Antithrombotic Therapy in Children

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(CHEST 1998; 114:7488–7698)

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 are 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 differs from adults because of important ontogenetic 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. Since the first publication of this chapter in the 1995 CHEST antithrombotic supplement,2a the authors have become aware of the initiation of five multinational randomized, controlled intervention trials assessing specific aspects of anticoagulant therapy in children. Until the results of these trials are available, modified adult guidelines remain the primary source for recommendations in children.

This chapter 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 adults is presented, as are the indications for and the 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. New information available on the use of low-molecular-weight heparin (LMWH) is included. In the third section, the five multinational trials assessing aspects of anticoagulant therapy in children are briefly described. Many of the recommendations are extrapolated from clinical trials in adults and are interpreted within the context of the available information for pediatric patients.

Medline searches of the literature were conducted from 1966 to 1998 using combinations of key words (children, newborns, heparin, warfarin, aspirin, antiplatelet agents, thrombolysis, thrombosis, embolism, mechanical and biological prosthetic heart valves) and supplemented by additional references located through the bibliographies of listed articles. All articles were graded as level 1 to 5. Recommendations were based on strength of study methods (grades A, B, and C) and benefit/risk assessment (grades 1 or 2). Prospective single-arm cohort studies that compared results to the current approach in adults were classified as level IV. Retrospective case series comparing results to the adult literature were classified as level V. Complete reference lists of the level V studies, which constitute the overwhelming majority, are available upon request.

Antithrombotic Agents and the Young

Heparin Therapy in Pediatric Patients

Mechanism of Action: Heparin’s anticoagulant activities, 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.3–5 Sick premature newborns, a population of children at significant risk for thrombotic events, frequently have plasma levels of AT that are <0.30 U/mL, potentially influencing their response to heparin.5 Fetal reference ranges are now available and show that AT levels range from 0.20 U/mL to 0.37 U/mL at gestational ages of 19 to 38 weeks.6

Heparin functions as an antithrombotic agent by catalyzing AT’s ability to inactive specific coagulation enzymes, of which thrombin is the most sensitive.7 The capacity of plasmas from newborns to generate thrombin is both delayed and decreased compared to adults:8,9 it is similar to plasma from adults receiving therapeutic amounts of heparin.8 Following infancy, the capacity of plasmas to generate thrombin increases, but throughout childhood, remains approximately 25% less than that of adults.10 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.8,10 These observations support the hypothesis that optimal dosing of heparin will differ in pediatric patients and adults.

Therapeutic Range: Therapeutic doses of heparin are the amounts of heparin required to achieve the adult therapeutic range based upon the activated partial thromboplastin time (APTT). The recommendations for standardizing APTT values to heparin levels in adults should be extrapolated to children (Table 1). 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 anti-factor Xa level of 0.3 to 0.7 U/mL.11 In pediatric patients, APTT values correctly predict therapeutic heparin concentrations approximately 70% of the time.12

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

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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

IV study). A bolus dose of 50 U/kg was insufficient, resulting in subtherapeutic APTT values in 60% of children.12 Bolus doses of 75 to 100 U/kg result in therapeutic APTT values in 90% of children (M. Andrew, MD; unpublished data; 1995). Maintenance heparin doses are age dependent, with infants having the highest requirements (28 U/kg/h) and children over 1 year of age having lower requirements (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).13 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).14,15 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.16

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 the adult in animal models and humans.13,16 Second, the delay in diagnosis of thrombotic complications in children may result in more extensive disease at the time of presentation, accelerating heparin clearance.16,17 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.13,22,23 A nomogram initially used in adults was adapted, tested, and modified for children (Table 1).12,22 Heparin dosing nomograms can be adapted into preprinted order sheets, which 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 supplement. One level IV study in children suggests that major bleeding from heparin therapy is not frequent in the treatment of DVT or PE in children.12 However, many children were treated with suboptimal amounts of heparin in this study,12 and there are case reports of major bleeding due to heparin in children. 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 on the occurrence of osteoporosis in children receiving heparin therapy. 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.24-26 In the absence of an alternative etiology for heparin-associated thrombocytopenia, pediatric patients should be evaluated for heparin-induced thrombocytopenia (HIT) and treated with alternative therapy. 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 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 3). Protamine sulfate can be administered in a concentration of 10 mg/mL at a rate not to exceed 5 mg/min. Patients with known hypersensitivity reactions to fish and those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.

LMWH Therapy in Pediatric Patients

Potential Advantages of LMWH for Children: LMWHs have several potential advantages over initial short-term heparin therapy for DVT or PE, as well as the traditional 3 months of oral anticoagulants. The potential advantages of LMWH for children include predictable pharmacokinetics that result in minimal monitoring, which is critically important in pediatric patients with poor or nonexistent venous access; subcutaneous administration; lack of interference by other drugs or diet such as exists for coumadin; reduced risk of heparin-induced thrombocytopenia; and probable reduced risk of the osteoporosis that occurs with long-term heparin use.
Orgaran consists mainly of heparin sulfate, a small quantity of dermatan sulfate and a minor amount of chondroitin sulfate, and does not contain any heparin fragments. Orgaran has a much higher anti-Xa/anti-IIa ratio compared to heparin or LMWH. Orgaran 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 following the bolus dose, every 4 h until steady state is reached, and then daily to maintain a therapeutic range of 0.4–0.8 U/mL.

