Antithrombotic Therapy in Children

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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 testing of specific therapeutic modalities, yet common enough to present significant management dilemmas that required therapeutic intervention.1,2 However, optimal prevention and treatment of children with thromboembolic complications likely differ from 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 have paradoxically 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. However, until these trials are conducted, modified adult guidelines remain the primary source for recommendations in children.

This article has two objectives: first, to summarize the evidence showing that the interaction of antithrombotics with the hemostatic system of the young differs from adults; and second, to discuss the indications, monitoring, therapeutic range, factors influencing dose-response relationships, and side effects of antithrombotic agents in children. Many of the recommendations are extrapolated from clinical trials in adults and interpreted within the context of the available information for pediatric patients.

To our knowledge, the literature on the use of antithrombotic agents in children has not been summarized previously. MEDLINE searches of the literature were conducted from 1966 to 1995 using combinations of key words (children, newborns, heparin, warfarin, aspirin, antiplatelet agents, thrombolysis, thrombosis, embolism, mechanical and biologic prosthetic heart valves) and supplemented by additional references located through the bibliographies of listed articles. All articles were graded as level I to V and recommendations classified into grade A, B, and C. Prospective single-arm cohort studies that compared results with the current approach in adults were classified as level IV. Retrospective case series comparing results with the adult literature were classified as level V. Complete reference lists of the level V studies, which constitute the overwhelming majority, are available on request.

Mechanism of Action of Heparin: Age-Dependent Features

Heparin’s anticoagulant activities, which are mediated by catalysis of antithrombin III (ATIII), can be impaired in the presence of decreased plasma levels of ATIII. Some pediatric patients requiring heparin therapy have very low levels of ATIII reflecting physiologic, congenital, and/or acquired etiologies. For example, plasma concentrations of ATIII are physiologically low at birth (approximately 0.50 U/mL) and increase to adult values by 3 months of age.3,5 Sick prematures, a population of children at significant risk for thrombotic events, frequently have plasma levels of ATIII that are less than 0.30 U/mL, potentially influencing their response to heparin.5

Heparin functions as an antithrombotic agent by catalyzing the ability of ATIII to inactivate specific coagulation enzymes, of which thrombin is the most sensitive.6 The capacity of plasma from newborns to generate thrombin is both delayed and decreased compared with adults.7,8 and similar to plasma from adults receiving therapeutic amounts of heparin.7 Following infancy, the capacity of plasma to generate thrombin increases but remains approximately 25% less throughout childhood than for adults.9 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 with adults.7,9 These observations support the hypothesis that optimal dosing of heparin in pediatric patients will differ from 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 heparin levels in adults should be extrapolated to children. The recommended therapeutic range for the treatment of venous thrombotic disease in adults is an APTT that reflects a heparin level by protamine titration of 0.2 to 0.4 U/mL or an antifactor Xa level of 0.3 to 0.7 U/mL.10 In pediatric patients, APTT values correctly predict whether heparin concentrations are therapeutic approximately 70% of the time.11

Doses

The doses of heparin required in pediatric patients to achieve adult therapeutic APTT values have been assessed using a weight-based nomogram (one level IV study).11 A bolus dose of 50 U/kg was insufficient, resulting in subtherapeutic APTT values in 60% of children.11 Bolus doses of 75 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 older than 1 year of age having lower requirements (20 U/kg/h). The doses of heparin required for older children are similar to the weight-adjusted requirements in adults (18 U/kg/h).12 The duration of heparin therapy for the treatment of deep vein thrombosis (DVT) is a minimum of 5 days, and 7 to 10 days for extensive DVT or pulmonary embolism (PE).13,14 Oral anticoagulant therapy can be initiated on day 1 of heparin therapy except for extensive DVT or PE when oral anticoagulant therapy should be delayed.15

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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>

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

Pharmacokinetics

There are at least two plausible explanations for the high heparin requirement in young children. First, heparin is cleared more quickly in the young compared with the adult in both animal models16 and in humans.17,18 Second, the delay in diagnosis of thrombotic complications in children may result in more extensive disease at the time of presentation, accelerating heparin clearance.19,20

Monitoring

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.12,21,22 A nomogram initially used in adults was adapted, tested, and modified for children (Table 1).11,21 Heparin-dosing nomograms can be adapted into preprinted order sheets that facilitate rapid anticoagulation.

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 journal. Only one level IV study in children suggests that major bleeding from heparin therapy is not frequent in the treatment of DVT/PE in children.11 However, many children were treated with suboptimal amounts of heparin in this study,11 and there are case reports of major bleeding 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 is no information to our knowledge on the occurrence of osteoporosis in children receiving heparin therapy. However, given the convincing relationship between heparin and osteoporosis in adults, it seems prudent to avoid long-term use of heparin in children. The third adverse effect is the association of thrombocytopenia with heparin therapy in pediatric patients.23-25 In the absence of an alternative etiology for heparin-associated thrombocytopenia, pediatric patients should be evaluated for heparin-induced thrombocytopenia and treated with alternative therapy as outlined for adults.

Treatment of Heparin-Induced Bleeding

If anticoagulation 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 required to neutralize heparin is based on the amount of heparin received in the previous 2 h (Table 2). Protamine sulfate can be administered in a concentration of 10 mg/mL at a rate not to exceed 5 mg/min. Patients with known hypersensitivity reactions to fish and those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.

ORAL ANTICOAGULANT THERAPY IN PEDIATRIC PATIENTS Age-Dependent Features

Oral anticoagulants function by reducing plasma concentrations of the vitamin K-dependent proteins. At birth, levels of the vitamin K-dependent coagulant factors (FII, FVII, FIX, FX) and inhibitors (protein C, protein S) are approximately 50% of adult values.3-5,26-28 These levels are similar to those found in adults receiving oral anticoagulants for the treatment of venous thrombotic disease.9 A small number of newborns have evidence of a functional vitamin K deficiency state, indicated by significant levels of descarboxy vitamin K-dependent proteins at birth.29 Vitamin K deficiency significantly increases the sensitivity to oral anticoagulants and potentially, the risk of bleeding. Following the neonatal period, levels of the vitamin K-dependent proteins rapidly

Table 2—Reversal of Heparin Therapy*

<table>
<thead>
<tr>
<th>Time Since Last Heparin Dose, min</th>
<th>Protamine Dose, mg/100 U of Heparin Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>1.0 mg/100</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.
increase and are within the adult range of normal by 6 months. However, average values of the vitamin K-dependent proteins remain approximately 20% lower than adult values until the late teenage years.

