Antithrombotic Therapy in Children

Paul Monagle, MBBS; Alan D. Michelson, MD; Edward Bovill, MD; and Maureen Andrew, MD, Chair

Abbreviations: ALL = acute lymphoblastic leukemia; APTT = activated partial thromboplastin time; AT = antithrombin; BT = Blalock-Taussig; CI = confidence interval; CVL = central venous line; DVT = deep venous thrombosis; FDA = Food and Drug Administration; FFP = fresh frozen plasma; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; HUS = hemolytic-uremic syndrome; ICH = intracranial hemorrhage; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; OA = oral anticoagulant; PARKAA = Prophylactic Antithrombin Replacement in Kids (Acute Lymphoblastic Leukemia Treated With Asparaginase); PC = protein C; PE = pulmonary thromboembolism; PRO-TEKT = Prophylaxis of Thromboembolism in Kids Trial; PS = protein S; PT = prothrombin time; RCT = randomized controlled trial; SK = streptokinase; TE = thromboembolism; TPA = tissue plasminogen activator; TPN = total parenteral nutrition; UK = urokinase

Antithrombotic therapy is required for the prevention and treatment of thromboembolic complications in specific pediatric patient populations. Recommendations for antithrombotic therapy in children have been loosely extrapolated from recommendations for adults because thromboembolic events in children were rare enough to hinder the testing of specific therapeutic modalities, yet were common enough to present significant management dilemmas that required therapeutic intervention. However, the optimal prevention and treatment of thromboembolisms (TEs) in children likely differ from those of adults because of important ontogenic features of hemostasis that affect both the pathophysiology of the thrombotic processes and the response to antithrombotic agents.

Advances in tertiary-care pediatrics, paradoxically, have resulted in rapidly increasing numbers of children requiring antithrombotic therapy. Intervention trials are now both feasible and urgently needed to provide validated guidelines for antithrombotic therapy in children. Since the first publication of this article in the 1995 CHEST antithrombotic supplement, at least five multinational, randomized, controlled intervention trials assessing specific aspects of anticoagulant therapy in children have been initiated, and one of these is now complete. More rigorous trials are needed. Until the results of these trials are available, modified adult guidelines remain the primary source for recommendations in children.

This article is divided into three parts. In the first section, the evidence showing that the interaction of antithrombotic agents with the hemostatic system of the young differs from that of adults is presented, as well as the indications, monitoring, therapeutic range, factors influencing dose-response relationships, and side effects of antithrombotic agents in children. In the second section, the specific indications for antithrombotic therapy in pediatric patients are discussed. In the third section, the current studies, ongoing difficulties, and key areas requiring further multicenter trials assessing aspects of anticoagulant therapy in children are briefly discussed. Many of the recommendations are extrapolated from clinical trials in adults and are interpreted within the context of the available information for pediatric patients.

An MEDLINE search of the literature was conducted from 1966 to 1999 using combinations of key words (eg, children, newborns, heparin, warfarin, aspirin, antiplatelet agents, thrombolysis, thrombosis, embolism, and mechanical and biological prosthetic heart valves) and were supplemented by additional references located through the bibliographies of listed articles. All articles were graded by design and methodology. Recommendations were based on the strength of the study methods and on a benefit-risk assessment.

Heparin Therapy in Pediatric Patients

Mechanism of Action

The anticoagulant activities of heparin, which are mediated by catalysis of antithrombin (AT), can be impaired in the presence of decreased plasma levels of AT. Some pediatric patients requiring heparin therapy have very low levels of AT, reflecting physiologic, congenital, and/or acquired etiologies. For example, plasma concentrations of AT are physiologically low at birth (approximately 0.50 U/mL) and increase to adult values by 3 months of age. Sick premature newborns, a population of children at significant risk for TEs, frequently have plasma levels of AT that are < 0.30 U/mL, potentially influencing their response to heparin therapy. Fetal reference ranges are now available and show that AT levels range from 0.20 to 0.37 U/mL at gestational ages of 19 to 38 weeks.

Heparin functions as an antithrombotic agent by catalyzing the ability of AT to inactivate specific coagulation enzymes, of which thrombin is the most sensitive. The capacity of plasmas from newborns to generate thrombin is both delayed and decreased compared to adults and is similar to plasma from adults receiving therapeutic amounts of heparin therapy. Following infancy, the capacity of plasmas to generate thrombin increases but remains approximately 25% less than for adults throughout childhood. At heparin concentrations in the therapeutic range, the capacity of plasma to generate thrombin is delayed and decreased by 50 to 25% in newborns and children, respectively, compared to adults. These observations support the hypothesis that the optimal dosing of heparin will differ in pediatric patients from that of adults.

Therapeutic Range

Therapeutic doses of heparin are the amounts of heparin required to achieve the adult therapeutic range based on the activated partial thromboplastin time (APTT). The recommendations for standardizing APTT values to hep-
arin levels in adults should be extrapolated to children. The recommended therapeutic range for the treatment of venous TEs in adults is an 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 0.3 to 0.7 U/mL. In pediatric patients, APTT values correctly predict therapeutic heparin concentrations approximately 70% of the time.

Doses

The doses of heparin required in pediatric patients to achieve adult therapeutic APTT values have been assessed using a weight-based nomogram (in one prospective cohort study). A bolus dose of 50 U/kg was insufficient, resulting in subtherapeutic APTT values in 60% of children. Bolus doses of 50 to 100 U/kg result in therapeutic APTT values in 90% of children (unpublished data). Maintenance heparin doses are age-dependent, with infants having the highest requirements (28 U/kg/h) and children >1 year of age having lower requirements (ie, 20 U/kg/h) (Table 1). The doses of heparin required for older children are similar to the weight-adjusted requirements in adults (18 U/kg/h). The duration of heparin therapy for the treatment of deep venous thrombosis (DVT), again extrapolated from adult data, is a minimum of 5 days and 7 to 10 days for extensive DVT or pulmonary embolism (PE). Oral anticoagulant (OA) therapy can be initiated on day 1 of heparin therapy, or later if 7 to 10 days of heparin therapy is required.

Pharmacokinetics

There are at least two plausible explanations for the increased heparin requirement in young children. First, heparin is cleared more quickly in the young compared to adults in animal models and humans. Second, the delay in diagnosis of TEs in children may result in more extensive disease at the time of presentation, accelerating heparin clearance.

Table 1—Protocol for Systemic Heparin Administration and Adjustment for Pediatric Patients

<table>
<thead>
<tr>
<th>APTT, s</th>
<th>Bolus, U/kg</th>
<th>Hold, min</th>
<th>Rate Change, %</th>
<th>Repeat APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>50</td>
<td>0</td>
<td>+10</td>
<td>4 h</td>
</tr>
<tr>
<td>50–59</td>
<td>0</td>
<td>0</td>
<td>+10</td>
<td>4 h</td>
</tr>
<tr>
<td>60–85</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Next day</td>
</tr>
<tr>
<td>86–95</td>
<td>0</td>
<td>0</td>
<td>−10</td>
<td>4 h</td>
</tr>
<tr>
<td>96–120</td>
<td>0</td>
<td>30</td>
<td>−10</td>
<td>4 h</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0</td>
<td>60</td>
<td>−15</td>
<td>4 h</td>
</tr>
</tbody>
</table>

IV. Obtain blood for APTT 4 h after administration of the heparin loading dose and 4 h after every change in the infusion rate.
V. When APTT values are therapeutic, a daily CBC and APTT.

Monitoring

An appropriate dosage adjustment of IV heparin therapy can be problematic. Nomograms are convenient to use and have been successful in achieving therapeutic APTT levels in a timely manner in adults. A nomogram initially used in adults was adapted, tested, and modified for children (Table 1). Heparin-dosing nomograms can be adapted into preprinted order sheets that facilitate rapid anticoagulation. Point-of-care APTT monitors are now available. However, to date and to our knowledge, there have been no studies validating the use of these instruments in children.

Adverse Effects

There are at least three clinically important adverse effects of heparin. First, bleeding, a major complication of heparin in adults, is discussed in detail elsewhere in this supplement (see page 108). One cohort study in children suggests that major bleeding from heparin therapy is not frequent in the treatment of DVT/PE in children. However, many children were treated with suboptimal amounts of heparin in this study, and there are case reports of major bleeding in children due to heparin. The risk of bleeding may increase when therapeutic doses of heparin are used more uniformly, particularly in children with serious underlying disorders. A second adverse effect is osteoporosis. There are only three case reports of pediatric heparin-induced osteoporosis, in two of which patients received concurrent steroid therapy. The third patient received high-dose IV heparin therapy for a prolonged period. However, given the convincing relationship between heparin and osteoporosis in adults, long-term use of heparin in children should be avoided when other alternative anticoagulants are available. The third adverse effect is the association of thrombocytopenia with heparin therapy in pediatric patients. There have been a number of case reports of pediatric heparin-induced thrombocytopenia (HIT) in the literature in patients ranging in age from 3 months to 15 years. Five cases were due to therapeutic heparin, and one was due to prophylactic heparin to maintain a central venous line (CVL). However, there remain no well-designed studies to assess the incidence or natural history of HIT in children. A high index of suspicion is required to diagnose HIT in children, as many patients in the neonatal ICU or pediatric ICU who are exposed to heparin have multiple reasons for thrombocytopenia and/or thrombosis. Protocols for the use of danaparoid in adults have been adapted for children, but there is limited experience with their use (Table 2).

Treatment of Heparin-Induced Bleeding

If anticoagulation therapy with heparin needs to be discontinued for clinical reasons, termination of the heparin infusion will usually suffice because of the rapid clearance of heparin. If an immediate effect is required, IV protamine sulfate rapidly neutralizes heparin activity by virtue of its positive charge. The dose of protamine sulfate
Table 4—Dosing of Reciparin and Enoxaparin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight-Dependent Dose of Reciparin*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 5 kg</td>
</tr>
<tr>
<td>Initial treatment dose</td>
<td>150</td>
</tr>
<tr>
<td>Initial prophylactic dose</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Age-Dependent Dose of Enoxaparin†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 mo</td>
</tr>
<tr>
<td>Initial treatment dose</td>
<td>1.5</td>
</tr>
<tr>
<td>Initial prophylactic dose</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Values given as U/kg/dose q12h.  †Enoxaparin has 110 anti-factor Xa U/mg.  Values given as mg/kg/dose q12h.

Mechanism of Action

Like heparin, the anticoagulant activities of LMWH are mediated by catalysis of AT.

Therapeutic Range

Therapeutic doses of LMWH are extrapolated from adults and are based on anti-factor Xa levels. The guideline for therapeutic LMWHs is an anti-factor Xa level of 0.50 to 1.0 U/mL in a sample taken 4 to 6 h following a subcutaneous injection.