Orgaran is predominantly removed from the circulation through the kidney. Consequently, Orgaran is contraindicated in patients with severe impaired renal function. Subcutaneous Orgaran is frequently used in adults, although there is no published pediatric dose information.

**Mechanism of Action:** Like heparin, anticoagulant activities of LMWHs are mediated by catalysis of AT.

**Therapeutic Range:** Therapeutic doses of LMWH are extrapolated from adults and are based on an 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 to achieve adult therapeutic anti-factor Xa levels in pediatric patients have been assessed for two LMWHs, enoxaparine (Lovenox; Rhone-Poulenc; Collegeville, PA) and reviparin (Clivarin, Knoll BASF Pharma; Ludwigshafen, Germany). A weight-adjusted nomogram was used to adjust LMWH doses into the therapeutic range (two level IV studies). Therapeutic doses of LMWH are age dependent, with infants having increased requirements (Table 4). The doses required for older children are similar to the weight-adjusted requirements for adults (Table 4). 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 lower levels of AT.

**Monitoring:** Nomograms for the adjustment of therapeutic doses of LMWH have been validated (Table 5).

**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 LMWH. Equimolar concentrations of protamine sulfate neutralize the anti-factor IIa activity but result in only partial neutralization of the anti-factor Xa activity. In animal models, however, bleeding is completely reversed by protamine sulfate. The dose of protamine sulfate is dependent on the dose of LMWH used at the time of administration. If protamine is given within 3 to 4 h of the LMWH, then a maximal neutralizing dose is 1 mg of protamine per 100 U (1 mg) of LMWH given in last-dose IV over 10 min. 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. A review of clinical studies to date, however, has failed to substantiate that claim. The FDA recently issued a warning concerning the danger of spinal hematoma occurring in adult patients undergoing epidural or lumbar punctures while receiving LMWH. Preliminary studies show that a significant proportion of children have substantial anti-factor Xa plasma activity 12 h following a subcutaneous treatment dose of LMWH. 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 unfractionated heparin for the equivalent antithrombotic effect. In particular, prior to lumbar punctures or epidural procedures, at least 2 doses of LMWH should be withheld and, if possible, anti-factor Xa levels should be determined prior to the procedure.

**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. These levels are similar to those found in adults receiving oral anticoagulants for the treatment of venous thrombotic disease. 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. Thirty-nine 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 increase and are within the adult range of normal by 6 months. Thirty-nine 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 of and decrease in amounts of thrombin generated in plasma from newborns and children. Thirty-nine The pattern of thrombin generation in newborns is similar to plasma from adults receiving therapeutic amounts of oral anticoagulants. Forty-one Because of the potential risk of bleeding from further anticoagulation and the presence of borderline vitamin K status, oral anticoagulant therapy is avoided when possible during the first month of life. Thirty-nine Forty-two In older children receiving oral anticoagulants, the capacity of plasma to generate thrombin is delayed and is decreased by 25% compared to plasma from adults with similar international normalized ratios (INRs). Forty-one Forty-three 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, is significantly lower in children compared to adults at similar INR values.

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

<table>
<thead>
<tr>
<th>Anti-Factor Xa Level</th>
<th>Hold Next Dose</th>
<th>Dose Change</th>
<th>Repeat Anti-Factor Xa level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35 U/mL</td>
<td>No</td>
<td>Increase by 25%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.35-0.49 U/mL</td>
<td>No</td>
<td>Increase by 10%</td>
<td>4 h after next dose</td>
</tr>
<tr>
<td>0.5-1.0 U/mL</td>
<td>No</td>
<td>No</td>
<td>Next day, then 1 wk later and monthly thereafter while receiving Reviparin-Xa treatment at (4 h after AM dose)</td>
</tr>
<tr>
<td>1.1-1.5 U/mL</td>
<td>No</td>
<td>Decrease by 20%</td>
<td>Before next dose</td>
</tr>
<tr>
<td>1.6-2.0 U/mL</td>
<td>3 h</td>
<td>Decrease by 30%</td>
<td>Before next dose, the 4 h after next dose</td>
</tr>
<tr>
<td>&gt;2.0 U/mL</td>
<td>Until anti-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>