Decreased concentrations of the vitamin K-dependent coagulation proteins, particularly prothrombin, contribute to the delay and decreased amounts of thrombin generated in plasma from newborns and children. The pattern of thrombin generation in newborns is similar to plasma from adults receiving therapeutic amounts of oral anticoagu-
lants. Because of the potential risk of bleeding from further anticoagulation and presence of borderline vitamin K status, oral anticoagulant therapy is avoided when possible during the first month of life. For older children receiving oral anticoagulants, the capacity of their plasma to generate thrombin is delayed and decreased by 25% compared with plasma from adults with similar international normalized ratios (INRs). The latter raises the issue of whether the optimal INR therapeutic range for children will be lower than for adults. This hypothesis is further supported by the observation that plasma concentrations of a marker of endogenous thrombin generation, prothrombin fragment 1.2, are significantly lower in children compared with adults at similar INR values.

**Therapeutic Range**

The most commonly used test for monitoring oral anticoagulant therapy is the prothrombin time (PT), 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 there are no clinical trials (to our knowledge) that have assessed the optimal INR range for children based on clinical outcomes. The recommended therapeutic range for the treatment of venous thrombotic disease is an INR between 2 and 3. The recommended therapeutic range for children with mechanical prosthetic heart valves is an INR between 2.5 and 3.5. Experience with INR ranges of 1.5 to 2.0 is minimal in pediatrics. However, the available biologic data (previous section) and limited clinical data suggest that optimal therapeutic INR ranges may be lower in children. Clinical trials are urgently needed to test this hypothesis.

**Dose Response**

Of the five publications that provide information on loading doses for oral anticoagulant therapy in children, four were level V and one was level IV. Of the six publications that provide information on maintenance doses for oral anticoagulants required to achieve an INR between 2 and 3 in children, five are level V and one is level IV. Maintenance doses for oral anticoagulants are age dependent, with infants having the highest (0.32 mg/kg) and teenagers the lowest (0.09 mg/kg) requirements. For adults, weight-adjusted doses for oral anticoagulants are not precisely known but are in the range of 0.04 to 0.08 mg/kg for an INR of 2 to 3. The mechanisms responsible for the age dependency of oral anticoagulant doses are not completely clear. Table 3 provides a nomogram for loading and maintaining oral anticoagulants in children. Guidelines for the duration of therapy with oral anticoagulants in children reflect recommendations for adults with similar disorders. Patients with their first venous thrombotic event are treated for 3 months while those with mechanical prosthetic heart valves are treated for life. Optimal treatment for children with recurrent DVT/PE, beyond the initial treatment, is uncertain.

**Monitoring**

Monitoring oral anticoagulant therapy in children is difficult and requires close supervision with frequent dose adjustments. In contrast to adults, only 10 to 20% of children can be safely monitored monthly. Reasons contributing to the need for frequent monitoring include diet, medications, primary medical problems, and age distribution.

Breast-fed infants are very sensitive to oral anticoagulants owing to the low concentrations of vitamin K in breast milk. In contrast, some children are resistant to oral anticoagulants owing to impaired absorption, requirements for total parenteral nutrition (TPN) that is routinely supplemented with vitamin K, and nutrient formulas that are all supplemented with vitamin K (55 to 110 μg/L) to protect against hemorrhagic disease of the newborn.

Most children are receiving multiple medications, both on a long-term basis to treat their primary problems or intermittently to treat acquired problems (eg, infections). These medications influence dose requirements for oral anticoagulants in a fashion similar to adults. The most commonly used medications in children that affect the INR are listed in Table 4. Most children have serious primary problems that influence the biologic effect and clearance of oral anticoagulants, as well as the risk of bleeding.

The age distribution of children requiring oral anticoagulants is skewed with the two largest groups comprised of children younger than 1 year of age and teenagers. Teenagers are not necessarily compliant with their medication.

| Table 3—Protocol for Oral Anticoagulation Therapy to Maintain an INR Between 2 and 3 for Pediatric Patients |
|--------------------------------------------------|--------------------------------------------------|
| **INR** | **Action** |
| 1.1-1.4 | Repeat loading dose |
| 1.5-1.9 | 50% of loading dose |
| 2.0-3.0 | 50% of loading dose |
| 3.0-4.0 | 25% of loading dose |
| >4.5 | Hold until INR <4.5 then restart at 50% less than the previous dose. |

| **III. Maintenance oral anticoagulation dose guidelines** | **INR** | **Action** |
|--------------------------------------------------|--------------------------------------------------|
| 1.1-1.4 | Increase by 20% of dose |
| 1.5-1.9 | Increase by 10% of dose |
| 2.0-3.0 | No change |
| 3.1-4.0 | Decrease by 10% of dose |
| 4.1-4.5 | Decrease by 20% of dose |
| >4.5 | Hold dose, check INR daily until INR <4.5, then restart at 20% less than the previous dose |
and infants are a difficult group of patients to monitor owing to poor venous access and complicated medical problems. The problems with monitoring oral anticoagulant therapy in children have limited its use, even in conditions in which it is strongly indicated. Potential solutions for optimizing therapy with oral anticoagulants in children include pediatric anticoagulation clinics, whole blood PT/INR monitors used at home, and clinical trials to determine if lower, safer INR ranges are as efficacious.

Adverse Effects of Oral Anticoagulants

Bleeding is the main complication of oral anticoagulants. Minor bleeding that is of no clinical consequence (bruising, nosebleeds, heavy menses, coffee-ground emesis, microscopic hematuria, bleeding from cuts and loose teeth, ileostomy) occurs in approximately 20% of children receiving oral anticoagulants (one level IV study). The risk of serious bleeding in children receiving oral anticoagulants for mechanical prosthetic valves is acceptable at less than 3.2/100 patient-years (13 level V studies) (subsequent section). Significant bleeding complications occur in approximately 1.7% of children receiving oral anticoagulants for secondary prevention.

Nonhemorrhagic complications of oral anticoagulants, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Although oral anticoagulants do not affect bone density in adults, the effects on children have not been assessed. At this time, to our knowledge, there are no other serious complications of oral anticoagulants reported in the pediatric population.