Doses

The doses of LMWH required in pediatric patients to achieve adult therapeutic anti-factor Xa levels have been assessed for two LMWHs, enoxaparin (Lovenox; Aventis Pharma; Laval, Quebec) and reviparin (Clivarin; Knoll Pharmaceuticals; North Mount Olive, NJ). For both LMWHs, peak anti-factor Xa levels occur 2 to 6 h following an injection. Children less than approximately 2 months of age or < 5 kg in weight have increased requirements per kilogram, which likely is due to a larger volume of distribution, but the pharmacokinetics are similar. A weight-adjusted nomogram was used to adjust LMWH doses into the therapeutic range (Table 4). A weight-adjusted nomogram was used to adjust LMWH doses into the therapeutic range (Table 4). The doses required for older children are similar to the weight-adjusted requirements for adults. Potentially, LMWH may be used for several months. However, when this route of treatment is chosen, sensitive tests of bone density should be considered to monitor for early signs of osteoporosis.

Pharmacokinetics

Plausible explanations for the increased requirement of LMWH per body weight in young children include altered heparin pharmacokinetics and/or a decreased expression of anticoagulant activity of heparin in children due to decreased plasma concentrations of AT.

Table 2—Protocol for the Use of Danaparoid in Pediatric Patients

| Orgaran consists mainly of heparan sulfate, a small quantity of dermatan sulfate, and a minor amount of chondroitin sulfate and does not contain any heparin fragments. Danaparoid has a much higher anti-factor Xa/anti-factor IIa ratio compared to heparin or LMWH. Danaparoid has a decreased cross-reactivity rate (< 10%) with heparin-induced antibody as compared to LMWH (> 90%). Loading dose: 30 U/kg body weight Initial maintenance dose: 1.2–2.0 U/kg/h Monitoring: Anti-factor Xa activity can be monitored immediately Danaparoid is predominately removed from the circulation through the kidney. Consequently, danaparoid is contraindicated in patients with severe impaired renal function. Subcutaneous danaparoid is frequently used in adults, however, there is no published pediatric dose information. |

Table 3—Reversal of Heparin Therapy

<table>
<thead>
<tr>
<th>Time Since Last Heparin Dose, min</th>
<th>Protamine Dose, mg/100 U heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>1.0</td>
</tr>
<tr>
<td>30–60</td>
<td>0.5–0.75</td>
</tr>
<tr>
<td>60–120</td>
<td>0.375–0.5</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0.25–0.375</td>
</tr>
</tbody>
</table>

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

Nomograms for the adjustment of therapeutic doses of LMWH have been validated (Table 5).42,43

Treatment of LMWH-Induced Bleeding

If anticoagulation with LMWH needs to be discontinued for clinical reasons, termination of the subcutaneous injections will usually suffice. If an immediate effect is required, protamine sulfate has not been shown to completely reverse the activity of LMWH. Equimolar concentrations of protamine sulfate neutralize the anti-factor Xa activity but result in only partial neutralization of the anti-factor IIa activity. However, in animal models, bleeding is completely reversed by protamine sulfate.46–49 The dose of protamine sulfate is dependent on the dose of LMWH used at the time of administration. If protamine sulfate is given within 3 to 4 h of the LMWH, then a maximal neutralizing dose is 1 mg protamine sulfate per 100 U (1 mg) LMWH administered IV in the last dose over 10 min.40 The same instructions for protamine sulfate administration for the reversal of heparin should be followed (Table 3).

Initial studies suggested that LMWH would cause less bleeding than unfractionated heparin for a similar antithrombotic effect. However, a review of clinical studies to date has failed to substantiate that claim.50 In 1997, the US Food and Drug Administration (FDA) issued a warning concerning the danger of spinal hematoma occurring in adult patients undergoing epidural or lumbar punctures while receiving LMWH.51 The results of preliminary studies show that a significant proportion of children have existing CNS structural abnormalities, and two thigh hematomas. The same study described 30 patients who received prophylactic LMWH, of whom 2 had minor bleeding. No major bleeding complications occurred. Further studies are required to determine the true bleeding risk from LMWH in children. Until such evidence is available, the risk of bleeding complications from LMWH should be considered to be similar to that for heparin for the equivalent antithrombotic effect. In particular, prior to lumbar punctures or epidural procedures, at least two doses of LMWH should be withheld and, if possible, anti-factor Xa levels should be determined prior to the procedure.

OA Therapy in Pediatric Patients

Age-Dependent Features

OAs function by reducing plasma concentrations of the vitamin K-dependent proteins. At birth, levels of the vitamin K-dependent coagulant factors (FII, FVII, FIX, and FX) and inhibitors (protein C [PC] and protein S [PS]) are at approximately 50% of adult values.5–54–56 These levels are similar to those found in adults receiving OAs for the treatment of venous TEs.15,16 A small number of newborns have evidence of a functional vitamin K deficiency state, which is indicated by significant levels of descarboxy vitamin K-dependent proteins at birth.57 Vitamin K deficiency significantly increases the sensitivity to OAs and, potentially, the risk of bleeding. Following the neonatal period, levels of the vitamin K-dependent proteins rapidly increase and are within the adult range of normal by 6 months.7–9 However, average values of the vitamin K-dependent proteins remain approximately 20% lower than adult values until the late teenage years.58

Decreased concentrations of the vitamin K-dependent coagulation proteins, particularly prothrombin, contribute to the delay and decreased amounts of thrombin generated in plasmas from newborns and children.15,16 The pattern of thrombin generation in newborns is similar to that in plasma from adults receiving therapeutic amounts of OAs.59 Because of the potential risk of bleeding from further anticoagulation and the presence of borderline vitamin K status, OA therapy is avoided when possible during the first month of life.57–60 For older children receiving OAs, the capacity of their plasmas to generate thrombin is delayed and is decreased by 25% compared to plasmas from adults with similar international normalized ratios (INRs).59,61 The latter raises the issue of whether the optimal INR therapeutic range for children will be lower than that for adults. This hypothesis is further supported by the observation that plasma concentrations of a marker

---

**Table 5—Nomogram for Monitoring Reviparin/Enoxaparin in Pediatric Patients**

<table>
<thead>
<tr>
<th>Anti-Factor Xa Level U/mL</th>
<th>Hold Next Dose?</th>
<th>Dose Change?</th>
<th>Repeat Anti-Factor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.35</td>
<td>No</td>
<td>Increase by 25%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.35–0.49</td>
<td>No</td>
<td>Increase by 10%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>No</td>
<td>No</td>
<td>Next day, then 1 wk later and monthly thereafter while receiving reviparin-Na treatment (at 4 h after AM dose)</td>
</tr>
<tr>
<td>1.1–1.5</td>
<td>No</td>
<td>Decrease by 20%</td>
<td>Before next dose</td>
</tr>
<tr>
<td>1.6–2.0</td>
<td>3 h</td>
<td>Decrease by 30%</td>
<td>Before next dose then 4 h after next dose</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>Until anti-factor Xa 0.5 U/mL</td>
<td>Decrease by 40%</td>
<td>Before next dose, if not &lt; 0.5 u/mL, repeat q12h</td>
</tr>
</tbody>
</table>

---
of endogenous thrombin generation, prothrombin fragment 1.2, is significantly lower in children than in adults at similar INR values.61

**Therapeutic Range**

The most commonly used test for monitoring OA therapy is prothrombin time (PT), which is reported as an INR. Unfortunately, most pediatric studies have not reported their PT results as INRs, which hinders the interpretation and generalizability of the results. Currently, therapeutic INR ranges for children are directly extrapolated from recommendations for adult patients because, to our knowledge, there are no clinical trials that have assessed the optimal INR range for children based on clinical outcomes. The recommended therapeutic target for the treatment of venous TEs is an INR of 2.5 with a range between 2.0 and 3.0. The recommended therapeutic range for children with mechanical prosthetic heart valves is an INR target of 3.0 (INR range, 2.5 to 3.5).62 Low-dose OA therapy (INR target range, 1.4 to 1.9) is currently used in pediatric patients for a variety of reasons. First, children with a new thrombus and a long-term predisposing cause for recurrent TEs are treated with therapeutic doses of OA for 3 months followed by a low-dose regimen. Second, children with an old thrombus or significant risk for TE are treated initially with a low-dose regimen. Third, children with substantial bleeding risks, or those in whom monitoring is not possible, may be treated with low-dose warfarin. A single cohort study suggests that low-dose OA may provide an effective treatment strategy in selected children, but further evaluation is required before low-dose therapy can be widely recommended.63

**Dose Response**

Seven publications provide information on loading doses for OA therapy in children.1,63–68 Five studies were case series, and two were cohort studies.1,63 An initial dose of 0.2 mg/kg, with subsequent dose adjustments made according to a nomogram using INR values, was evaluated in two prospective cohort studies.1,63 With this dosing regimen, all patients achieve their target INR range and 79% attain their target INR in <7 days. The length of time required to achieve a minimal INR of 2.0 is age-dependent, ranging from a median of 5 days in infants to 3 days in teenagers. The overlap with heparin is approximately 5 days. Because of the length of time required to achieve a therapeutic range, higher loading doses of 0.3 and 0.4 mg/kg were tested but resulted in excessively high INR values on days 3 to 5 in at least 50% of children and cannot be generally recommended.63 Eight publications provide information on maintenance doses1,63–67,69,70 for OAs required to achieve an INR between 2.0 and 3.0 in children. Of these studies, five are case series and three are prospective cohort studies. Maintenance doses for OAs are age-dependent, with infants having the highest requirements and teenagers having the lowest requirements. 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 = 262) found that infants required an average of 0.32 mg/kg and teenagers 0.09 mg/kg warfarin to maintain a target INR of 2 to 3.63 For adults, weight-adjusted doses for OAs are not precisely known but are in the range of 0.04 to 0.08 mg/kg for an INR of 2 to 3.71 In a single cohort study in children, the average dose requirement of OAs to maintain a target INR of 1.4 to 1.9 is 0.08 mg/kg with a range of 0.03 to 0.17 mg/kg.63 The mechanisms responsible for the age dependency of OA doses are not completely clear. Table 6 provides a nomogram for loading and monitoring OAs in children.1 Guidelines for the duration1,72 of therapy with OAs in children reflect recommendations for adults with similar disorders. The optimal treatment for children with recurrent DVTs and PEs, beyond the initial treatment, is uncertain.