**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 extrapolated directly from recommendations for adult patients because there are no clinical trials that have assessed the optimal INR range for children based upon clinical outcomes. The recommended therapeutic range for the treatment of venous thrombotic disease is an INR between 2.0 and 3.0. 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. One and Four However, the available biological data (see previous section) and limited clinical data suggests 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, one-four four were level V and one was level IV. One of the seven publications that provide information on maintenance doses for oral anticoagulants required to achieve an INR between 2.0 and 3.0 in children, one-four seven,four twenty-five five are level V and two are level III. Maintenance doses for oral anticoagulants are age dependent, with infants having the highest 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 = 115) found that infants required an average of 0.32 mg/kg and teenagers 0.09 mg/kg of warfarin to maintain a target INR of 2 to 3. Fifty-two The mechanisms responsible for the age dependency of oral anticoagulant doses are not completely clear. Table 6 provides a nomogram for loading and monitoring oral anticoagulants in children. Four Guidelines for the duration of therapy with oral anticoagulants in children reflect recommendations for adults with similar disorders. One Hundred and Fifty-three 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, due to the low concentrations of vitamin K in breast milk. In contrast, some children are resistant to oral anticoagulants due to impaired absorption, requirements for total parenteral nutrition, which is routinely supplemented with vitamin K; and nutrient formulas, which are 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 that of adults. The most commonly used medications in children that affect the INR are listed in Table 7. 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 <1 year of age and teenagers. Teenagers are not necessarily compliant with their medication, and infants are a difficult group of patients to monitor due to poor venous access as well as their complicated medical problems.

The problems with monitoring oral anticoagulants in children have limited their use, even in conditions in which they are 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.

Whole Blood Monitors for Children: Whole blood monitors use various techniques to measure the time from application of fresh samples of capillary whole blood to coagulation of the sample. The monitors include a batch-specific calibration code that converts the result into a calculated INR. There are two "point of care" monitors evaluated in the pediatric population, the CoaguChek (Boehringer Ingelheim; Mannheim, Germany) and the ProTime Microcoagulation System (International Technidyne Corp; Edison, NJ). Both monitors were shown to be acceptable and reliable for use in the outpatient laboratory and at home settings. Parents and patients undertook a formal education program prior to using the monitors. The major advantages identified by families included reduced trauma of venipunctures, minimal interruption of school and work, ease of operation, and portability.

Adverse Effects of Oral Anticoagulants: Bleeding is the main complication of oral anticoagulants. Minor bleeding, which is of minor 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 <3.2% patient-years (13 level V studies) (see below). 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, 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-dependent factor replacement (either fresh frozen plasma or

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Increase</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Increase or no change</td>
</tr>
<tr>
<td>Amodiallic (Amoxil)</td>
<td>Slight increase</td>
</tr>
<tr>
<td>Cefaclor (Ceclor)</td>
<td>Increase</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Decrease</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>Increase</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Increase</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Increase</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Increase</td>
</tr>
</tbody>
</table>

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prothrombin complex concentrates) are dependent on the clinical problem. Table 8 provides guidelines for reversal of oral anticoagulant therapy in children with no bleeding and those with significant bleeding.

**Antiplatelet Therapy in Pediatric Patients**

**Age-Dependent Features:** Compared to platelets from adult control subjects, neonatal platelets are hyporeactive to thrombin, adenosine diphosphate (ADP)/epinephrine, and thromboxane A2.74,74a This hyporeactivity of neonatal platelets is the result of a defect intrinsic to neonatal platelets.74,74a Paradoxically, the bleeding time is short in newborns, due to increased RBC size, high hematocrit values, and increased levels and multimeric forms of von Willebrand factor.75–77 No studies of platelet function in healthy children were identified, except for the bleeding time, which, relative to adults, is prolonged throughout childhood according to two of three studies.40,78,79 These physiologic differences suggest that the optimal dosage of antiplatelet agents in newborns and children may also differ from that in adults.

**Therapeutic Range, Dose Response, and Monitoring of Antiplatelet Agents:** There is no therapeutic range for or need to monitor aspirin, the most commonly used antiplatelet agent, and 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 shunts, some endovascular stents, and some cerebrovascular events.49 For mechanical prosthetic heart valves, aspirin doses of 6 to 20 mg/kg/d were used in nine studies,50,64,67,80–84 either alone or in combination with 6 mg/kg/d of dipyridamole in 3 divided doses.84 High dose aspirin, 80 to 100 mg/kg/d, is used in 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.85 The effects of aspirin last for approximately 7 days. The second most commonly used antiplatelet agent, prescribed for patients with mechanical prosthetic heart valves, is dipyridamole in doses of 2 to 5 mg/kg/d.84,81,83

Glycoprotein (GP)IIb-IIIa antagonists are a new class of antiplatelet drugs that are now available in IV form (ReoPro, Aggrastat, Intreglin) and will soon be available in oral form.86 These drugs, which are either chimeric antibodies (ReoPro; Centocor; Malvern, PA), peptides (Intreglin; COR Therapeutics; South San Francisco, CA), or nonpeptide small molecules (Aggrastat; Merck; West Point, PA), 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.86 However, 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.87 The appropriate therapeutic ranges for these assays may prove to be different in children because of the agent-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).88–90 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 (ICH) 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 antiplatelet therapy, as 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.93–99

**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. Transfusions of platelet concentrates and/or the use of products that enhance platelet adhesion (plasma products containing high concentrations of von Willebrand factor), or D-des amino arginine vasopressin may be helpful.