Treatment of Oral Anticoagulant-Induced Bleeding

Vitamin K is the antidote for oral anticoagulants. The dose to be administered and concurrent use of vitamin K factor replacement (either fresh frozen plasma or prothrombin complex concentrates) are dependent on the clinical problem. Table 5 provides guidelines for reversal of oral anticoagulant therapy in children with no bleeding and those with significant bleeding.

Antithrombotic Agents

Age-Dependent Features

Compared with adult controls, neonatal platelets are hyperreactive to thrombin, adenosine diphosphate/epinephrine, and thromboxane A2. This hyperreactivity of neonatal platelets is the result of a defect intrinsic to neonatal platelets. Paradoxically, the bleeding time is short in newborns owing 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 may also differ from adults.

Therapeutic Range, Dose Response, and Monitoring of Antiplatelet Agents

There is no therapeutic range or need to monitor antiplatelet agents. To our knowledge, there are no studies that compare different doses of aspirin, the most commonly used antiplatelet agent, in children. Empiric low doses of 1 to 5 mg/kg/d have been proposed as adjutant therapy for Blalock-Taussig shunts, some endovascular stents, and some cerebrovascular events. For mechanical prosthetic heart valves, aspirin doses of 6 to 20 mg/kg/d were used in several studies. High-dose aspirin therapy, 80 to 100 mg/kg/d, is used in patients with Kawasaki 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 mechanical prosthetic heart valves, is dipyridamole in doses of 2 to 5 mg/kg/d.

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). Clearance of both salicylate and indomethacin is slower in newborns potentially placing them at risk 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 (level V). Indomethacin does prolong the bleeding time in newborns, but the evidence linking indomethacin to intracranial hemorrhage is weak.

In older children, aspirin rarely causes clinically important hemorrhage, except in the presence of an underlying hemostatic defect or in children also treated with anticoagulants or thrombolytic therapy. The relatively low doses of aspirin used as antplatelet therapy, as compared with 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**

It is unusual for antiplatelet agents alone to cause serious bleeding. More frequently, antiplatelet agents are one of several other causes of bleeding such as an underlying coagulopathy and antithrombotic agents. Transusions of platelet concentrates and/or the use of products that enhance platelet adhesion (plasma products containing high concentrations of von Willebrand factor or D-des amino arginine vasopressin) may be helpful.

**MECHANISM OF ACTION OF THROMBOLYTIC AGENTS: AGE-DEPENDENT FEATURES**

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 (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, intermittent cerebral ischemic attack, other neurologic disease, and hypertension. It seems prudent to consider similar problems in children as relative contraindications to thrombolytic therapy.

**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 can usually be obtained rapidly and helps to determine the need for cryoprecipitate and/or plasma replacement. A commonly used lower limit for fibrinogen level is 100 mg/dL. The APTT may not be helpful in the presence of low fibrinogen levels, concurrent heparin therapy, and presence of fibrin/fibrinogen degradation products (FDPs). Measurement of FDPs 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 and in higher doses to lyse large- vessel thrombi or PE. Table 6 presents the most commonly used dose regimens for thrombolytic therapy in pediatric patients with arterial or venous thromboembolic complications. These protocols come from two level IV studies and several level V studies. The optimal doses for each of UK, SK, and tPA are not known for pediatric patients. Based on the Thrombolysis in Myocardial Infarction II trial, doses of 150 mg of recombinant tPA (rTPA) caused more bleeds into the CNS than 100 mg (1.5% vs 0.5%, respectively). It seems likely that there will be an upper dose limit based on safety.

**Adverse Effects of Thrombolytic Therapy**

Based on a composite review of the literature (255 patients) and two level IV 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. Although the incidence of bleeding into the CNS could not be accurately determined from the literature, it was reported in less than 3% of patients.

**Treatment of Bleeding Due to Thrombolytic Therapy**

Before thrombolytic therapy is used, it is advisable, when possible, to correct other concurrent hemostatic problems such as thrombocytopenia or vitamin K deficiency. 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 thrombolytic agent and administering cryoprecipitate (usual dose of one bag per 5 kg) and other blood products as indicated. If the bleeding is life-threatening, an antifibrinolytic agent can also 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 abnormalities differ. For example, myocardial infarction and cerebrovascular accidents (CVAs) 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 7.

**Venous Thromboembolic Disease**

**Incidence:** The incidence of venous thromboembolic complications (DVT/PE) is age dependent, with the lowest risk occurring in children. Estimates of the incidence of DVT/PE in the general pediatric population are 0.07/10,000 and 5.3/10,000 hospital admissions. Comparable
incidences of DVT/PE in the adult population are approximately 2.5 to 5.0%.99-101 Other comparisons illustrating the lower risk of DVT/PE during childhood are the less than 1% incidence of clinically apparent DVT/PE following lower limb or scoliosis surgery,102 and the low frequency of DVT/PE in children with heterozygote congenital prethrombotic states.41,103 Several mechanism(s) likely contribute to the protective effect of age for DVT/PE.104 These include a reduced capacity to generate thrombin,8,105 increased capacity of α2-macroglobulin to inhibit thrombin,106 presence of a circulating anticoagulant at birth,107-109 and others such as enhanced antithrombotic potential by the vessel wall.110

Clinical Features: Despite the protective effects of age, increasing numbers of children are developing DVT/PE as secondary complications of their underlying disorders. In contrast to adults, in whom DVT/PE is idiopathic in 40% of patients, only 5% of DVT/PE cases are idiopathic in children.41 Ninety-five percent of DVT/PE in pediatric patients are secondary to serious disorders such as prematurity, cancer, trauma/surgery, congenital heart disease, and systemic lupus erythematosus.41,103,111-113 Congenital prethrombotic disorders account for less than 10% of DVT/PE in children.41,103 The ages of greatest risk for DVT/PE are infants younger than 1 year of age and teenagers.41,111,113 DVT in the lower extremities is the most frequent noncentral venous line thrombotic complication in children.103 The clinical presentations and treatment of DVT/PE are similar to that for the adult.41,98,103,114

Central Venous Lines: Forty percent of DVT in children and more than 80% in newborns occur in the upper venous system secondary to the use of central venous lines (CVLs).41,103,113 CVLs are placed for short-term intensive care or long-term supportive care for children requiring TPN or cancer therapy. CVL-related DVTs are not trivial as they require repeated anesthesia for replacement, provide a source for PE,115-118 cause superior vena cava syndrome,118-122 chylothorax,118,119,123,124 and eventual destruction of the upper venous system,33,125 and contribute to postphlebitic syndrome in the upper extremities. The long-term consequences of extensive CVL-related DVTs are not known at this time. However, the available information strongly suggests that CVL-related DVTs are not benign.