**Monitoring**

Monitoring OA therapy in children is difficult and requires close supervision with frequent dose adjustments.1,63 In contrast to adults, only 10 to 20% of children can be safely monitored monthly.1 Reasons contributing to the need for frequent monitoring include diet, medications, and primary medical problems. Breast-fed infants are very sensitive to OAs due to the low concentrations of vitamin K in breast milk.73–75 In contrast, some children are resistant to OAs due to impaired absorption,79 the requirements for total parenteral nutrition (TPN), which is routinely supplemented with vitamin K, and nutrient formulas, which are all supplemented with vitamin K (55 to 110 μg/liter) to protect against hemorrhagic diseases of the newborn.76,79

Most children are receiving multiple medications, both on a long-term basis, to treat their primary problems, or

<table>
<thead>
<tr>
<th>INR Action</th>
<th>INR Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1–1.3</td>
<td>Repeat initial loading dose</td>
</tr>
<tr>
<td>1.4–1.9</td>
<td>50% of initial loading dose</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>50% of initial loading dose</td>
</tr>
<tr>
<td>3.1–3.5</td>
<td>25% of loading dose</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1–1.4</td>
<td>Increase by 20% of dose</td>
</tr>
<tr>
<td>1.5–1.9</td>
<td>Increase by 10% of dose</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>No change</td>
</tr>
<tr>
<td>3.1–3.5</td>
<td>Decrease by 10% of dose</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>Hold until INR &lt;3.5 then restart at 20% less than previous dose</td>
</tr>
</tbody>
</table>

*Reproduced with permission of Michelson et al.3
access as well as complicated medical problems. The problems with monitoring OAs in children have limited their use, even in conditions in which they are strongly indicated. Potential solutions for optimizing therapy with OAs in children include pediatric anticoagulation clinics, whole-blood PT/INR monitors used at home, and clinical trials to determine whether lower, safer INR ranges are as efficacious.

Whole-Blood Monitors for Children

Whole-blood monitors use various techniques to measure the time from the 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 (CoaguChek; Boehringer Mannheim; Mannheim, Germany; and ProTime Microcoagulation System; International Technidyne Corp; Edison, NJ). Both monitors were shown to be acceptable and reliable for use in the outpatient laboratory and in 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.

Adverse Effects of OAs

Bleeding is the main complication of OA therapy. Minor bleeding that is of minor clinical consequence (eg, bruising, nosebleeds, heavy menses, coffee-ground emesis, microscopic hematuria, bleeding from cuts and loose teeth, or ileostomy) occurs in approximately 20% of children receiving OAs. The risk of serious bleeding in children receiving OAs for mechanical prosthetic valves is < 3.2% per patient-year (13 case series). Significant bleeding complications occur in approximately 1.7% of children receiving OAs for other indications.

Nonhemorrhagic complications of OAs, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Although OAs do not appear to affect bone density in adults, OAs do cause bony abnormalities in the fetus and are an integral part of the warfarin embryopathy. Because of the potential risk for adverse effects on bone formation in rapidly growing children, a cross-sectional study assessing bone density was performed in 33 children who had received OAs for > 1 year. This study suggests that long-term OA therapy may influence bone density in growing children. This observation requires confirmation by further studies. Further studies are urgently required to define bone disease in children that has been induced by OAs and to assess potentially effective prevention strategies.

Treatment of OA-Induced Bleeding

Vitamin K is the antidote for OAs. The dose to be administered and the concurrent use of vitamin K-dependent factor replacement (ie, either fresh frozen plasma [FFP] or prothrombin complex concentrates) are dependent on the clinical problem. Table 8 provides guidelines for the reversal of OA therapy in children with no bleeding and in those with significant bleeding.

Alternative Antithrombotic Therapy in Children

There are an increasing number of antithrombotic agents used in adults, the majority of which have been tested in large clinical trials. However, there are almost no

Table 8—Reversal of Oral Anticoagulation Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Significant bleeding that is not life-threatening and will not cause morbidity: treat with vitamin K1 as in 1A plus 50 U/kg IV.</td>
<td></td>
</tr>
<tr>
<td>B. Significant bleeding that is life-threatening and will cause morbidty: treat with vitamin K1 IV (5 mg) by slow infusion over 10–20 min because of the risk of anaphylactic shock. Consider giving prothrombin concentrate (containing factors II, VII, IX, and X) 50 U/kg IV rather than FFP (20 mL/kg IV).</td>
<td></td>
</tr>
</tbody>
</table>

Reproduced with permission of Michelon et al.
data on these drugs in children. Danaparoid is used frequently in adults with HIT, although there remain only a handful of case reports of use in children. Lepirudin is approved for the treatment of HIT in a number of countries. To our knowledge, there are no published data on the use of Hirudin or lepirudin in children. There is limited experience with the use of argatroban in adults, but to our knowledge, there are no published data on the use of argatroban in children.

In addition to pharmacologic therapy, venous interruption devices (eg, inferior vena cava [IVC] filters) are used for specific clinical indications in adults. The most common indication for the use of IVC interruption is to prevent a PE in the presence of a contraindication to anticoagulant therapy in a patient with or at high risk for proximal DVT. In the only randomized trial of filter placement, the rate of PE was reduced. However, the reduced rate of PE was associated with an increase in DVT in the group receiving filters. The overall survival rate was not different in the two groups. Only a handful of anecdotal reports of successful and failed IVC filters in children have been published. In contrast to adults, temporary filters often are used in children and are removed when the source of PE is no longer present. 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.

Antiplatelet Therapy in Pediatric Patients

Age-Dependent Features

Compared to adult control subjects, neonatal platelets are hyporeactive to thrombin, adenosine diphosphate/epinephrine, and thromboxane A2. This hyporeactivity of neonatal platelets is the result of a defect that is intrinsic to neonatal platelets. Paradoxically, the bleeding time is short in newborns due to increased RBC size, high hematocrit, and increased levels and multimeric forms of von Willebrand factor. No studies of platelet function in healthy children were identified except for the bleeding time, which, relative to adults, is prolonged throughout childhood in two of three studies. These physiologic differences suggest that the optimal dosage of antiplatelet agents in newborns and children also may differ from that of adults.

Therapeutic Range, Dose Response, and Monitoring of Antiplatelet Agents

There is a need to monitor aspirin, the most commonly used antiplatelet agent. To our knowledge, there are no studies that compare different doses of aspirin in children. Empiric low doses of 1 to 5 mg/kg/d have been proposed as adjuvant therapy for Blalock-Taussig (BT) shunts, for some endovascular stents, and for some cerebrovascular events. For mechanical prosthetic heart valves, aspirin doses of 6 to 20 mg/kg/d were used in eight studies, either alone or in combination with 6 mg/kg/d dipyridamole in three divided doses. High-dose aspirin, 80 to 100 mg/kg/d, is used in the treatment of Kawasaki's disease during the acute phase (up to 14 days), then 3 to 5 mg/kg/d for 7 weeks or longer if there is echocardiographic evidence of coronary artery abnormalities. The effects of aspirin last for approximately 7 days. The second most commonly used antiplatelet agent, for patients with mechanical prosthetic heart valves, is dipyridamole in doses of 2 to 5 mg/kg/d.

Ticlopidine and clopidogrel are related compounds. Both drugs selectively inhibit adenosine diphosphate-induced platelet aggregation. The antiplatelet effect of ticlopidine (and probably that of clopidogrel) is additive to that of aspirin. Studies in adults have used ticlopidine at doses of 250 mg every 12 h, and clopidogrel at 75 mg daily. There is no reported use in children, and dosage recommendations are unknown.

Glycoprotein (GP) IIb/IIIa antagonists are a new class of antiplatelet drugs that are now available in IV form (abciximab, tirofiban, and eptifibatide) and may soon be available in oral form. These drugs, which are chimeric antibody fragments (abciximab), peptides (eptifibatide), or nonpeptide small molecules (tirofiban), act by binding to the platelet surface GP IIb-IIIa complex, thereby inhibiting fibrinogen-mediated platelet aggregation. Because fibrinogen binding to the platelet GP IIb-IIIa complex is the final common pathway of platelet aggregation, these drugs are powerful antiplatelet agents. However, to our knowledge, there are as yet no reports of their use in children. Although GP IIb-IIIa antagonist therapy may need to be monitored, the optimal assays are still under investigation. The appropriate therapeutic ranges for these assays may prove to be different in children, because of the age-dependent differences in platelet function described above.

Adverse Effects of Antiplatelet Agents

Newborns may be exposed to antiplatelet agents due to maternal ingestion (aspirin as treatment for preeclampsia) or therapeutically (indomethacin as medical therapy for patent ductus arteriosus). The clearance of both salicylate and indomethacin is slower in newborns, 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 clinically important bleeding in newborns is weak. Indomethacin does prolong the bleeding time in newborns, but the evidence linking indomethacin to ICH is weak.

In older children, aspirin rarely causes clinically important hemorrhaging, except in the presence of an underlying hemostatic defect or in children also treated with anticoagulants or receiving thrombolytic therapy. The relatively low doses of aspirin used as antiplatelet therapy, compared to the much higher doses used for anti-inflammatory therapy, seldom cause other side effects. For example, although aspirin is associated with Reye's syndrome, this appears to be a dose-dependent effect of aspirin.
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 antithrombotic agents. Transfusions of platelet concentrates and/or the use of products that enhance platelet adhesion (e.g., plasma products containing high concentrations of von Willebrand factor or deamino-8-D-arginine vasopressin) may be helpful.

Thrombolytic Agents

Mechanism of Action of Thrombolytic Agents

The actions of thrombolytic agents are mediated by converting endogenous plasminogen to plasmin. At birth, plasma concentrations of plasminogen are reduced to 50% of adult values (i.e., 21 mg/100 mL). The decreased levels of plasminogen in newborns slow the generation of plasmin and reduce the thrombolytic effects of streptokinase (SK), urokinase (UK), and tissue plasminogen activator (tPA) in an in vitro fibrin clot system. A similar response occurs in children with acquired plasminogen deficiency. Supplementation of plasmas with plasminogen increases the thrombolytic effect of all three agents.

Contraindications

There are well-defined contraindications to thrombolytic therapy in adults. These include a history of stroke, transient ischemic attacks, other neurologic disease, and hypertension. Similar problems in children should be considered as relative, but not absolute, contraindications to thrombolytic therapy.

Choice of Thrombolytic Agent

To our knowledge, there are no studies that compare the cost, efficacy, and safety of different thrombolytic agents in children. Although SK is the cheapest of the three agents, it has the potential for allergic reactions and may be less effective in children with physiologic or acquired deficiencies of plasminogen. UK was widely used for pediatric patients, but a US FDA warning has substantially diminished the use of UK in North America. tPA has become the agent of choice in children for several reasons, including the US FDA warning regarding UK, experimental evidence of improved clot lysis in vitro compared to UK and SK, fibrin specificity, and low immunogenicity. However, tPA is considerably more expensive than either SK or UK, and the increased in vitro clot lysis by tPA has not been extended into clinical trials in children. There is minimal or no experience with other thrombolytic agents in children.

Therapeutic Range and Monitoring of Thrombolytic Agents

There is no therapeutic range for thrombolytic agents. The correlation between hemostatic parameters and efficacy/safety of thrombolytic therapy is too weak to have useful clinical predictive value. However, in patients with bleeding, the choice and doses of blood products used can be guided by appropriate hemostatic monitoring. The most useful single assay is the fibrinogen level, which usually can 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 heparin therapy, and the presence of fibrin/fibrinogen degradation products. Measurement of fibrin/fibrinogen degradation products and/or D-dimers is helpful in determining whether a fibrinolytic effect is present.