**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 (21 mg/100 mL).3,4,100 The decreased levels of plasminogen in newborns slows the generation of plasmin101 and reduces the thrombolytic effects of streptokinase (SK), urokinase (UK) and tissue plasminogen activa-

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**Table 8—Reversal of Oral Anticoagulation Therapy**

1. No bleeding
   A) Rapid reversal of oral anticoagulants is necessary and the patient will require oral anticoagulants again in the near future: give vitamin K, 0.5 to 2 mg subcutaneously or IV (not intramuscularly), depending on the patient’s size.
   B) Rapid reversal of oral anticoagulants is necessary and the patient will not require oral anticoagulants again: vitamin K1, 2–5 mg subcutaneously or IV (not intramuscularly).

2. Significant bleeding
   A) Significant bleeding that is not life-threatening and will not cause morbidity: treat with vitamin K1, as in 1A plus FFP (20 mL/kg IV).
   B) Significant bleeding that is life-threatening and will cause morbidity: 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, X), 50 U/kg IV rather than FFP (20 mL/kg IV).
tor (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 the efficacy/safety of thrombolytic therapy is too weak to have useful clinical predictive value. In patients with bleeding, however, 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 is not obtained rapidly and helps 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. Measurement of fibrin/fibrinogen degradation products and/or D-dimers are helpful in determining whether a fibrinolytic effect is present.

Dose Response: Thrombolytic agents are used in low doses, usually to restore catheter patency, and in higher doses to lyse large vessel thrombi or PE. Table 9 presents the most commonly used dose regimens for thrombolytic therapy in pediatric patients with arterial or VTE 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 upon the Thrombolysis in Myocardial Infarction II trial, doses of 150 mg rt-PA caused more bleeds into the central nervous system than 100 mg (1.5% vs 0.5% respectively). It seems likely that there will be an upper dose limit based on safety.

Route of administration: There are no published studies that compare local to systemic thrombolytic therapy in children. From 1986 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 thrombolysis to unblock central venous lines (CVLs). Complete or partial lysis was achieved in 70% of cases, with major bleeding occurring in 11% of children. A recent level IV study reported successful lysis in only one of seven patients and 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 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 thrombosis when the catheter is already in situ.

Adverse Effects of Thrombolytic Therapy: Based upon 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. A recent review of the literature specifically examined the incidence of intracerebral hemorrhage (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 analyzed (1.5%). When subdivided according to age, ICH was identified in 2 of 468 children (0.4%) after the neonatal period, 1 of 83 term infants (1.2%), and 11 of 86 preterm infants (13.8%). In the largest study of premature infants included in this review, however, the incidence of ICH was the same in the control arm that did not receive thrombolytic therapy. The incidence of ICH in adults treated with thrombolytic therapy also varies with age and is between 0.3 and 5.0%.

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 1 bag/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 pathologies differ. For example, myocardial infarction and cere-

Table 9—Thrombolytic Therapy for Pediatric Patients

<table>
<thead>
<tr>
<th>Low Dose for Blocked Catheters</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Instillation</strong></td>
<td>none</td>
</tr>
<tr>
<td>UK (5,000 U/mL) 1.5–3 mL/ lumen 2–4 h</td>
<td>None</td>
</tr>
<tr>
<td>UK (150 U/kg/h) per lumen 12–48 h</td>
<td>Fibrinogen, TCT* PT, APTT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Load, U/kg</th>
<th>Systemic Thrombolytic Therapy†</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>4,400</td>
<td>4,400 U/kg/h 6–12 h</td>
</tr>
<tr>
<td>SK</td>
<td>2,000</td>
<td>2,000 U/kg/h 6–12 h</td>
</tr>
<tr>
<td>tPA</td>
<td>None</td>
<td>0.1–0.6 mg/kg/h for 6 h</td>
</tr>
</tbody>
</table>

*TCT = thrombin clotting time.†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.

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brovascular accidents (CVA) are two of the more common indications for antithrombotic therapy in adults and are the least common in children.2 The current indications for antithrombotic therapy in children are provided in Table 10.

**Venous Thromboembolic Disease**

**Incidence:** The incidence of venous thromboembolic complications (DVT/PE) is age dependent, with the lowest risk occurring in children.11,112,113 Estimates of the incidence of DVT/PE in the general pediatric population are between 0.07/10,000 and 5.3/10,000 hospital admissions.114–116 Comparable incidences of DVT/PE in the adult population are approximately 2.5 to 5.0%.117–119 Other comparisons illustrating the lower risk of DVT/PE during childhood are <1% incidence of clinically apparent DVT/PE following lower limb or scoliosis surgery,120 and the low frequency of DVT/PE in children with heterozygote congenital prothrombotic states.53,121 Several mechanisms likely contribute to the protective effect of age for DVT/PE.122 These include a reduced capacity to generate thrombin,122 increased capacity of α2-macroglobulin to inhibit thrombin,124 presence of a circulating anticoagulant at birth,125,126 and others, such as enhanced antithrombotic potential by the vessel wall.128