The incidence of CVL-related thrombosis reported in the literature varies reflecting differing underlying disorders, diagnostic tests, and indices of suspicion. For example, the incidence of CVL-related thrombosis in children receiving long-term TPN varies from 1% based on clinical diagnosis,126,127 to 35% based on ventilation perfusion scans or echocardiography,128 to 75% based on venography.33 In many patient populations, the incidence is not accurately known. This information is important to identify populations of children in whom prophylactic antithrombotic therapy should be tested in clinical trials.

Patency of CVL is frequently maintained by intermittent boluses of heparin (200 to 300 U) daily, weekly, or monthly. For infants less than 10 kg, a lower dose of 10 U/kg is frequently used to avoid transient anticoagulation of the infant. There is only one small level II study assessing the need for prophylactic heparin.129 The study was conducted in children with cancer using echocardiography of the heart as the outcome measure, not venography.129 Although it reported no benefit from flushing CVLs with heparin, the design and outcome measures limits the generalizability of this study. Local instillation of UK is the most commonly used therapy for treating a malfunctioning line that is “blocked” (Table 6). Based on several level V studies, patency is restored in approximately 80% of patients.

Inherited Prothrombotic Complications: Inherited prothrombotic disorders include the following: deficiencies of ATIII, protein C, protein S, and plasminogen; dysfibrinogenemias; and activated protein C resistance.130 In general,

<table>
<thead>
<tr>
<th>Table 6—Thrombolytic Therapy for Pediatric Patients</th>
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<tbody>
<tr>
<td>Low Dose for Blocked Catheters</td>
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<tr>
<td>Regimen</td>
</tr>
<tr>
<td>Instillation UK (5,000 U/mL) 1.5-3 mL/lumen</td>
</tr>
<tr>
<td>2-4 h</td>
</tr>
<tr>
<td>Infusion UK (150 U/kg/h) per lumen 12-48 h</td>
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<tr>
<td>Fibrinogen, TCT* PT, APTT</td>
</tr>
<tr>
<td>Systemic Thrombolytic Therapy1</td>
</tr>
<tr>
<td>Load, U/kg Maintenance</td>
</tr>
<tr>
<td>UK 4,400 4,400 U/kg/h 6-12 h Fibrinogen, TCT*</td>
</tr>
<tr>
<td>SK 2,000 2,000 U/kg/h 6-12 h Same</td>
</tr>
<tr>
<td>tPA None 0.1-0.6 mg/kg/h for 6 h Same</td>
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* TCT thrombin clotting time.

1 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.

<table>
<thead>
<tr>
<th>Table 7—Indications for Antithrombotic Agents in Pediatric Patients</th>
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<tr>
<td>I. Treatment</td>
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<tr>
<td>Venous thromboembolic complications</td>
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<tr>
<td>Arterial thromboembolic complications</td>
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<tr>
<td>II. Treatment: probable</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Some forms of stroke</td>
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<tr>
<td>III. Prophylaxis</td>
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<tr>
<td>Mechanical prosthetic heart valves</td>
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<td>Cardiac catheterization</td>
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<td>Central arterial catheters</td>
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</table>

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patients with heterozygote deficiencies are protected during childhood except in the presence of a secondary challenge. In the population-based registry of 137 consecutive children with DVT/PE, less than 10% had an inherited prothrombotic disorder.41 However, this study was conducted prior to our knowledge of activated protein C (APC) resistance. Although there is agreement on the initial treatment with anticoagulants and the need for prophylaxis in high-risk situations, there is a paucity of information on the benefits and safety for long-term prophylaxis vs careful monitoring with intermittent prophylaxis.

**Homozygous Protein C or S Deficiency**

In contrast to heterozygous protein C or S deficiency, homozygous protein C/S deficiency presents within hours of birth with purpura fulminans, cerebral and/or ophthalmic damage that occurred in utero, and, on rare occasions, large vessel thrombosis. Purpura fulminans is an acute, lethal syndrome of rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis.131-133 Since 1980, 40 patients with homozygous protein C deficiency and 1 patient with homozygous protein S deficiency were described in the literature (references available on request). Thirty-three patients presented in the neonatal period and 8 as children or adults. All patients presenting at birth with purpura fulminans had undetectable levels of protein C or S, whereas patients with delayed presentation had detectable levels of protein C ranging from 0.05 to 0.20 U/mL. These children usually presented with DVT following a minor secondary insult and developed oral anticoagulant-induced skin necrosis.

**Short-term Treatment**: Numerous forms of therapy have been used in individual patients, including fresh frozen plasma (FFP), protein C concentrate, cryoprecipitate, protrombin complex concentrate, heparin, low molecular weight heparin (LMWH), aspirin, sulfipyrazone, corticosteroids, vitamin K, aprotinin, and ATIII concentrate. One approach is to initiate treatment with 10 to 20 mL/kg of FFP every 12 h.134 Plasma protein C levels achieved with these doses of FFP varied from 15 to 32% at 30 min after infusion, and 4 to 10% at 12 h.135 Doses of protein C concentrate administered in the literature have ranged from 20 to 60 U/kg. A dose of 60 U/kg resulted in peak protein C levels above 0.60 U/mL.136 Replacement of protein C should be continued until the clinical lesions resolve, which is usually 6 to 8 weeks.

The one newborn with homozygous protein S deficiency was treated with both FFP and cryoprecipitate, which contain similar amounts of protein S.137 A pharmacokinetic study was performed following the infusion of 10 mL/kg of FFP.137 The recovery of protein S at 2 h was 0.23 U/mL and at 24 h, 0.14 U/mL with the protein S entirely in the C4b-bound fraction on crossed immunoelectrophoresis. The approximate half-life of protein S in this infant was 36 h.