Dose Response

Thrombolytic agents are used in low doses, usually to restore catheter patency (Table 9), and in higher doses to lyse large-vessel TEs or PEs. Table 10 presents the most commonly used dose regimens for thrombolytic therapy in pediatric patients with arterial or venous TEs. These protocols come from case series. The optimal doses for each condition for UK, SK, and tPA are not known for pediatric patients. Based on the Thrombolysis in Myocardial Infarction II trial, doses of 150 mg recombinant tPA caused more bleeding into the CNS than 100 mg (1.5% vs 0.5%, respectively). These data suggest that there is an upper dose limit that is based on safety.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Single-Lumen CVL</th>
<th>Double-Lumen CVL</th>
<th>SC Port</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA ≤ 10 kg</td>
<td>0.5 mg diluted in 0.9% NaCl to volume required to fill line</td>
<td>0.5 mg per lumen diluted in 0.9% NaCl to fill volume of line. Treat one lumen at a time</td>
<td>0.5 mg diluted with 0.9% NaCl to 3 mL</td>
</tr>
<tr>
<td>tPA ≥ 10 kg</td>
<td>1.0 mg in 1.0 mL, 0.9% NaCl; Use amount required to fill volume of line, to maximum of 2 mL in 2 mg</td>
<td>1.0 mg/mL. Use amount required to fill volume of line, to a maximum of 2 mL (2 mg/lumen). Treat one lumen at a time</td>
<td>2.0 mg diluted with 0.9% NaCl to 3 mL</td>
</tr>
</tbody>
</table>

*SC = subcutaneous.
Table 10—Thrombolytic Therapy for Pediatric Patients*

| Systemic Thrombolytic Therapy† |
|-------------------------------|-----------------|
| Regimen                      | Monitoring      |
| UK 4,400 U/kg               | None            |
| SK 2,000 U/kg               | None            |
| tPA None                     | None            |
| *tPA 0.1–0.6 mg/kg for 6 h  | PT, APTT        |
| *TCT 4,400 U/kg/h per lumen 2–4 h | Fibrinogen, TCT |
| *SK 2,000 U/kg/h per lumen 2–4 h | PT, APTT      |
| *tPA None                     | PT, APTT        |
| TCT 4,400 U/kg/h per lumen 2–4 h | Fibrinogen, TCT |
| SK 2,000 U/kg/h per lumen 2–4 h | PT, APTT      |
| tPA None                      | PT, APTT        |
| *tPA 0.1–0.6 mg/kg for 6 h   | Same            |

*Start heparin therapy either during or immediately on completion of thrombolytic therapy. A loading dose of heparin may be omitted. The length of time for optimal maintenance is uncertain. Values provided are starting suggestions; some patients may respond to longer or shorter courses of therapy.

†TCT = thrombin clotting time.

Route of Administration

To our knowledge, there are no published studies that compare local to systemic thrombolytic therapy in children. From 1966 to 1997, there were 70 cases reported in the English-language literature of local thrombolytic therapy in children, excluding femoral artery thrombosis following cardiac catheter and low-dose thrombolyis to unblock CVLs. Complete or partial lysis was achieved in 70% of cases, with major bleeding occurring in 11% of children. A retrospective cohort reported successful lysis in only one of seven patients, with five major complications in three patients. 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 with new thrombus formation. 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 catheter use in children. There are no reported cases of pulse-spray thrombolysis in children.

Adverse Effects of Thrombolytic Therapy

Based on a review of the pediatric literature (255 patients) and on two retrospective cohort studies, the incidence of bleeding requiring treatment with packed RBCs occurs in approximately 20% of pediatric patients. The most frequent problem was bleeding at sites of invasive procedures that required treatment with blood products. A review of the literature specifically examined the incidence of ICH during thrombolytic therapy in children. There was no information about concurrent heparin administration in this study. In total, ICH was found in 14 of 929 patients (1.5%) analyzed. When subdivided according to age, ICH was identified in 2 of 468 children (0.4%) after the neonatal period, in 1 of 83 term infants (1.2%), and in 11 of 86 preterm infants (13.8%). However, in the largest study of premature infants included in this review, the incidence of ICH was the same in the control arm, which did not receive thrombolytic therapy. The incidence of ICH in adults receiving thrombolytic therapy also varies with age and the indication for thrombolysis. The incidence of ICH in adults is between 0.3% and 1.0% when treating acute myocardial syndromes, but it may be as high as 20% in the treatment of acute stroke.

Treatment of Bleeding Due to Thrombolytic Therapy

Before thrombolytic therapy is used, the correction of other concurrent hemostatic problems, such as thrombocytopenia or vitamin K deficiency, is advised. Clinically mild bleeding, which is usually oozing from a wound or puncture site, can be treated with local pressure and supportive care. Major bleeding from a local site can be treated by stopping the infusion of the thrombolytic agent, administering a cryoprecipitate (usual dose, 1 bag per 5 kg), and administering other blood products as indicated. If the bleeding is life threatening, an antifibrinolytic agent also can be used.

Indications for Antithrombotic Therapy in Pediatric Patients

Although the general indications for antithrombotic therapy in pediatric patients are similar to adults, the frequency of specific disease states and underlying pathologic conditions differ. For example, myocardial infarctions and cerebrovascular accidents are two of the more common indications for antithrombotic therapy in adults and are the least common in children. The current indications for antithrombotic therapy in children are provided in Table 11.

Venous Thromboembolic Disease

Incidence: The incidence of venous thromboembolic complications (i.e., DVT and PE) is age-dependent, with the lowest risk occurring in children. Estimates of the incidence of DVT and PE in the general pediatric population are 0.07 events per 10,000 hospital admissions and 5.3 events per 10,000 hospital admissions, respectively. Two prospective large-registry studies reported the incidence of symptomatic neonatal DVT to be 0.24 to 0.26 events per 10,000 births. Comparable incidences of DVT and PE in the adult population are approximately 2.5 to 5.0%, 165–167 Other comparisons illustrating the lower risk of DVT and PE during childhood are the < 1% incidence of clinically apparent DVT and PE following lower limb or scoliosis surgery, and the low frequency of DVT and PE in children with heterozygote congenital prothrombotic states. Several mechanisms likely contribute to the protective effect of age for DVT and PE. These mechanisms include a reduced capacity to generate thrombin, an increased capacity of α2-macro-
globulin to inhibit thrombin,\textsuperscript{171} the presence of a circulating anticoagulant at birth,\textsuperscript{172–174} and others, such as an enhanced antithrombotic potential by the vessel wall.\textsuperscript{175–177}

**Clinical Features:** Despite the protective effects of age, increasing numbers of children are developing DVT and PE as secondary complications of their underlying disorders. In contrast to adults, in whom DVT and PE are idiopathic in 40% of patients, only 5% of cases of DVT and PE are idiopathic in children.\textsuperscript{72,178} Ninety-five percent of cases of DVT and PE in pediatric patients are secondary problems to serious diseases such as prematurity, cancer, trauma/surgery, congenital heart disease, and systemic lupus erythematosus.\textsuperscript{72,163,164,169,179,180} Less than 1% of cases of DVT in neonates are idiopathic.\textsuperscript{164} Congenital prethrombotic disorders alone account for < 10% of cases of DVT and PE in children.\textsuperscript{72,169} The frequency of congenital prethrombotic disorders in children with secondary DVT is uncertain (Table 12).\textsuperscript{163,164,181–184} The greatest risk for developing DVT and PE occurs in infants < 1 year of age and in teenagers.\textsuperscript{72,161,164,169} DVT in the lower extremities is the most frequent non-CVL-related TE in children.\textsuperscript{169} The clinical presentations and treatments for DVT and PE in children are similar to those for the adult.\textsuperscript{72,162,169,185}

**CVLs:** Over 50% of cases of DVT in children and over 80% of cases in newborns occur in the upper venous system secondary to the use of CVLs.\textsuperscript{72,163,164,169} CVLs are placed for short-term intensive care or for long-term supportive care for children requiring TPN or therapy for cancer. Cases of CVL-related DVT are not trivial as they require repeat anesthesia for CVL replacement, provide a source for PE,\textsuperscript{186–189} cause superior vena cava syndrome,\textsuperscript{190,191} chylothorax,\textsuperscript{186,190,193,194} and eventual destruction of the upper venous system,\textsuperscript{105} and contribute to postphlebitic syndrome in both the upper and lower extremities. A cross-sectional study assessed the incidence of PE in children receiving TPN at home and reported an incidence of 35% and a mortality rate from PE of 12%.\textsuperscript{190} A prospective registry of 244 children with CVL-related DVT reported an incidence of postphlebitic syndrome of 9.5% and a DVT-related mortality rate of 3.7%.\textsuperscript{197} Further study is required to document the true extent of long-term morbidity and mortality of patients with CVL-related DVT.

The incidence of CVL-related TEs reported in the literature varies, reflecting different underlying disorders, diagnostic tests, and indexes of suspicion. For example, the incidence of CVL-related TEs in children receiving long-term TPN varies from 1%, based on clinical diagnosis,\textsuperscript{190,199} to 35%, based on ventilation-perfusion scans or echocardiography,\textsuperscript{195} to 75%, based on venography.\textsuperscript{195} In a prospective cohort, 18% of children in an intensive-care setting with CVLs in place for 48 h developed CVL-related DVT.\textsuperscript{200} The recently completed Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated With Asparaginase (PARKAA) study\textsuperscript{5} reported an incidence of 37% for venographically proven DVT in children with acute lymphoblastic leukemia (ALL) who were receiving asparaginase therapy, and it reported that ultrasound missed approximately 80% of those clots.\textsuperscript{6} In many patient populations, the incidence is not accurately known. This information is important in

### Table 11—Indications for Antithrombotic Agents in Pediatric Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Treatment</td>
<td>Venous thromboembolic complications</td>
</tr>
<tr>
<td></td>
<td>Arterial thromboembolic complications</td>
</tr>
<tr>
<td>II. Treatment: probable</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Some forms of stroke</td>
</tr>
<tr>
<td>III. Prophylaxis</td>
<td>Mechanical prosthetic heart valves</td>
</tr>
<tr>
<td></td>
<td>Biological prosthetic heart valves</td>
</tr>
<tr>
<td></td>
<td>Cardiac catheterization</td>
</tr>
<tr>
<td></td>
<td>Central arterial catheters</td>
</tr>
<tr>
<td>IV. Prophylaxis: probable</td>
<td>Endovascular stents</td>
</tr>
<tr>
<td></td>
<td>BT shunts</td>
</tr>
<tr>
<td></td>
<td>Fontans</td>
</tr>
<tr>
<td></td>
<td>Central venous catheters</td>
</tr>
<tr>
<td></td>
<td>Atrial venous fibrillation</td>
</tr>
<tr>
<td>V. Other</td>
<td>Kawasaki’s disease</td>
</tr>
<tr>
<td></td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td></td>
<td>Extra/corporeal membrane oxygenation</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Continuous venovenous hemoperfusion</td>
</tr>
</tbody>
</table>

### Table 12—Frequency of Venous TE in Members of Families With Combined Thrombophilias*  

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Associated With FV-R506Q</th>
<th>Sole Defect</th>
<th>FV-R506Q Only</th>
<th>Neither Defect</th>
<th>Source of Extracted Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>VTE, %</td>
<td>No.</td>
<td>VTE, %</td>
<td>No.</td>
</tr>
<tr>
<td>Protein C deficiency (6 families)</td>
<td>23</td>
<td>70</td>
<td>34</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>Protein S deficiency (7 families)</td>
<td>18</td>
<td>72</td>
<td>21</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Antithrombin III deficiency (6 families)</td>
<td>12</td>
<td>92</td>
<td>7</td>
<td>57</td>
<td>5</td>
</tr>
</tbody>
</table>

*VTE = venous TE; FV = factor V. Reprinted from Seligsohn and Zivelin with permission.\textsuperscript{206}
order to identify populations of children in whom prophylactic antithrombotic therapy should be tested in clinical trials.