**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/PEs are idiopathic in children.43 Ninety-five percent of DVT/PE cases in pediatric patients are problems secondary to serious diseases, such as prematurity, cancer, trauma/surgery, congenital heart disease, and systemic lupus erythematosus.53,121,129–131 Congenital prothrombotic disorders alone account for <10% of DVT/PE cases in children.53,121 The frequency of congenital prothrombotic disorders in children with secondary DVT is uncertain, but it may be substantial.132–137 The ages of greatest risk for DVT/PE are infants of age <1 year and teenagers.53,121,131 DVT in the lower extremities is the most frequent non-CVL thrombotic complication in children.121 The clinical presentations and treatment of DVT/PE are similar to those in the adult.53,116,121,138

**Central Venous Lines:** Forty percent of DVT in children and over 50% in newborns occur in the upper venous system secondary to the use of CVLs.53,121,133 CVLs are placed for short-term intensive care or for long-term supportive care in children requiring total parenteral nutrition or therapy for cancer. CVL-related DVTs are not trivial, as they require repeat anesthesia for replacement; provide a source for PE,139–142 cause superior vena cava syndrome,142–146 chylothorax,142,143,147,148 and eventual destruction of the upper venous system; and contribute to postphlebitic syndrome in the upper extremities. The long-term consequences of extensive CVL-related DVT 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 different underlying disorders, diagnostic tests, and indexes of suspicion. For example, the incidence of CVL-related thrombosis in children receiving long-term total parenteral nutrition varies from 1%, based on clinical diagnosis,130,151 to 35%, based on ventilation perfusion scans or echocardiography, to 75%, based on venography.44 In many patient populations, the incidence is not accurately known. This information is important in identifying 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 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, level II study assessing the need for prophylactic heparin.152 The study was conducted in children with cancer using echocardiography of the heart as the outcome measure, not venography.152 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 the most commonly used therapy for treating a malfunctioning line that is “blocked” (Table 9). Based on several level V studies, patency is restored in approximately 80% of patients.

**Inherited Prothrombotic Conditions:** Inherited thrombophilia is usually defined by the following features: (1) positive family history; (2) early age of onset; (3) recurrent disease; and (4) multiple or unusual locations. Over half these individuals have associated environmental risk factors such as surgery, pregnancy, trauma, etc., and half or more of the individuals fulfilling these criteria will have demonstrable abnormalities in the following four genes: AT, protein C (PC), protein S (PS), and activated protein

---

**Table 10—Indications for Antithrombotic Agents in Pediatric Patients**

<table>
<thead>
<tr>
<th>I. Treatment</th>
<th>Venous thromboembolic complications</th>
</tr>
</thead>
<tbody>
<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>Blalock-Taussig shunts</td>
</tr>
<tr>
<td></td>
<td>Fontan's operation</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>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Continuous veno-venous hemoperfusion</td>
</tr>
</tbody>
</table>
Antithrombin homozygous (1) types in morphism, hyperhomocysteinemia More with abnormalities of AT and deficiency in combination appears deficiency of in bosis these C677T.155-157 The IIG20210A, 3%, to 0.1% For number of factors for abnormalities of PC, PS, and AT, however, C resistance/factor V Leiden (FV-R506Q). A large number of other candidate genes have been proposed as risk factors for inherited thrombophilia; most of these candidates, however, have not undergone careful segregation or population studies to define their pathogenic role. In fact, some of the seemingly obvious candidates, such as abnormalities in fibrinolysis, do not appear to confer inheritable risk.154 These latter studies are however hampered by the low prevalence of most of these inherited abnormalities in the general population.

Our understanding of inherited thrombophilia has been revolutionized over the past 5 years by the description of a number of relatively high-prevalence genetic risk factors, including factor V Leiden, prothrombin G20210A (IIG20210A) polymorphism, and hyper-homocysteinemia (MTHFR-C677T). For example, in the general white population, these risk factors are present in 3 to 8% and 2 to 3%, respectively, for heterozygous FV-R506Q and IIG20210A, and in 12 to 15% for homozygous MTHR C677T.155-157 The prevalence of these risk factors varies with race. These prevalence figures contrast with the 0.4% and 0.1% prevalence observed for PC and AT deficiencies, respectively.158,159

Recent reports demonstrate an increased risk of thrombosis in families with a second genetic abnormality.160 Most reports have described a combination of FV-R506Q with abnormalities of PC, PS, or AT. These findings begin to shed light on the marked variability in clinical expression of these syndromes. The effect of genetic dosage has long been evident from the severely affected neonates with homozygous PC and PS deficiency. Homozygous AT deficiency appears to be incompatible with survival.

Once one moves away from the well-defined homozygous cases, the risk and severity appear to vary with the type and number of underlying genetic abnormalities (Table 11). High risk is conferred by the following: (1) types I and II AT deficiency, especially in combination with FV-R506Q; (2) heterozygous PC and PS deficiency in combination with FV-R506Q; and (3) in homozygotes for FV-506Q. Mild-to-moderate risk is associated with isolated heterozygous PC and PS deficiency and AT deficiency due to mutations in the heparin binding site. More recent studies are beginning to suggest that either hyperhomocysteinemia or the prothrombin polymorphism, in association with another risk factor, confer additive risk for VTE disease, probably similar to the combination of FVR506Q with other biochemical risk factors described above.164-167 although the results have been mixed. Multigenic risk is best demonstrated with the combination of AT deficiency, and FV-R506Q163 is more varied in PC and PS deficiencies associated with FV506Q.161,162 In general, in affected families with heterozygous mutations, the earliest onset is at midteenage years, with childhood causing a clustering of women in their late teens and early twenties. Diagnosis of patients with suspected inherited thrombophilia should include a panel of tests including at least PC, PS, AT, and FV-R506Q. Many laboratories also add the prothrombin polymorphism G20210A and a homocysteine level.