**Long-term Treatment**: The modalities used for long-term treatment of infants with homozygous protein C deficiency include oral anticoagulant therapy, intermittent protein C replacement with protein C concentrate, and liver transplantation.138 Currently, most children are treated with oral anticoagulants. When therapy with oral anticoagulants is initiated, the infant should continue receiving protein C (or S) replacement until the INR is approximately between 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 protein C or S deficiency but with detectable plasma concentrations have also been treated with LMWH.139 The latter approach avoids the risk of oral anticoagulant-induced skin necrosis and likely decreases the risk of bleeding associated with high doses of oral anticoagulants.139

**Arterial Thromboembolic Disease**

**Etiology**: The most common cause of arterial thromboembolic disease in children is catheters. These include cardiac catheterization and central or peripheral arterial lines in the intensive care setting. Noncatheter-related arterial thrombotic complications are rare and occur in Takayasu’s arteritis,140141 arteries from transplanted organs,142-144 giant coronary aneurysms secondary to Kawasaki disease,73145149 as complications of some forms of congenital heart disease and cerebral vessels from local lesions, or embolic from cardiac or other locations.

**Cardiac Catheterization**: In the absence of prophylactic anticoagulation, the incidence of symptomatic thrombotic complications following cardiac catheterization via the femoral artery is approximately 40%130 (Table 8). Younger children (younger than 10 year of age) have an increased incidence compared with older children.130 Prophylactic anticoagulation with aspirin does not significantly reduce the incidence of arterial thrombosis (one level II study).151 However, anticoagulation with 100 to 150 U/kg of heparin reduces the incidence from 40 to 8%.150 Recent advances in interventional catheterization have resulted in the use of larger catheters and sheaths that may increase the risk of thrombotic complications. A short limb and claudication are the long-term consequences of femoral artery thrombosis in children.

**Umbilical Artery Catheterization**: Umbilical arterial cath-

### Table 8—Cardiac Catheterization in Children: Arterial

<table>
<thead>
<tr>
<th>Study, yr</th>
<th>Level</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Bleeding</th>
<th>TE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freed, 1974</td>
<td>II</td>
<td>Aspirin (15 mg/kg)</td>
<td>37</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Freed, 1974</td>
<td></td>
<td>Placebo</td>
<td>58</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Freed, 1974</td>
<td>I</td>
<td>Heparin (1 mg/kg)</td>
<td>37</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Freed, 1974</td>
<td></td>
<td>Placebo</td>
<td>40</td>
<td>0</td>
<td>10*</td>
</tr>
</tbody>
</table>

*TE=thromboembolic event.

1p<0.05.
eterization is necessary for the administration of supportive care critical to the survival of sick newborns (Table 9). 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 level I study,\textsuperscript{152} and several level II studies.\textsuperscript{153-157} Three outcomes were assessed: patency, local thrombus, and intracranial hemorrhage (ICH). Patency, which is likely linked to the presence of local thrombus, is prolonged by the use of low-dose heparin (one level I and four level II studies).\textsuperscript{152,154-157} Local thrombus, detected by ultrasound, was not decreased in two level II studies. However, the power was low.\textsuperscript{153,156} ICH as an outcome was not increased in one level II study with a small sample size (15 per arm).\textsuperscript{157} In one level III study, heparin was implicated as a risk factor for ICH in low-birth-weight infants.\textsuperscript{158} This study was retrospective and the 95% confidence interval around the odds ratio of 3.9 was large (1.4 to 11.0), and the magnitude of the risk uncertain.\textsuperscript{158}

**Kawasaki Disease:** In patients with Kawasaki disease, aspirin is initially given in high doses (80 to 100 mg/kg/d during the acute phase, up to 14 days) as an anti-inflammatory agent, then in lower doses as an antplatelet agent (3 to 5 mg/kg/d for 7 weeks or longer) to prevent coronary aneurysm thrombosis and subsequent infarction (the major cause of death in Kawasaki disease) (Table 10). Although no level I or level II studies have been performed, two level III studies\textsuperscript{145,149} suggest that aspirin can reduce the coronary involvement in Kawasaki disease. A level I study\textsuperscript{73} demonstrated that the combination of IV γ-globulin and aspirin is more efficacious in this regard than aspirin alone.

### Biologic Prosthetic Heart Valves

Valvular heart diseases in childhood encompass a wide variety of abnormalities with greatly variable presentations. The valve lesion may be isolated, or an integral part of more complex intracardiac lesions, or the result of treatment of the underlying congenital defect. Thromboembolic events, either of the valve or a CVA, are some of the most serious complications of successful cardiac valve replacement.

The failure of biologic prosthetic heart valves in children poignantly illustrates the fallacy of extrapolating recommendations for adults to children, without evaluation in clinical trials. Commercially prepared biologic prostheses became available in 1971 and achieved excellent early results in adult

### Table 9—Umbilical Artery Catheterization*

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Bleeding</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al, 1987\textsuperscript{153}</td>
<td>II</td>
<td>HB-PU</td>
<td>61</td>
<td>NR\textsuperscript{1}</td>
<td>13 TE</td>
</tr>
<tr>
<td>Horgan et al, 1987\textsuperscript{156}</td>
<td>II</td>
<td>Heparin</td>
<td>59</td>
<td>NR</td>
<td>16 TE</td>
</tr>
<tr>
<td>Rajani et al, 1979\textsuperscript{152}</td>
<td>I</td>
<td>Heparin</td>
<td>52</td>
<td>NR</td>
<td>18 TE</td>
</tr>
<tr>
<td>David et al, 1981\textsuperscript{154}</td>
<td>II</td>
<td>Placebo</td>
<td>30</td>
<td>NR</td>
<td>19 B</td>
</tr>
<tr>
<td>Bosque et al, 1986\textsuperscript{155}</td>
<td>II</td>
<td>Heparin (C)</td>
<td>18</td>
<td>NR</td>
<td>15 B</td>
</tr>
<tr>
<td>Horgan et al, 1987\textsuperscript{156}</td>
<td>II</td>
<td>Heparin</td>
<td>59</td>
<td>NR</td>
<td>8 B</td>
</tr>
<tr>
<td>Ankola et al, 1993\textsuperscript{157}</td>
<td>II</td>
<td>Heparin</td>
<td>15</td>
<td>4 ICH</td>
<td>11 B</td>
</tr>
</tbody>
</table>

* B=blocked; TE=thromboembolic event; HB-PU=heparin bonded-polyurethane; PVC=polyvinyl chloride; C=continuous; I=intermittent.