A randomized controlled trial (RCT) comparing low-dose OAs (1 mg) with placebo in adults with CVLs showed that the incidence of DVT, based on venography, was safely reduced from 37 to 9.5%. A similar study comparing 2,500 IU fragmin, an LMWH administered subcutaneously daily, to no therapy in adults with cancer and who had catheters showed a reduction in venographically identified thrombosis at 90 days from 62 to 6%. The relative risk reduction was 6.75 (95% confidence interval [CI], 1.05 to 43). The complexity of the primary illness in most children with CVL-related DVT, and the intensity of their therapy, whether medical or surgical, increases the potential for bleeding complications from prophylactic anticoagulation. In addition, oral anticoagulation therapy or subcutaneous LMWH therapy is more difficult to administer in small children. The results of the recently closed Prophylaxis of Thromboembolism in Kids Trial (PROTEKT) will demonstrate safety and, potentially, efficacy, although further studies are required in children who are <3 months old.

The patency of CVL is frequently maintained by intermittent boluses of heparin (200 to 300 U) daily, weekly, or monthly. For infants weighing <10 kg, a lower dose of 10 U/kg is frequently used to avoid transient anticoagulation of the infant. There is only one small randomized trial assessing the need for prophylactic heparin. The study was conducted in children with cancer using echocardiography of the heart as the outcome measure, not venography. Although the study reported no benefit from flushing CVLs with heparin, the design and outcome measure limits the generalizability of this study. Local instillation of UK is historically the most commonly used therapy for treating a malfunctioning line that is blocked, although, as previously mentioned, the use of UK has decreased substantially since the FDA warning. Based on several case series, patency is restored in approximately 80% of patients.

**Congenital Prothrombotic Conditions**

Congenital thrombophilia is usually defined as having the following features: (1) positive family history; (2) early age of onset of TE; (3) recurrent disease; and (4) multiple or unusual locations. Clinically, the most significant inherited prothrombotic conditions are deficiencies of AT, PC, and PS because of the large increase in relative risk these deficiencies confer. Activated PC resistance/factor V Leiden (FV-R506Q) and prothrombin G20210A (H2G20210A) polymorphism, while having less impact on individual risk, are significant because of their frequencies in certain populations. A large number of other candidate genes have been proposed as risk factors for congenital thrombophilia; however, most of these candidates have not undergone careful segregation or population studies to define their pathogenic roles. In fact, some of the seemingly obvious candidates, such as abnormalities in fibrolysis, do not appear to confer heritable risk. These latter studies, however, are hampered by the low prevalence of most of these inherited abnormalities in the general population.

Another report demonstrated an increased risk for thrombosis in families with a second genetic abnormality. Most reports have described a combination of FV-R506Q with abnormalities of PC, PS, and AT. These findings begin to shed light on the marked variability in clinical expression of these syndromes. The effect of more severe deficiencies has long been evident from the severely affected neonates with homozygous PC and PS deficiencies. Once one moves away from the well-defined homozygous cases, the risk and severity of TEs appear to vary with the type and number of underlying genetic abnormalities (Table 12).

The role of these congenital prothrombotic states in childhood thrombosis remains controversial. If one considers the deficiencies of AT, PC, and PS in addition to the factor V Leiden and prothrombin gene mutations, large family studies found negligible rates of thrombosis in children who were <15 years of age. A number of cohort studies have failed to identify AT deficiency in children with both arterial and venous TEs. Those studies that reported higher frequencies of AT deficiency did not distinguish between acquired and inherited deficiencies. Cohort studies have reported conflicting results concerning the incidence of heterozygous PC deficiency in children with thromboembolic disease. From 1966 to 1999, there were 40 case reports of children with heterozygous PS deficiency and TEs during childhood. In these cases, 21 children had venous TEs, 11 had arterial TEs, and 5 had both venous and arterial TEs, and for 3 children the site of thrombosis was not clear. Eleven studies, the majority of which were case series or case control studies, have examined the frequency of the factor V Leiden mutation in children with TEs in a variety of clinical situations. These studies are summarized in Table 13. Further studies assessed the relationship between childhood stroke (ie, arterial ischemic stroke and sino-
Table 13—Frequency of the Factor V Leiden Mutation in Children With Thrombosis*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Location of TE and/or</th>
<th>Heterozygote</th>
<th>Homozygote</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Population</td>
<td>Heterozygote</td>
<td>Homozygote</td>
</tr>
<tr>
<td>Nowak-Gottl et al284/1996</td>
<td>ALL</td>
<td>3/3 (100%)</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>Hausler et al225/1999</td>
<td>non-CVL TE</td>
<td>2/8 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gurgey239/1999</td>
<td>VTE/ATE</td>
<td>15/63 (23%)</td>
<td>5/63 (8%)</td>
</tr>
<tr>
<td>Aschka et al239/1996</td>
<td>VTE/ATE</td>
<td>29/125 (23%)</td>
<td>3/125 (2%)</td>
</tr>
<tr>
<td>Sifontes et al231/1996</td>
<td>VTE</td>
<td>3/14 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sifontes et al239/1998</td>
<td>non-CNS TE</td>
<td>5/34 (15%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hagstrom et al231/1998</td>
<td>non-CNS TE</td>
<td>4/32 (13%)</td>
<td>0/32 (0%)</td>
</tr>
<tr>
<td>Sifontes et al231/1997</td>
<td>Cancer</td>
<td>1/32 (3%)</td>
<td>0/32 (0%)</td>
</tr>
<tr>
<td>Mullen et al229/1996</td>
<td>VTE</td>
<td>0/6 (0%)</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td>Seixas et al231/1997</td>
<td>PVT</td>
<td>0/20 (0%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>Ong et al231/1998</td>
<td>CPB</td>
<td>0/9 (0%)</td>
<td>0/9 (0%)</td>
</tr>
</tbody>
</table>

PVT = portal vein thrombosis; CPB = cardiopulmonary bypass; ATE = arterial thromboembolism. See Table 12 for any abbreviations not used in text.

Homozygous PC or PS Deficiency

In contrast to heterozygous PC or PS deficiency, homozygous PC/PS deficiency presents within hours of birth with purpura fulminans, cerebral and/or ophthalmic damage that occurred in utero, and, on rare occasions, large-vessel TEs. Purpura fulminans is an acute, lethal syndrome of rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis. An international database of mutations in the PC gene lists only 17 cases, and approximately 25 further kindreds are reported in the literature. At least one case of purpura fulminans due to homozygous PS deficiency has been reported. All patients presenting at birth with purpura fulminans had undetectable levels of PC or PS. Homozygous PC deficiency may be present with large-vessel TEs during childhood or early adult life. PC levels in these patients ranged from 0.05 to 0.20 U/mL. These children usually presented with DVT following a minor secondary insult and developed OA-induced skin necrosis.

Short-term Treatment: Numerous forms of therapy have been used in individual patients, including FFP, PC concentrate, cryoprecipitate, prothrombin complex concentrate, heparin, LMWH, aspirin, sulfipyrazone, corticosteroids, vitamin K, aprotinin, and AT concentrate. Plasma PC levels achieved with these doses of FFP varied from 15 to 32% at 30 min after infusion, and from 4 to 10% at 12 h. Doses of PC concentrate administered in the literature have ranged from 20 to 60 U/kg. A dose of 60 U/kg resulted in peak PC levels above 0.60 U/mL. The replacement of PC should be continued until the clinical lesions resolve, which is usually 6 to 8 weeks.

The one newborn with homozygous PS deficiency was treated with both FFP and cryoprecipitate, which contain similar amounts of PS. A pharmacokinetic study was performed following the infusion of 10 mL/kg FFP, and a recovery of PS at 2 h of 0.23 U/mL and at 24 h of 0.14 U/mL was reported. The PS was entirely in the C4b-bound fraction on crossed immunoelectrophoresis. The approximate half-life of PS in this infant was 36 h.

Long-term Treatment: The modalities used for long-term management of infants with homozygous PC deficiency include OA therapy, intermittent PC replacement with PC concentrate, and liver transplantation. PC replacement may not prevent further TEs in the presence of a risk factor such as a CVL. Currently, the majority of children are treated with OAs. When therapy with OAs is initiated, the infant should continue receiving PC (or PS) replacement until the INR is between approximately 3.0 and 4.5 to avoid skin necrosis. To some extent, these patients need to be titrated for the lowest dose that prevents skin necrosis. Patients with homozygous PC or PS deficiency, but with detectable plasma concentrations, have also been treated with LMWH. The latter approach avoids the risk of OA-induced skin necrosis and likely decreases the risk of bleeding associated with high doses of OAs.

Arterial Thromboembolic Disease

Etiology: The most common etiology of arterial TEs in children is catheter use. This includes cardiac catheterization and central or peripheral arterial lines in the intensive-care setting. Non-catheter-related arterial TEs are rare and occur in patients with Takayasu’s arteritis, in arteries from transplanted organs, in giant coronary aneurysms secondary to Kawasaki’s disease, and as complications of some forms of congenital heart disease, and in cerebral vessels from local lesions or lesions that are embolic from cardiac or other locations.