As stated previously, patients with heterozygote deficiencies are usually protected during childhood, except in the presence of a secondary challenge such as a CVL. The reported incidence of inherited prothrombotic disorders in children with DVT/PE varies from 10 to over 60%,168-173 In children with cancer and DVT/PE, the reported incidence is 3%,174 the incidence of CVL-related DVT/PE is 83%,175 and the incidence of congenital heart disease and DVT/PE is 56%176 (n = 32, 18, 9, respectively). These three studies varied in design from retrospective case series to prospective cohort studies. In particular, different definitions of prothrombotic disorders (for example, some included elevated lipoprotein plasma levels) and different patient selection procedures (idiopathic or secondary) make the true incidence of prothrombotic disorders in children with DVT/PE uncertain. Screening for prothrombotic disorders in children with thrombosis, regardless of the presence or absence of clinical risk factors, is probably worthwhile. The role of screening children with major illnesses, or, for example, children about to have a CVL inserted, in order to administer prophylactic therapy is unknown.

Although there is agreement on the initial treatment of DVT/PE in children with anticoagulants and on the need for prophylaxis in high-risk situations, there is a paucity of information on the risks and benefits of long-term prophylaxis versus careful monitoring with intermittent prophylaxis. Further studies are required.

**Homozygous PC or PS Deficiency**

In contrast to heterozygous PC or PS deficiency, homozygous PC/PS deficiency presents within hours of birth.

---

**Table 11—Frequency of VTE 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.  VTE, %</td>
<td>No.  VTE, %</td>
<td>No.  VTE, %</td>
<td>No.  VTE, %</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>23  70</td>
<td>34  35</td>
<td>20  10</td>
<td>30  7</td>
<td>Koeleman et al, 1994202</td>
</tr>
<tr>
<td></td>
<td>(6 families)</td>
<td></td>
<td></td>
<td></td>
<td>Zoller et al, 1995168</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>18  72</td>
<td>21  19</td>
<td>21  19</td>
<td>44  2</td>
<td>Van Boven et al, 1996163</td>
</tr>
<tr>
<td></td>
<td>(7 families)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>12  92</td>
<td>7  57</td>
<td>5  20</td>
<td>11  0</td>
<td></td>
</tr>
<tr>
<td>deficiency</td>
<td>(6 families)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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with purpura fulminans, cerebral and/or ophthalmic damage which 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. Since 1980, 44 patients with homozygous PC deficiency and 1 patient with homozygous PS deficiency were reported in the literature (references available upon request). Thirty-three patients presented in the neonatal period and eight as children or adults. All patients presenting at birth with purpura fulminans had undetectable levels of PC or PS, whereas patients with delayed presentation had detectable levels of PC, 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), PC concentrate, cryoprecipitate, prothrombin complex concentrate, heparin, LMWH, aspirin, sulfinpyrazone, corticosteroids, vitamin K, aprotinin, and AT concentrate. One approach is to initiate treatment with 10 to 20 mL/kg of FFP q12h. 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 >0.60 U/mL. Replacement of PC should be continued until the clinical lesions resolve, which is usually in 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 of FFP and reported a recovery of PS at 2 h of 0.23 U/mL and at 24 h of 0.14 U/mL. 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 oral anticoagulant therapy, intermittent PC replacement with PC concentrate, and liver transplantation. PC replacement may not prevent further thrombosis in the presence of a risk factor such as a CVL. Currently, the majority of children are treated with oral anticoagulants. When therapy with oral anticoagulants is initiated, the infant, to avoid skin necrosis, should continue receiving PC or PS replacement until the INR is between approximately 3.0 and 4.5. 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 oral-anticoagulant-induced skin necrosis and likely decreases the risk of bleeding associated with high doses of oral anticoagulants.

### 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, 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 cerebral vessels from local lesions or emboli 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% (Table 12). Younger children (<10 years of age) have an increased incidence compared to older children. Prophylactic anticoagulation with aspirin does not significantly reduce the incidence of arterial thrombosis (one level II study). However, anticoagulation with 100 to 150 U/kg of heparin reduces the incidence from 40 to 8% (one level II study). One level II study suggests that 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 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 thrombotic complications. Further heparin boluses are frequently used in prolonged procedures (≥60 min), especially during interventional catheterizations; the benefits of this practice, however, are not known. A short limb and claudication are the long-term consequences of femoral artery thrombosis in children.