1 NR=not reported.

1 p<0.05

mg/kg/d for 7 weeks or longer) to prevent coronary aneurysm thrombosis and subsequent infarction (the major cause of death in Kawasaki disease) (Table 10). Although no level I or level II studies have been performed, two level III studies\textsuperscript{145,149} suggest that aspirin can reduce the coronary involvement in Kawasaki disease. A level I study\textsuperscript{73} demonstrated that the combination of IV γ-globulin and aspirin is more efficacious in this regard than aspirin alone.

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The failure of biologic prosthetic heart valves in children poignantly illustrates the fallacy of extrapolating recommendations for adults to children, without evaluation in clinical trials. Commercially prepared biologic prostheses became available in 1971 and achieved excellent early results in adult

### Table 10—Treatment of Kawasaki Disease*

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</th>
<th>n</th>
<th>Age, yr</th>
<th>Treatment</th>
<th>Dose, mg/kg/d</th>
<th>Outcome Coronary Aneurysm, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newburger, 1986\textsuperscript{155}</td>
<td>I</td>
<td>84</td>
<td>2.3</td>
<td>ASA</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>Koren et al, 1985\textsuperscript{145}</td>
<td>III</td>
<td>36</td>
<td>2.7</td>
<td>γ-Globulin+ASA</td>
<td>400+100</td>
<td>6.8</td>
</tr>
<tr>
<td>Daniels et al, 1997\textsuperscript{149}</td>
<td>III</td>
<td>9</td>
<td>4.4</td>
<td>ASA</td>
<td>68.6 (started day 9)</td>
<td>68 no aneurysms</td>
</tr>
</tbody>
</table>

*This is a retrospective review in which clinical, laboratory, and treatment characteristics of 9 patients with Kawasaki disease who developed coronary aneurysms were compared with 68 patients with Kawasaki disease who did not develop coronary aneurysms. In this study, the difference in the dose of ASA was not significant. However, ASA therapy was begun on day 14.7+3.9 in the group who developed aneurysms versus day 9.4+3.8 in those patients who did not (a significant difference [p<0.001]).
Table 11—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves With No Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</th>
<th>n</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 al,53 1988</td>
<td>V</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>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>Solymar et al,70 1991</td>
<td>V</td>
<td>(186)5</td>
<td>1-19 yr</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*TE=thromboembolic event; HEM=hemorrhage; Ao=aortic; M=mitral. This is an updated version of Rao et al.54 1989.
1NR=not reported.
2The death was secondary to a mitral valve thrombosis.
3The number of patients treated with no antithrombotic therapy could not be determined. (186) refers to the entire patient population of the study.70

patients. Biologic prosthetic heart valves rapidly became the “valve of choice” for the pediatric age group.139 Subsequently, it became evident that premature degeneration and calcification of porcine valves occurred in most children.160-167 The accelerated failure of biologic prosthetic heart valves in children was confirmed by many groups. Current recommendations are that, in general, mechanical prosthetic heart valves be used in the mitral position in children and biologic prosthetic heart valves be reserved for patients who require tricuspid or pulmonary valve replacements. Children with biologic prosthetic heart valves are treated following adult recommendations and are followed up for evidence of valve dysfunction.

Mechanical Prosthetic Heart Valves

Antithrombotic therapy with oral anticoagulants is clearly indicated for adults with mechanical prosthetic heart valves. Alternatives to oral anticoagulants have been pursued for children because of the issue of safe monitoring.

Table 12—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves Treated With Antiplatelet Agents

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</th>
<th>n</th>
<th>Dose</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>Serra et al,55 1987</td>
<td>V</td>
<td>24</td>
<td>ASA 6 mg/kg/d</td>
<td>5-20 yr</td>
<td>St. Jude</td>
<td>Ao</td>
<td>68</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIP 25 mg/kg</td>
<td></td>
<td></td>
<td>M</td>
<td>19</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>McGrath et al,56 1987</td>
<td>V</td>
<td>30</td>
<td>ASA 900 mg/d</td>
<td>4-20 yr</td>
<td>St. Jude</td>
<td>Ao,M</td>
<td>32</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIP 150 mg/kg/d</td>
<td></td>
<td></td>
<td>≥2</td>
<td>NR1</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>El Makhlouf et al,60 1987</td>
<td>V</td>
<td>150</td>
<td>ASA 20 mg/kg/d</td>
<td>2-16 yr</td>
<td>Various</td>
<td>Ao,M</td>
<td>≥2</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIP 5 mg/kg/d</td>
<td></td>
<td></td>
<td>≥2</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>overall</td>
<td>23.3</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Bradley et al,70 1985</td>
<td>V</td>
<td>10</td>
<td>ASA 6.1 mg/kg/d</td>
<td>&lt;19 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIP 1.9 mg/kg/d</td>
<td></td>
<td></td>
<td>M</td>
<td>12</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td>Solymar et al,70 1991</td>
<td>V</td>
<td>(186)5</td>
<td>ASA 12 mg/kg/d</td>
<td>1-20 yr</td>
<td>Various</td>
<td>Ao</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIP 3 mg/kg/d</td>
<td></td>
<td></td>
<td>M</td>
<td>2.5</td>
<td>0</td>
<td>2 CVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥2</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Borkon et al,71 1986</td>
<td>V</td>
<td>8</td>
<td>Not provided</td>
<td>3 wk-17 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>1.1</td>
<td>01</td>
<td>1M1</td>
</tr>
<tr>
<td>LeBlanc et al,72 1993</td>
<td>V</td>
<td>20</td>
<td>ASA 10 mg/kg/d</td>
<td>1-17 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIP 3 mg/kg/d</td>
<td></td>
<td></td>
<td>M</td>
<td>1.7</td>
<td>01</td>
<td>0</td>
</tr>
</tbody>
</table>

*DIP=dipyridamole; Ao=aortic; M=mitral; TE=thromboembolic event; HEM=hemorrhage (HEM). CVA=cerebral vascular accident. This is an updated version of Rao et al.54 1989.
1NR=not reported.
2No hemorrhage. The number of patients treated with antiplatelet agents could not be determined. (186) refers to the entire patient population of the study.70
3Secondary to a mitral valve thrombosis.
4Parentheses indicate estimated number.
due to thromboembolic events and one due to a bleed.35,58,70,168 One of the three patients had discontinued treatment with oral anticoagulants and the anticoagulant status of the other two could not be determined. With one exception, the rate of major bleeding was less than 3.5%/patient-years (Table 13). In one study, two patients required blood transfusions (rate of 8.2%/patient-years) and recovered eventuvely.39 Adjunct therapy with antiplatelet agents was used in one study.35 Based on information available for adults and children, it seems reasonable to consider acetylsalicylic acid (ASA) in combination with oral anticoagulants for high-risk patients. High-risk patients include those with prior thromboembolic events, atrial fibrillation, large left atrium, left atrial thrombi, ball valves, and mitral valves.