Cardiac Catheterization: In the absence of prophylactic anticoagulation, the incidence of symptomatic TEs following cardiac catheterization via the femoral artery is approximately 40% (Table 14). Younger children (ie, those <10 years of age) have an increased incidence of TEs compared to older children. Prophylactic anticoagulation therapy with aspirin does not significantly reduce the incidence of arterial TEs. However, anticoagulation therapy with 100 to 150 U/kg heparin reduces the incidence from 40 to 5%. The results from a more recent, small randomized trial suggested that a 50-U/kg bolus of
heparin may be as efficacious as 100 U/kg when given immediately after arterial puncture; however, this study was underpowered, and one could not recommend 50 U/kg as the optimal prophylaxis at this time. Recent advances in interventional catheterization have resulted in the use of larger catheters and sheaths that may increase the risk of TEs. Further heparin boluses are frequently used in prolonged procedures (ie, those > 60 min), especially during interventional catheterizations; however, the benefits of this practice are not known. A short limb and claudication are the long-term consequences of femoral artery TEs in children.

Umbilical Artery Catheterization: Umbilical arterial catheterization is necessary for the administration of supportive care that is critical to the survival of sick newborns (Table 15). Umbilical artery catheter tips are positioned either high (ie, at the level of T5 to T10) or low (ie, at the level of L3 to L5). The optimal position to minimize TEs remains uncertain. The position of the umbilical artery catheters may affect the frequency of both TEs and ICHs. A low-dose continuous heparin infusion (3 to 5 U/h) is commonly used to maintain catheter patency. The effectiveness of heparin was assessed in one large trial and in five smaller randomized trials. The following three outcomes were assessed: patency; local thrombus; and ICH. Patency, which is likely linked to the presence of local thrombus, is prolonged by the use of low-dose heparin. The incidence of local thrombus, detected by ultrasound, was not decreased in two randomized studies. However, the power of these studies was low. The incidence of ICH as an outcome was not increased in two randomized studies. However, the sample size in one study was small (15 per arm). In the other study, the odds ratio for ICH and heparin use was 1.49 (95% CI, 0.62 to 3.59). In two cohort studies, heparin was implicated as a risk factor for ICH in low-birth-weight infants. One study was retrospective, and the 95% CI around the odds ratio of 3.9 was large (95% CI, 1.4 to 11.0), and the magnitude of the risk was uncertain. The second study reported a positive correlation between heparin dose and frequency of ICH.

### Table 14—Cardiac Catheterization in Children: Arterial

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Type of Study</th>
<th>Intervention</th>
<th>Patients, No.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freed et al 290/1974</td>
<td>RCT</td>
<td>Aspirin (15 mg/kg)</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Freed et al 290/1974</td>
<td>RCT</td>
<td>Placebo</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>Freed et al 290/1974</td>
<td>RCT</td>
<td>Heparin (1 mg/kg)</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Freed et al 290/1974</td>
<td>RCT</td>
<td>Placebo</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Saxena et al 291/1997</td>
<td>RCT</td>
<td>Heparin 50 IU/kg</td>
<td>183</td>
<td>0</td>
</tr>
<tr>
<td>Saxena et al 291/1997</td>
<td>RCT</td>
<td>Heparin 100 IU/kg</td>
<td>183</td>
<td>0</td>
</tr>
</tbody>
</table>

*Indicates a p value < 0.05.

### Table 15—Umbilical Artery Catheterization*

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Type of Study</th>
<th>Intervention</th>
<th>Patients, No.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al 297/1987</td>
<td>RCT</td>
<td>HB-PU</td>
<td>61</td>
<td>NR</td>
</tr>
<tr>
<td>Horgan et al 300/1987</td>
<td>RCT</td>
<td>Heparin</td>
<td>59</td>
<td>NR</td>
</tr>
<tr>
<td>Rajani et al 298/1979</td>
<td>RCT</td>
<td>Heparin</td>
<td>52</td>
<td>NR</td>
</tr>
<tr>
<td>David et al 298/1981</td>
<td>RCT</td>
<td>Heparin</td>
<td>32</td>
<td>NR</td>
</tr>
<tr>
<td>Bosque and Weaver 299/1986</td>
<td>RCT</td>
<td>Heparin (C)</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Horgan et al 300/1987</td>
<td>RCT</td>
<td>Heparin (I)</td>
<td>19</td>
<td>NR</td>
</tr>
<tr>
<td>Horgan et al 300/1987</td>
<td>RCT</td>
<td>No heparin</td>
<td>52</td>
<td>NR</td>
</tr>
<tr>
<td>Ankola and Atakent 301/1993</td>
<td>RCT</td>
<td>Heparin</td>
<td>15</td>
<td>4 ICH</td>
</tr>
<tr>
<td>Chang et al 302/1997</td>
<td>RCT</td>
<td>No heparin</td>
<td>5,558</td>
<td>19 ICH</td>
</tr>
</tbody>
</table>

* = blocked; HB-PU = heparin-bonded polyurethane; PVC = polyvinyl chloride; C = continuous; I = intermittent; NR = not reported.
† = No hemorrhage.
‡ = Indicate a p value < 0.05.
however, severity of illness was also positively correlated with heparin dose, and the effect could not be differenti-
ated.atrip. Large well-designed studies are required to deter-
mine whether low-dose heparin infusion affects the inci-
dence of ICH.

Kawasaki’s Disease

In patients with Kawasaki’s 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 anti-inflammatory agent,
then in lower doses as an antiplatelet agent (3 to 5 mg/kg/d
for ≥ 7 weeks) to prevent coronary aneurysm thrombosis
and subsequent infarction (the major cause of death in
Kawasaki’s disease). Although no randomized controlled
studies have been performed (to our knowledge), two
cohort studiesatrip have suggested that aspirin can reduce
the coronary involvement in patients with Kawasaki’s
disease. A 1995 meta-analysisatrip concluded that children
treated with IV gamma globulin and aspirin had a signifi-
cantly lower incidence of coronary artery aneurysms than
those treated with aspirin alone. Much of the treatment
difference in this analysis was due to one randomized
study that demonstrated that the combination of IV
gamma globulin and aspirin is more efficacious in this
regard than aspirin alone.atri The meta-analysis made a
number of conclusions about the optimal dosing of aspirin
and gamma globulin. However, significant methodologic
flaws in the analysis suggest that the conclusions should be
viewed with some caution. Further studies are required.

Prosthetic Heart Valves in Children

Biological Prosthetic Heart Valves in Children: Valvular
heart diseases in childhood encompass a wide variety of
abnormalities with greatly variable presentations. The
valve lesion may be isolated, may be an integral part of
more complex intracardiac lesions, or may be the result of
treatment of the underlying congenital defect. TEs, either
of the valve or due to a cerebrovascular accident, are some
of the most serious complications of successful cardiac
valve replacement.

The failure of biological prosthetic heart valves in
children poignantly illustrates the fallacy of extrapolating
recommendations for adults to children without evaluation
in clinical trials. Commercially prepared biological pros-
theses became available in 1971 and achieved excellent
early results in adult patients. Biological prosthetic heart
valves rapidly became the “valve of choice” for the pedi-
aric age group.atrip Subsequently, the premature degener-
ation and calcification of porcine valves was identified in
the majority of children.atrip The accelerated failure of
biological prosthetic heart valves in children was con-
firmed by many groups. Current recommendations are
that, in general, mechanical prosthetic heart valves should
be used in the mitral and aortic positions in children and
biological prosthetic heart valves should be reserved for
patients who require tricuspid or pulmonary valve replace-
ments.atrip Children with biological prosthetic heart
valves are treated following adult recommendations and
should be observed for evidence of valve dysfunction.

Mechanical Prosthetic Heart Valves in Children: Anti-
thrombotic therapy with OAs is clearly indicated for adults
with mechanical prosthetic heart valves (Tables 16, 17,
atrip Alternatives to OAs have been pursued for
children because of the issue of safe monitoring.

No Therapy: With no antithrombotic therapy, TEs
occurred at a rate of 5.7% per patient-year with St. Jude
valves,atrip and at rates of 6.8 to 27.3% per patient-year
for other types of valves (Table 16).atri There was one death
due to mitral valve thrombosis.atrip

Antiplatelet Agents: One cohort study reported no
differences in survival or number of TEs in children with
left-sided St. Jude valves treated with warfarin to maintain
a PT of 1.5 times control, or aspirin (5 to 6 mg/kg) and
dipyridamole (6 mg/kg).atri The linearized TE rates were
2.6% and 1.7% per patient-year, respectively (p = 0.6).
Bleeding linearized event rates were 1.5% per patient-year
in the warfarin group and 0 in the antiplatelet group
(p = 0.09). Numerous case series have reported the use of
empiric low doses of aspirin (6 to 20 mg/kg/d) and/or
dipyridamole (2 to 5 mg/kg/d) for the prevention of TEs in
the absence of therapy with OAs. With antiplatelet agents
alone, TEs occurred at rates of 1.1 to 68% per patient-
year, with three of eight studies having TE rates of > 5%
per patient-year (Table 17). There was only one major

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Study Type</th>
<th>No.</th>
<th>Age</th>
<th>Valve Type</th>
<th>Position</th>
<th>TE% pt-yr</th>
<th>HEM% pt-yr</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sade et al189/1988</td>
<td>Observational</td>
<td>48</td>
<td>5 mo–21 yr</td>
<td>St. Jude</td>
<td>Ao, M</td>
<td>NR</td>
<td>0</td>
<td>1 M1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ao + M</td>
<td>NR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>overall</td>
<td>5.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(186)†</td>
<td>1–19 yr</td>
<td>Various</td>
<td>Ao</td>
<td>6.8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>20.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>± E2 valves</td>
<td>27.3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*HEM = hemorrhage; Ao = aortic; M = mitral; pt-yr = patient-year. See Table 15 for abbreviations not used in text.
†The death was secondary to a mitral valve thrombosis.
‡The number of patients treated with no antithrombotic therapy could not be determined. Number refers to the entire patient population of the study.atrip
episode of bleeding, which was not fatal and did not result in long-term morbidity (Table 17). There were eight patients who died due to TEs for whom information on anticoagulant therapy could not be determined.320

*Oral Anticoagulation Therapy: With OAs, the incidence of TEs was uniformly < 5% per patient-year (Table 18). There were five deaths due to TEs and two deaths due to bleeding.66,88,314,319 Three of the five patients had discontinued OA therapy, and the anticoagulant status of the other two patients could not be determined. With one exception, the rate of major bleeding was < 3.5% per patient-year (Table 18). In one study, two patients required blood transfusions (rate, 8.2% per patient-year) and recovered uneventfully.64 Adjuvant therapy with antiplatelet agents was used in one study.66 Based on information available for adults and children, a reasonable approach is to consider therapy with aspirin in combination with OAs for high-risk patients. High-risk patients include those with prior TEs, atrial fibrillation, a large left atrium, left atrial thrombi, ball valves, and mitral valves.