<table>
<thead>
<tr>
<th>Study</th>
<th>Level</th>
<th>Intervention</th>
<th>Patient No.</th>
<th>Bleeding</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freed et al, 1974</td>
<td>II</td>
<td>Aspirin (15 mg/kg)</td>
<td>37</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Freed et al, 1974</td>
<td>I</td>
<td>Placebo</td>
<td>58</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Freed et al, 1974</td>
<td>I</td>
<td>Heparin (1 mg/kg)</td>
<td>37</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Saxena et al, 1997</td>
<td>II</td>
<td>Placebo</td>
<td>40</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Saxena et al, 1997</td>
<td>II</td>
<td>Heparin 50 IU/kg</td>
<td>183</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Saxena et al, 1997</td>
<td>II</td>
<td>Heparin 100 IU/kg</td>
<td>183</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

*TE = thrombotic event.

†p < 0.05.
Umbilical Artery Catheterization: Umbilical arterial catheterization is necessary for the administration of supportive care critical to the survival of sick newborns (Table 13). Umbilical artery catheter tips are either positioned high (level of T5 to T10) or low (level of L3 to L5). The optimal position to minimize thrombotic complications remains uncertain. The position the umbilical artery catheters may affect both the frequency of thrombosis and ICH.199–202 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 study203 and five level II studies.204–208 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 (one level I and four level II studies).203,205–208 Local thrombus, detected by ultrasound, was not decreased in two level II studies. The power, however, was low.204,207 ICH as an outcome was not increased in two level II studies. The sample size in one study, however, was small (15 per arm).208 In the other study, the odds ratio for ICH and heparin use was 1.49 (95% CI, 0.62 to 3.59).209 In two level III studies, heparin was implicated as a risk factor for ICH in low-birth-weight infants.210 One study was retrospective, the 95% CI around the odds ratio of 3.9 was large (1.4 to 11.0), and the magnitude of the risk was uncertain.210 The second study reported a positive correlation between heparin dose and frequency of ICH, although severity of illness was also positively correlated with heparin dose, and the effect could not be differentiated.211 Large, well-designed studies are required to determine whether low-dose heparin infusion affects the incidence 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 antiinflammatory agent, then in lower doses as an antiplatelet 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’s disease). Although no level I or level II studies have been performed, two level III studies194,195 suggest that aspirin can reduce the coronary involvement in Kawasaki’s disease. A recent meta-analysis concluded that children treated with IV γ-globulin and aspirin had a significantly lower incidence of coronary artery aneurysms than those treated with aspirin alone.212 Much of the treatment difference in this analysis was due to one level I study that demonstrated that the combination of IV γ-globulin and aspirin is more efficacious in this regard than is aspirin alone.213 The meta-analysis made a number of conclusions about optimal dosing of aspirin and gammaglobulin. Significant methodological flaws in the analysis, however, suggest that the conclusions should be viewed with some caution. Further studies are required.

### Table 13—Umbilical Artery Catheterization*

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Bleeding Event (B or TE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al, 1987204</td>
<td>II</td>
<td>HB-PU</td>
<td>61</td>
<td>NR†</td>
</tr>
<tr>
<td>Horgan et al, 1987207</td>
<td>II</td>
<td>PVC</td>
<td>64</td>
<td>NR</td>
</tr>
<tr>
<td>Rajani et al, 1979203</td>
<td>I</td>
<td>Heparin</td>
<td>59</td>
<td>NR</td>
</tr>
<tr>
<td>David et al, 1981206</td>
<td>II</td>
<td>Placebo</td>
<td>32</td>
<td>NR</td>
</tr>
<tr>
<td>Bosque and Weaver, 1986205</td>
<td>II</td>
<td>Heparin (C)</td>
<td>26</td>
<td>NR</td>
</tr>
<tr>
<td>Horgan et al, 1987207</td>
<td>II</td>
<td>Heparin (I)</td>
<td>26</td>
<td>4 B‡</td>
</tr>
<tr>
<td>Ankola and Atakent, 1993206</td>
<td>II</td>
<td>No heparin</td>
<td>45</td>
<td>0 B‡</td>
</tr>
<tr>
<td>Chang et al, 1997209</td>
<td>II</td>
<td>No heparin</td>
<td>85</td>
<td>17 ICH</td>
</tr>
</tbody>
</table>

*B = blocked; TE = thromboembolic event; HB-PU = heparin bonded-polyurethane; PVC = polyvinyl chloride; C = continuous; I = intermittent.
†NR = not reported.
‡No hemorrhage.
§p < 0.05.
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 patients. Biological prosthetic heart valves rapidly became the ‘valve of choice’ for the pediatric age group.\(^{213}\) Subsequently, it became evident that premature degeneration and calcification of porcine valves occurred in the majority of children.\(^{214-221}\) The accelerated failure of biological 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 and aortic positions in children and that biological prosthetic heart valves be reserved for patients who require tricuspid or pulmonary valve replacements.\(^{222,223}\) Children with biological prosthetic heart valves are treated following adult recommendations and are followed 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.