**Conclusion:** The available data support the recommendation for oral anticoagulation in children with mechanical prosthetic heart valves. Problems of effectively monitoring oral anticoagulants can be addressed through anticoagulation clinics for children and the use of whole blood monitors in the clinic and at home.169

**Other Cardiac Disorders**

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

**Blalock-Taussig Shunts:** These shunts are used as a form of palliative surgery used to enhance systemic, subclavian artery, to pulmonary artery blood flow in patients with severe or progressive cyanosis, usually secondary to pulmonary stenosis.170,171 "Modified" Blalock shunts, in which a polytet (Gore-Tex) tube graft is taken from the side of the subclavian artery and anastomosed to the pulmonary, have been used since 1980. Because of its short length and very high flow, acute thrombosis is less common. Since 1980, 624 children with Blalock-Taussig shunts were described in 20 level V studies. The incidence of thrombotic occlusion ranged from 1 to 17%. Many investigators used antithrombotic therapy beginning with therapeutic doses of heparin and followed by low-dose aspirin (1 to 10 mg/kg/d).173

**Fontan Operation:** The Fontan operation involves a direct right atrium to pulmonary artery connection as the source of pulmonary blood flow for patients with univentricular hearts.173,175 Since 1988, a modified Fontan operation involving a double cavopulmonary anastomosis and placement of a polytet baffle within the right atrium has been used.176 Potential sites for thromboembolic complications include the surface of the polytet tube and the blind stump of the main pulmonary artery.177 Since 1980, 486 children with Fontan operations were described in 26 studies. Only 3 of the 26 reports described the use of antithrombotic therapy that began with heparin and was followed with oral anticoagulants for 3 months. It is uncertain if long-term an-

### Table 13—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves Treated With Warfarin

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</th>
<th>n</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 al.57 1986</td>
<td>V</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>0.5</td>
</tr>
<tr>
<td>El Makhlouf et al.59 1987</td>
<td>V</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 al.58 1990</td>
<td>V</td>
<td>40</td>
<td>4 mo-15 yr</td>
<td>St. Jude</td>
<td>Ao</td>
<td>0</td>
<td>0</td>
<td>1 M</td>
</tr>
<tr>
<td>Stewart et al.51 1987</td>
<td>V</td>
<td>30</td>
<td>6-17 yr</td>
<td>Various</td>
<td>Ao,M</td>
<td>2.3</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Bradley et al.30 1985</td>
<td>V</td>
<td>20</td>
<td>&lt;19 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>0</td>
<td>8.2</td>
</tr>
<tr>
<td>Milano et al.169 1986</td>
<td>V</td>
<td>71</td>
<td>=15 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schaffer et al.198 1987</td>
<td>V</td>
<td>33</td>
<td>9-48 mo</td>
<td>St. Jude</td>
<td>Ao</td>
<td>0.13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Solymar et al.70 1991</td>
<td>V</td>
<td>(156)</td>
<td>1-20 yr</td>
<td>Various</td>
<td>Ao</td>
<td>2.1</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>Schaff et al.85 1984</td>
<td>V</td>
<td>48</td>
<td>6 mo-18 yr</td>
<td>Starr-Edwards</td>
<td>M</td>
<td>5.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Borkon et al.71 1986</td>
<td>V</td>
<td>22</td>
<td>3 wk-17 yr</td>
<td>St. Jude</td>
<td>Ao</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Human et al.196 1982</td>
<td>V</td>
<td>56</td>
<td>2-12 yr</td>
<td>Various</td>
<td>M</td>
<td>n=3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antunes et al.200 1989</td>
<td>V</td>
<td>352</td>
<td>=20 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0.8</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Woods et al.35 1986</td>
<td>V</td>
<td>20</td>
<td>5 mo-16 yr</td>
<td>Various</td>
<td>Ao,M</td>
<td>1.8</td>
<td>0.9</td>
<td>1</td>
</tr>
</tbody>
</table>

* Ao=aortic; M=mitral, pulm=pulmonary; TE=thromboembolic event; HEM=hemorrhage.
1The anticoagulant used could not be determined.
2The death was due to a mitral valve thrombosis.
3Patients were treated with a combination of warfarin and ASA.
4Parentheses indicate estimated number.
ticoagulation is indicated for patients who have undergone Fontan operations for the prevention of intracardiac thrombi.

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

Other Disorders

Antithrombotic therapy is used in several other disorders in pediatric patients that are not discussed in this chapter. Readers are referred to other references for antithrombotic therapy in cardiopulmonary bypass, extracorporeal membrane oxygenation, and continuous veno-venous hemoperfusion.

Atrophie Blanche: Atrophie blanche (livedo vasculitis) is a superficial thrombotic disorder in which antiplatelet therapy may alleviate pain and decrease ulceration, according to a level V study.

Angina, Acute Myocardial Infarction, Transient Cerebral Ischemia, Stroke, 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 addressing 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 level V studies, aspirin and dipyridamole have been proposed to result in a more rapid rise in the platelet count in children with HUS. However, a level II study failed to confirm this hypothesis. Furthermore, there is no evidence that aspirin and dipyridamole favorably affect other outcome variables in HUS. A level I 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 level V study, aspirin and dipyridamole were hypothesized to diminish the thromboembolic complications of homocystinuria in patients who are unresponsive to pyridoxine. However, two other level V studies did not support this hypothesis.