**Conclusion:** The available data support the recommendation for oral anticoagulation therapy in children who have mechanical prosthetic heart valves. Problems of effectively monitoring OAs can be addressed through anticoagulation clinics for children1,63 and through the use of whole-blood monitors in the clinic and at home.320

**Other Cardiac Disorders**

Antithrombotic therapy is currently used for several other congenital heart lesions or as a consequence of their surgical treatments

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Study Type</th>
<th>No.</th>
<th>Dose</th>
<th>Age, yr</th>
<th>Valve Type</th>
<th>Position</th>
<th>TE/% pt-yr</th>
<th>HEM/% pt-yr</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serra et al1987</td>
<td>Observational</td>
<td>24</td>
<td>ASA 6.1 mg/kg/d</td>
<td>50–20</td>
<td>St. Jule</td>
<td>Ao</td>
<td>68</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>McGrath et al1987</td>
<td>Observational</td>
<td>30</td>
<td>ASA 900 mg/d</td>
<td>4–20</td>
<td>St. Jule</td>
<td>Ao, M</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>El Maklouf et al1987</td>
<td>Observational</td>
<td>15</td>
<td>ASA 20 mg/kg/d</td>
<td>2–6</td>
<td>Various</td>
<td>Ao, M</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Bradley et al1987</td>
<td>Observational</td>
<td>10</td>
<td>ASA 6.1 mg/kg/d</td>
<td>&lt; 19</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Solymar et al1991</td>
<td>Observational</td>
<td>24</td>
<td>ASA 12 mg/kg/d</td>
<td>1–20</td>
<td>Various</td>
<td>Ao</td>
<td>1.8</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Borkon et al1996</td>
<td>Observational</td>
<td>8</td>
<td>Not provided</td>
<td>7–17</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LeBlanc et al1993</td>
<td>Observational</td>
<td>20</td>
<td>ASA 10 mg/kg/d</td>
<td>1–17</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradley et al1995</td>
<td>Observational</td>
<td>16</td>
<td>ASA 5–6 mg/kg/d</td>
<td>3–16</td>
<td>St. Jule</td>
<td>Ao, M</td>
<td>1.7</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**BT Shunts:** BT shunts are one form of palliative surgery used to enhance systemic blood flow, subclavian artery blood flow, and pulmonary artery blood flow in patients with severe or progressive cyanosis that is usually secondary to pulmonary stenosis.321,322 Modified Blalock shunts, in which a tube graft (Gore-Tex; W.L. Gore & Associates; Newark, DE) is taken from the side of the subclavian artery and anastomosed to the pulmonary artery, have been used since 1980. Because of the short length and very high flow, acute thrombosis is less common. Since 1980, 647 children with BT shunts were described in 21 case series. The incidence of thrombotic occlusion ranged from 1 to 17%. Many investigators used antithrombotic therapy, beginning with therapeutic doses of heparin followed by low-dose aspirin (1 to 10 mg/kg/d).323 Although others324 have recommended intraoperative heparin with no further anticoagulation therapy.

**Fontan Operation:** The Fontan procedure, or a modified version, is the definitive palliative surgical treatment for most congenital univentricular heart lesions. TEs remain a major cause of early and late morbidity and mortality. The reported incidences of venous TEs and stroke ranged from 3 to 16% and 3 to 19%, respectively, in retrospective cohort studies in which thrombosis was the primary outcome, and ranged from 1 to 7% in retrospective studies assessing multiple outcomes. TEs 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. Despite
aggressive therapy, thromboembolic events following Fontan procedures have a high mortality rate 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 anticoagulation. Consequently, a wide variety of prophylactic anticoagulant regimens are in use. There is an ongoing large, multicenter, prospective trial of prophylactic anticoagulation therapy following Fontan procedures.325 The trial compares aspirin (5 mg/kg/d) to initial heparin therapy followed by warfarin (target INR, 2 to 3) as primary prophylaxis. Further studies are required to determine the optimal prophylactic anticoagulation therapy required.

Other Cardiac Disorders: Other likely cardiac indications for anticoagulation in children are atrial fibrillation and myocardial infarction.327 There are only case reports describing antithrombotic therapy for these patients. In the absence of data, the use of guidelines for antithrombotic therapy in adult patients is recommended.

Other Disorders

Antithrombotic therapy is used in several other disorders in pediatric patients that are not discussed in this article.232 Readers are referred to other references for antithrombotic therapy in cardiopulmonary bypass,328–331 extracorporeal membrane oxygenation,332–334 and continuous venovenous hemoperfusion.335–337

Atrophie Blanche: Atrophie blanche (livedo vasculitis) is a superficial thrombotic disorder in which antiplatelet therapy may alleviate pain and decrease ulceration.338

Angina, Acute Myocardial Infarction, and Peripheral Artery Disease: Although these are the typical indications for aspirin therapy in adults, they occur rarely in children. To our knowledge, there are no published studies address-

Table 18—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves Treated With OAs

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Study Type</th>
<th>No.</th>
<th>Age</th>
<th>Valve Type</th>
<th>Position</th>
<th>TE/pt-yr</th>
<th>HEM/pt-yr</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spevak et al197/1986</td>
<td>Observational</td>
<td>56</td>
<td>&lt; 5 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>1.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>El Makhlouf et al197/1987</td>
<td>Observational</td>
<td>83</td>
<td>2–16 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>2.3</td>
<td>0</td>
<td>4†</td>
</tr>
<tr>
<td>Harada et al197/1990</td>
<td>Observational</td>
<td>40</td>
<td>4 mo–15 yr</td>
<td>St. Jude</td>
<td>Ao, M</td>
<td>1.3</td>
<td>0</td>
<td>1 Mi</td>
</tr>
<tr>
<td>Stewart et al197/1987</td>
<td>Observational</td>
<td>30</td>
<td>6–17 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>2.30</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Bradley et al198/1985</td>
<td>Observational</td>
<td>20</td>
<td>&lt; 19 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>0</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Milano et al197/1986</td>
<td>Observational</td>
<td>71</td>
<td>15 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>0.7</td>
<td>0</td>
<td>1 Mi</td>
</tr>
<tr>
<td>Schaffer et al198/1987</td>
<td>Observational</td>
<td>33</td>
<td>9–48 mo</td>
<td>St. Jude</td>
<td>Ao, M</td>
<td>0.13</td>
<td>0</td>
<td>0.38</td>
</tr>
<tr>
<td>Solymar et al197/1991</td>
<td>Observational</td>
<td>(186)§</td>
<td>1–20 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>2.1</td>
<td>2.1</td>
<td>1 Mi</td>
</tr>
<tr>
<td>Schaff et al198/1984</td>
<td>Observational</td>
<td>48</td>
<td>6 mo–18 yr</td>
<td>Starr</td>
<td>Ao</td>
<td>5.3</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Borkon et al198/1986</td>
<td>Observational</td>
<td>22</td>
<td>3 wk–17 yr</td>
<td>St. Jude</td>
<td>Ao, M</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Human et al198/1982</td>
<td>Observational</td>
<td>56</td>
<td>2–12 yr</td>
<td>Various</td>
<td>M</td>
<td>n = 3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Antunes et al198/1989</td>
<td>Observational</td>
<td>352</td>
<td>&lt; 20 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>0.80.51.7</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Woods et al198/1986</td>
<td>Observational</td>
<td>20¶</td>
<td>5 mo–16 yr</td>
<td>Various</td>
<td>Ao, M</td>
<td>1.80</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>Champsaur et al199/1997</td>
<td>Observational</td>
<td>54</td>
<td>1–17 yr</td>
<td>Various</td>
<td>Ao &gt; 2</td>
<td>0.3</td>
<td>0.3</td>
<td>1 bleeding</td>
</tr>
<tr>
<td>Bradley et al198/1985</td>
<td>Observational</td>
<td>48</td>
<td>6 mo–18 yr</td>
<td>St. Jude</td>
<td>Ao, M</td>
<td>2.6</td>
<td>1.5</td>
<td>1 bleeding</td>
</tr>
</tbody>
</table>

*Pulm = pulmonary. See Table 16 for abbreviations not used in text.
†The type of anticoagulant used could not be determined.
‡Death was due to a mitral valve thrombosis.
§Parentheses indicate estimated number.
¶Patients were treated with a combination of warfarin and ASA.
ing the use of antiplatelet agents in these clinical settings in children.

**Hemolytic-Uremic Syndrome:** Participation of platelets in the thrombotic microangiopathy of hemolytic-uremic syndrome (HUS) makes the use of antiplatelet agents an attractive possibility. Based on two case series, aspirin and dipyridamole have been proposed to result in a more rapid rise in the platelet count in children with HUS. However, a randomized study failed to confirm this hypothesis. Furthermore, there is no evidence that aspirin and dipyridamole favorably affect other outcome variables in children with HUS. A well-designed randomized study showed no benefit of dipyridamole and heparin treatment over symptomatic therapy alone. Similarly, antiplatelet agents have not been shown to be useful in the related disorder of childhood thrombotic thrombocytopenia purpura.

**Homocystinuria:** In a case series, aspirin and dipyridamole were hypothesized to diminish the thromboembolic complications of homocystinuria in patients who are unresponsive to pyridoxine. However, two other case series did not support this hypothesis.

**KEY AREAS THAT URGENTLY REQUIRE FURTHER STUDY**

Since the CHEST consensus conferences began in 1986, there has been a gradual progression of recommendations, with increasing numbers of strong recommendations for antithrombotic therapy in adults. The first guidelines for antithrombotic therapy in pediatric patients occurred in 1995 and were primarily based on adult guidelines and case series in children. Over the last 5 years, through numerous studies, there has been significant improvement in our understanding of the physiology of hemostasis during infancy and childhood, and of the implications for various antithrombotic therapies. In addition, large registries and prospective cohort studies have identified specific clinical questions that require intervention trials to determine optimal therapy. At the time the 1998 CHEST supplement was published, there were five multicenter, multinational randomized controlled trials assessing the optimal use of anticoagulants in children with or at risk for specific thromboembolic complications. The PARKAA study has been completed and has provided important information about the incidence of CVL-related TEs in children with ALL who are receiving l-asparaginase. The Fontan A study (an RCT comparing aspirin to heparin-warfarin as primary prophylaxis against TEs following Fontan surgery) and the PRECLUDE trial (an RCT of placebo vs warfarin anticoagulation [INR, 2.0 to 2.5] for primary thromboembolic prophylaxis in children with systemic lupus erythematosus and antiphospholipid antibodies) are ongoing. The Reviparin in Venous Thromboembolism trial and PROTEKT have stopped prior to planned recruitment targets and are unlikely to answer their primary questions but will provide valuable information on the diagnosis of DVT and the safety of using LMWH in children.

The data from recent studies confirm that extrapolation of adult guidelines to infants and children is suboptimal. Determining the pharmacokinetics of various antithrombotic agents in infants and children, while important, does not determine the efficacy or safety of therapeutic regimens for the prevention or treatment of thromboembolic disease in children. There remains an urgent need for studies to determine safe and effective antithrombotic prophylaxis for CVLs, especially in small infants. The frequent, prolonged, off-label use of LMWH as a single agent to treat DVT in children needs adequate efficacy and safety study. The long-term impact of arterial thrombosis secondary to the use of vascular access devices needs to be proven prior to the consideration of more aggressive prophylactic regimes. The optimal anticoagulation therapy following many cardiac surgical procedures in children remains unclear. These studies will take many years to complete. There is now a collaborative international network capable of performing the needed studies. The challenge remains to convince both peer review agencies and pharmaceutical companies that pediatric trials require a specific dedicated approach.

