eur J Cardiothorac Surg 1989; 3:222–228
526 Sade RM, Crawford FA Jr, Fyfe DA, et al. Valve prostheses in children: a reassessment of anticoagulation. J Thorac Cardiovasc Surg 1988; 95:553–561
527 Cornish EM, Human DG, de Moor MM, et al. Valve replacement in children. Thorac Cardiovasc Surg 1987; 35:176–179
528 McGrath LB, Gonzalez-Lavin L, Eldredge WJ, et al. Thromboembolic and other events following valve replacement in a pediatric population treated with antiplatelet agents. Ann Thorac Surg 1987; 43:285–287
529 Woods A, Vargas J, Berri G, et al. Antithrombotic therapy in children and adolescents. Thromb Res 1986; 42:289–301
530 Schaff HV, Danielson GK, DiDonato RM, et al. Late results after Starr-Edwards valve replacement in children. J Thorac Cardiovasc Surg 1984; 88:583–589
531 Pass HI, Sade RM, Crawford FA, et al. Cardiac valve prostheses in children without anticoagulation. J Thorac Cardiovasc Surg 1984; 87:832–835
532 Williams WG, Pollock JC, Geiss DM, et al. Experience with aortic and mitral valve replacement in children. J Thorac Cardiovasc Surg 1981; 81:326–333
533 Human DG, Joffe HS, Fraser CB, et al. Mitral valve replacement in children. J Thorac Cardiovasc Surg 1982; 83:873–877
534 Donahoo JS, Gardner TJ. St. Jude Medical cardiac valve prosthesis in infants and children: early and intermediate experience. South Med J 1982; 75:1538–1540
535 Roschitz B, Beitzke A, Gamillscheg A, et al. Signs of thrombin generation in pediatric cardiac catheterization with unfractionated heparin bolus or subcutaneous low molecular weight heparin for antithrombotic cover. Thromb Res 2003; 111:335–341
536 Ruud E, Natvig S, Holmstrom H, et al. Low prevalence of femoral venous thrombosis after cardiac catheterizations in children: a prospective study. Cardiol Young 2002; 12:513–518
537 Vitiello R, McCrindle BW, Nykanen D, et al. Complications associated with pediatric cardiac catheterization. J Am Coll Cardiol 1998; 32:1433–1440
538 Vielhaber H, Kohlhase B, Koch HG, et al. Flush heparin during cardiac catheterisation prevents long-term coagulation activation in children without APC-resistance: preliminary results. Thromb Res 1996; 81:651–656
539 Burrows PE, Benson LN, Williams WG, et al. Iliofemoral arterial complications of balloon angioplasty for systemic obstructions in infants and children. Circulation 1990; 82:1697–1704
540 deVeber G, Andrew M. Canadian Pediatric Ischemic Stroke Registry. Analysis I. Pediatr Res 1994; 35:379A
541 Lancon JA, Killough KR, Tibbs RE, et al. Spontaneous dural sinus thrombosis in children. Pediatr Neurosurg 1999; 30:23–29
542 Kao A, Dlugos D, Hunter JV, et al. Anticoagulation therapy in cerebral sinovenous thrombosis and ulcerative colitis in children. J Child Neurol 2002; 17:479–482
543 Benedict SL, Bonkowsky JL, Thompson JA, et al. Cerebral sinovenous thrombosis in children: another reason to treat iron deficiency anemia. J Child Neurol 2004; 19:526–531
544 De Vivo DC, Holmes SJ, Dodge PR. Cerebrovascular disease in a pediatric population. Ann Neurol 1977; 2:261
545 Dusser A, Goutieres F, Aicardi J. Ischemic strokes in

children. J Child Neurol 1986; 1:131–136
546 deVeber G, Group TCPISS. Canadian Ischemic Stroke Gtudy Group: analysis of children with arterial ischemic stroke. Ann Neurol 2000; 17:562
547 Bowen MD, Burak CR, Barron TF. Childhood ischemic stroke in a nonurban population. J Child Neurol 2005; 20:194–197
548 Herguner MO, Incecik F, Elkay M, et al. Evaluation of 39 children with stroke regarding etiologic risk factors and treatment. Turk J Pediatr 2005; 47:116–119
549 Aydinli N, Tatli B, Caliskan M, et al. Stroke in childhood: experience in Istanbul, Turkey. J Trop Pediatr 2006; 52: 158–162
550 Sarnaik S, Soorya D, Kim J, et al. Periodic transfusions for sickle cell anemia and CNS infarction. Am J Dis Child 1979; 133:1254–1257
551 Wang WC, Kovnar EH, Tonkin IL, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. J Pediatr 1991; 118:377–382
552 Cohen DL. Neonatal subgaleal hemorrhage in hemophilia. J Pediatr 1978; 93:1022–1023
553 de Montalembert M, Beauvais P, Bachir D, et al. Cerebrovascular accidents in sickle cell disease: risk factors and blood transfusion influence; French Study Group on Sickle Cell Disease. Eur J Pediatr 1993; 152:201–204
554 Rana S, Houston PE, Surana N, et al. Discontinuation of long-term transfusion therapy in patients with sickle cell disease and stroke. J Pediatr 1997; 131:757–760
555 Pegelow CH, Adams RJ, McKie V, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. J Pediatr 1995; 126:896–899
556 Dobson SR, Holden KR, Nietert PJ, et al. Moyamoya syndrome in childhood sickle cell disease: a predictive factor for recurrent cerebrovascular events. Blood 2002; 99:3144–3150
557 Scothorn DJ, Price C, Schwartz D, et al. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. J Pediatr 2002; 140:348–354
558 Hulbert ML, Scothorn DJ, Panepinto JA, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr 2006; 149:710–712
559 Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. Blood 1999; 94:3022–3026
560 Sumoza A, de Bisotti R, Sumoza D, et al. Hydroxyurea (HU) for prevention of recurrent stroke in sickle cell anemia (SCA). Am J Hematol 2002; 71:161–165
561 Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. J Pediatr 2004; 145:346–352

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