Recomendations

Treatment of Venous Thromboembolism in Children

1. Children (older than 2 months of age) with DVT or PE should be treated with IV heparin sufficient to prolong the APTT to a range that corresponds to an antifactor Xa level of 0.3 to 0.7 U/mL. This grade C recommendation is based on grade A recommendations for adults and one level IV study in children.

2. It is recommended that treatment with heparin should be continued for 5 to 10 days and that treatment with oral anticoagulation should be overlapped with heparin for 4 to 5 days. For many patients, heparin and warfarin therapy can be started together and heparin therapy discontinued on day 6 if the PT (INR) is therapeutic. For massive PE or extensive DVT, a longer period of heparin therapy should be considered. This grade C recommendation is based on grade A recommendations for adults and one level IV study in children.

3. Long-term anticoagulant therapy should be continued for at least 3 months using oral anticoagulants to prolong the PT to an INR of 2.0 to 3.0. This grade C recommendation is based on grade A recommendations for adults and one level IV and six level V studies in children.

4. Indefinite oral anticoagulant therapy with an INR of 2 to 3, low-dose anticoagulant therapy (INR <2.0), or close monitoring should be considered for children with a first recurrence of venous thrombosis or a continuing risk factor, such as a CVL, ATIII deficiency, protein C or S deficiency, and lupus anticoagulants in the antiphospholipid antibody syndrome or systemic lupus erythematosus. This grade C recommendation is based on grade C recommendations for adults and one level V study in children.

5. Indefinite oral anticoagulant therapy with an INR of 2 to 3 should be considered for children with a second recurrence of venous thrombosis or a continuing risk factor, such as a CVL, ATIII deficiency, protein C or S deficiency, and lupus anticoagulants in the antiphospholipid antibody syndrome or systemic lupus erythematosus.

6. The use of thrombolytic therapy in the treatment of venous thromboembolism continues to be highly individualized. Further clinical investigation is needed before more definitive recommendations can be made.

7. Children with congenital prethrombotic disorders should receive short-term prophylactic anticoagulation in high-risk situations such as immobility, significant surgery, or trauma.

Treatment of Venous/Arterial Thromboembolism in Newborns

1. The use of anticoagulation therapy in the treatment of newborns with DVT, PE, or arterial thrombosis continues to be highly individualized. Further clinical investigation is needed before more definitive recommendations can be made.

2. If short-term anticoagulation therapy is not used, the thrombus should be closely monitored with objective tests and if extending, anticoagulation therapy instituted.

3. If anticoagulation is used, a short course (10 to 14 days) of IV heparin should be sufficient to prolong the APTT to the therapeutic range that corresponds to an antifactor Xa level of 0.3 to 0.7 U/mL. The thrombus should be closely monitored with objective tests for evidence of extension or recurrent disease. This grade C recommendation is based on unpublished data. If the thrombus extends following discontinuation of heparin therapy, oral anticoagulation therapy should be considered.

4. The use of thrombolytic agents in the treatment of venous thromboembolism continues to be highly individualized. Further clinical investigation is needed before more definitive recommendations can be made. Supplementation with plasminogen (FFP) may be helpful.

5. Prophylaxis for Cardiac Catheterization in Children and Newborns

Newborns and children requiring cardiac catheterization
via an artery should undergo prophylaxis with IV heparin in doses of 100 to 150 U/kg as a bolus. This grade B recommendation is based on one level II study in children younger than 10 years of age.150 Aspirin alone cannot be recommended (one level II study).151

Mechanical Prosthetic Heart Valves in Children

1. It is strongly recommended that children with mechanical prosthetic heart valves receive oral anticoagulation therapy. This grade C recommendation is based on grade C recommendations for adults and several level V studies in children.33,39,51,57,58,8-71,108,198-200

2. Levels of oral anticoagulation therapy that prolong the INR to 2.5 to 3.5 are recommended based on recommendations in adults.201

3. Children with mechanical prosthetic heart valves who suffer systemic embolism despite adequate therapy with oral anticoagulation therapy may benefit from the addition of aspirin, 6 to 20 mg/kg/d (adult level I study).202, Dipyridamole, 2 to 5 mg/kg/d, in addition to oral anticoagulation therapy is an alternative option (adult level I study).203,204

4. When full-dose oral anticoagulation therapy is contraindicated, long-term therapy with oral anticoagulation therapy sufficient to increase the INR 2 to 3 in combination with aspirin, 6 to 20 mg/kg/d, and dipyridamole, 2 to 5 mg/kg/d, may be used. This recommendation is an extrapolation of a level I study in adults.202 There is one level V study in children.35

Biologic Prosthetic Heart Valves in Children

Children rarely have biologic prosthetic heart valves. Further clinical investigation is needed before definitive recommendations can be made. One option is to treat children with biologic prosthetic valves according to adult recommendations.

Treatment of Kawasaki Disease in Children

In addition to IV γ-globulin (400 mg/kg for 4 consecutive days), children with Kawasaki disease should receive 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, to prevent the formation of coronary aneurysm thrombosis. This grade C recommendation is based on two level III studies.148,149

Fontan Operations

Further clinical investigation is needed before definitive recommendations can be made. One option is to initially treat patients with Fontan procedures with therapeutic amounts of heparin followed by oral anticoagulation therapy to achieve an INR of 2 to 3 for 3 months. Patients with fenestrations may benefit from treatment until closure.

Blalock-Taussig Shunts

Further clinical investigation is needed before definitive recommendations can be made. One option is to initially treat patients with Blalock-Taussig shunts with therapeutic amounts of heparin, followed by aspirin at doses of 3 to 5 mg/kg/d indefinitely.

Homozgyous Protein C- and S-Deficient Patients

1. It is recommended that newborns with purpura fulminans due to a homozygous deficiency of protein C or S should be treated initially with replacement therapy (either FFP or protein C concentrate) for approximately 6 to 8 weeks until the skin lesions have healed.

2. Following resolution of the skin lesions, and under control of replacement therapy, oral anticoagulation therapy can be introduced with target INR values of approximately 3 to 4.5. Treatment duration with oral anticoagulants is indefinite. Recurrent skin lesions should be treated with replacement therapy of protein C or S.

3. For patients with homozygous protein C and S deficiency but with measurable plasma concentrations, LMWH is a therapeutic option.159

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