**RECOMMENDATIONS**

**Venous Thromboembolic Disease in Children**

**First TE:** We recommend that children (> 2 months of age) who have had an initial TE should be treated in the short term with doses of IV heparin that are sufficient to prolong the APTT to a range that corresponds to an anti-factor Xa level of 0.3 to 0.7 U/mL, or with doses of LMWH that are sufficient to achieve an anti-factor Xa level of 0.5 to 1.0 U/mL 4 h after an injection (grade 1C+).

We recommend that initial treatment with heparin or LMWH should be continued for 5 to 10 days. For patients in whom subsequent OA therapy will be used, it can be started as early as day 1 and heparin/LMWH therapy discontinued on day 6 if the INR is therapeutic on 2 consecutive days. For massive PEs or extensive DVTs, a longer period of heparin or LMWH therapy should be considered (grade 1C+).

We recommend that anticoagulant therapy should be continued for at least 3 months using OAs to prolong the PT to a target INR of 2.5 (range, 2.0 to 3.0) or, alternatively, using LMWH to maintain an anti-factor Xa level of 0.5 to 1.0 U/mL (grade 2C).

For children who have experienced an idiopathic TE, we recommend that treatment be continued for at least 6 months with either OAs or LMWH (grade 2C).

Following the initial 3 months of therapy, for children with a first CVL-related DVT, we recommend prophylactic doses of OAs (INR, 1.5 to 1.8) or LMWH (anti-factor Xa levels, 0.1 to 0.3) as an option until the CVL is removed (grade 2C).

**Recurrent TE:** For recurrent non-CVL-related TEs, following the initial 3 months of therapy...
(recommendation, 1 to 3 months), we recommend that indefinite therapy with either therapeutic or prophylactic doses of OAs or LMWH be used (grade 2C).

For recurrent CVL-related TEs, following the initial 3 months of therapy, we recommend that prophylactic doses of OAs (INR, 1.5 to 1.8) or LMWH (anti-factor Xa level, 0.1 to 0.3) be continued until removal of the CVL. If the recurrence occurs while the patient is receiving prophylactic therapy, we recommend that therapeutic doses be continued until the CVL is removed or for a minimum of 3 months (all grade 2C).

**Primary Prophylaxis for Venous TE in Children:** We do not recommend primary prophylaxis for children with CVLs in general at this time, because there is no evidence for the efficacy or safety of this approach (grade 2C).

**Remark:** Short-term prophylactic anticoagulation therapy in high-risk situations such as immobility, significant surgery, or trauma is an option for children with known congenital prothrombotic disorders. However, to our knowledge, there are no published data on which to base a formal recommendation.

**Venous Thromboembolic Disease in Newborns**

**Remark:** There are insufficient data to make specific recommendations about anticoagulation therapy in the treatment of newborns with DVTs and PEs. Options include conventional anticoagulation therapy in age-appropriate doses, short-term anticoagulation therapy, or close monitoring of the thrombus with objective tests and use of anticoagulation therapy if thrombus extension occurs.

If anticoagulation therapy is used, we recommend a short course (10 to 14 days) of IV heparin that is sufficient to prolong the APTT to the therapeutic range that corresponds to an anti-factor Xa level of 0.3 to 0.7 U/mL, or, alternatively, a short course of LMWH that is sufficient to achieve an anti-factor Xa level at the low end of the adult therapeutic range (0.5 to 1.0 U/mL) may be used (all grade 2C compared to no treatment). Longer courses of anticoagulant therapy, up to 3 months, may be required dependent on the location and extent of the thrombus. The thrombus should be closely monitored with objective tests for evidence of extension or recurrent disease. If the thrombus extends following discontinuation of heparin therapy, we recommend oral anticoagulation therapy or extended LMWH therapy (grade 2C).

**Thrombolytic Therapy for Venous Thromboembolic Disease**

**Remark:** There are insufficient data to make specific recommendations about the use of thrombolytic agents in the treatment of venous TEs in neonates or children. Treatment needs to individualized. If thrombolytic therapy is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we recommend supplementation with plasminogen (FFP) (grade 2C).

**Congenital Prothrombotic Conditions**

**Homozygous PC-Deficient and PS-Deficient Patients:** We recommend that newborns with purpura fulminans due to a homozygous deficiency of PC or PS may be treated initially with replacement therapy (either FFP or PC concentrate) for approximately 6 to 8 weeks until the skin lesions have healed (grade 1C+).

Following resolution of the skin lesions, and under cover of replacement therapy, we recommend that oral anticoagulation therapy be introduced with target INR values of approximately 3 to 4.5. Treatment duration with OAs is indefinite. We recommend that replacement therapy with PC concentrate for PC-deficient patients may be used for long-term prophylaxis or as salvage therapy for recurrent skin lesions or thrombosis (grade 2C).

We recommend that for patients with homozygous PC and PS deficiency but with measurable plasma concentrations, LMWH is a therapeutic option (grade 2C).

**Treatment of Arterial Thromboembolism**

**Cardiac Catheterization:** We recommend that newborns and children requiring cardiac catheterization via an artery should undergo IV heparin prophylaxis (grade 1A).

We recommend heparin doses of 100 to 150 U/kg as a bolus (grade 2A compared with 50 U/kg).

**Remark:** The initial dose and further administration of heparin therapy need further evaluation before definite recommendations can be given, in particular in small infants having procedural catheters.

We recommend that clinicians not use aspirin alone (grade 1B).

**Arterial TE:** We recommend that children or neonates with an arterial TE be treated with therapeutic doses of IV heparin (grade 1C).

**Remark:** There are insufficient data to make a recommendation about the optimal duration of therapy.

We recommend that children or neonates with limb-threatening or organ-threatening arterial TEs who fail to respond to initial heparin therapy, and who have no known contraindications, be treated with thrombolytic therapy (grade 1C).
Remark: The use of surgery to treat arterial thrombosis in children should be individualized. There are insufficient data to make specific recommendations in children.

Treatment of Kawasaki’s Disease in Children

In addition to IV gamma globulin (2 g/kg as a single dose), children with Kawasaki’s disease should receive aspirin, 80 to 100 mg/kg/d, during the acute phase (up to 14 days) as an anti-inflammatory agent, then aspirin, 3 to 5 mg/kg/d, for ≥ 7 weeks to prevent the formation of coronary aneurysm thrombosis (grade 1C).

Prosthetic Heart Valves in Children

Biological Prosthetic Heart Valves in Children: Children with biological prosthetic heart valves should be treated following adult recommendations and observed for evidence of valve dysfunction.

Mechanical Prosthetic Heart Valves in Children

We recommend that children with mechanical prosthetic heart valves receive OA therapy (grade 1C+).

We recommend levels of OA therapy that prolong the target INR to 3.0 (range, 2.5 to 3.5) (grade 1C+).346

For children with mechanical prosthetic heart valves who suffer systemic embolisms despite adequate therapy with oral anticoagulation therapy, we recommend the addition of aspirin, 6 to 20 mg/kg/d, to the regimen. Dipyridamole, 2 to 5 mg/kg/d, in addition to oral anticoagulation therapy is an alternative option (grade 2C).

When full-dose oral anticoagulation therapy is contraindicated, we recommend long-term therapy with OAs sufficient to increase the INR to 2.5 (range, 2.0 to 3.0) in combination with aspirin, 6 to 20 mg/kg/d, (grade 1C+) and dipyridamole, 2 to 5 mg/kg/d (grade 2C).

Other Cardiac Disorders

BT Shunts: We recommend the initial treatment of patients with BT shunts with therapeutic amounts of heparin, followed by treatment with aspirin, at doses of 3 to 5 mg/kg/d, indefinitely (grade 2C).

Remark: Further clinical investigation is needed before definitive recommendations can be made.

Fontan Operations: We recommend aspirin or therapeutic amounts of heparin followed by oral anticoagulation therapy to achieve a target INR of 2.5 (range, 2 to 3) as therapeutic options (grade 2C). The optimal duration of prophylaxis is unknown. Patients with fenestrations may benefit from treatment until closure.

Remark: Further clinical investigation is needed before definitive recommendations for primary post-operative prophylaxis can be made.

ACKNOWLEDGMENT: We acknowledge the assistance of Lu Ann Brooker for conducting literature searches and for editing this article.

REFERENCES

41 Leaker M, Saxon BR. Heparin induced thrombocytopenia in a young child managed with Orgaran for cardiopulmonary bypass surgery [abstract]. Blood 1998; 92(10 suppl 2):361b
thrombin regulation during warfarin therapy in children compared to adults. Thromb Haemost 1998; 80:570–574
94 Kikumoto R, Tamao Y, Tesnka T. Selective inhibition of thrombin by (2R,4R)-4-methyl-l-[2-N2-[(3-methyl-1,2,3,4-tetrahydro-8-quinolinyl) sulfonyl]-l-arginyl]-2-piperidin carboxylic acid. Biochemistry 1984; 23:85–90
95 Yasuda T, Gold HK, Yanoita H. Comparative effects of aspirin, a synthetic thrombin inhibitor, and a monoclonal antiplatelet glycoprotein Ib/IIa antibody on coronary artery reperfusion, reocclusion, and bleeding with recombinant tissue-type plasminogen activator in a canine preparation. J Am Coll Cardiol 1990; 16:714–722
102 Rosethal D, McKinsey JF, Levy AM. Use of the Greenfield


126 Gershlick AH. Antiplatelet therapy following stent deployment. Heart 1997; 78:24–26


130 Coller BS. Monitoring platelet GPIIb/IIIa antagonist therapy. Circulation 1997; 96:3828–3832


145 Andrew M, Brooker L, Paes B, et al. Fibrin clot lysis by thrombolytic agents is impaired in newborns due to a low


147 Leaker M, Superina R, Andrew M. Fibrin clot lysis by tissue plasminogen activator (tPA) is impaired in plasma from pediatric liver transplant patients. Transplantation 1995; 60:144–147


149 Bovill E, Becker R, Tracy R. Monitoring thrombolytic therapy. Prog Cardiovase Dis 1992; 34:279–294

150 Public Health Service. Important drug warning regarding the use of Abhokinase (urokinase). Rockville, MD: US Food and Drug Administration, 1999


tional Congress of the British Association of Paediatric Surgeons, July 25–27, 1990


227 Hausler M, Duque D, Merz U, et al. The clinical outcome


311 Williams WG, Pollack JC, Geiss DM, et al. Experience with...