**No Therapy:** With no antithrombotic therapy, thromboemboli occurred at a rate of 5.7\(^{\%}\) patient-years with St. Jude valves\(^{65}\) and at rates of 6.8 to 27.3\(^{\%}\) patient-years for other types of valves\(^{81}\) (Table 14). There was one death due to mitral valve thrombosis.\(^{65}\)

**Antiplatelet Agents:** One level III study reported no difference in survival or thromboembolic events in children treated with coumadin to maintain a PT of 1.5 \(\times\) control \((n = 48)\), or aspirin \((5 \text{ to } 6 \text{ mg/kg})\) and dipyridamole \((6 \text{ mg/kg})\) \((n = 16)\).\(^{84}\) The linearized thromboembolic event rates were 2.6 and 1.7\(^{\%}\) patient-year, respectively \((p = 0.6)\). Bleeding linearized event rates were 1.5\(^{\%}\) patient-year in the coumadin group and 0 in the antiplatelet group \((p = 0.09)\). Numerous level V studies have reported the use of empiric low doses of aspirin \((6 \text{ to } 20 \text{ mg/kg/d})\) and/or dipyridamole \((2 \text{ to } 5 \text{ mg/kg/d})\) for the prevention of thromboembolic complications in the absence of oral anticoagulants. With antiplatelet agents alone, thromboemboli occurred at rates of 1.1 to 68\(^{\%}\) patient-years, with 3 of 8 studies having thromboembolic rates over 5\(^{\%}\) patient-years \((p = 0.6)\). There was only one major bleed. It was not fatal, and it did not result in long-term morbidity \((p = 0.6)\). There were eight deaths due to thromboembolic complications for which therapy could not be determined.\(^{64}\)

**Oral Anticoagulation Therapy:** With oral anticoagulants, the incidence of thromboembolic events were uniformly less than 5\(^{\%}\) patient-years \((p = 0.6)\). There were five deaths due to thromboembolic events and two due to bleeding.\(^{46,70,81,222,223,225}\) Three of the five patients had discontinued 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 \((p = 0.6)\). In one study, two patients required blood transfusions \((rate = 8.2\%)\) patient-years) and recovered uneventfully.\(^{80}\) Adjuvant therapy with antiplatelet agents was used in one study.\(^{46}\) Based on information available for adults and children, it seems reasonable to consider aspirin 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 of oral anticoagulation in children with mechanical prosthetic heart valves. Problems of effectively monitoring oral anticoagulants can be addressed through anticoagulation clinics for children and through the use of whole blood monitors in the clinic and at home.\(^{226}\)

**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:** Blalock-Taussig shunts are one 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 systemic stenosis.\(^{227,228}\) "Modified" Blalock shunts, where a polytetf (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

<table>
<thead>
<tr>
<th>Table 14—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves With No Antithrombotic Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source, yr</td>
</tr>
<tr>
<td>Sade et al.(^{66}) 1988</td>
</tr>
<tr>
<td>Solymar et al.(^{81}) 1991</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*TE = thromboembolic event; HEM = hemorrhage; Ao = aortic; M = mitral. Solymar et al\(^{81}\) is an updated version of Rao et al.\(^{66}\) 1989.

\(\S\)NR = not reported.

\(\S\)The death was secondary to a mitral valve thrombosis.

\(\S\)The number of patients treated with no antithrombotic therapy could not be determined. (186) refers to the entire patient population of the study.\(^{81}\)

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short length and very high flow, acute thrombosis is less common. Since 1980, 647 children with Blalock-Taussig shunts have been studied in 21 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), although others recommended intraoperative heparin with no further anticoagulation.\(^2,3\)

**Fontan Operation:** The Fontan procedure, or a modified version, is the definitive palliative surgical treatment for most congenital univentricular heart lesions. Thromboembolic complications remain a major cause of early and late morbidity and mortality. Reported incidences of venous thrombosis and stroke ranged from 3 to 16% and 3 to 19%, respectively, in the retrospective cohort studies where thrombosis was the primary outcome, and from 1 to 7% in the retrospective cohort studies assessing multiple outcomes. Thromboembolic complications may occur at any time following Fontan procedures, but often present months to years later. No predisposing factors have been identified with certainty, although this may be due to the inadequate power and 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 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 regimes are in current use. There is an urgent need for large, multicenter prospective trials of prophylactic anticoagulation therapy following Fontan procedures.\(^2,3\)

**Endovascular Stents:** Endovascular stents are used increasingly to manage a number of congenital heart lesions, including branch pulmonary artery stenosis, pulmonary vein stenosis, and coarctation of the aorta, and to treat postsurgical stenosis.\(^2,3\) Stents can be successfully used in infants <1 year of age. The small vessel size increases the risk of thrombosis. There are no studies assessing the role of anticoagulation or antiplatelet therapy to avoid stent occlusion. Heparin is commonly given at the time of stent insertion, followed by aspirin therapy. Further studies are required to determine the optimal prophylactic anticoagulation required.

Other likely cardiac indications for anticoagulation in children are atrial fibrillation and myocardial infarction.\(^2,3\) There are 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 in pediatric patients is used for several other disorders that are not discussed in this chapter. Readers are referred to other sources for antithrombotic therapy in cardiopulmonary bypass.\(^2,3\)–\(^7\) ex-

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**Table 15—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves Treated With Antiplatelet Agents**

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</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>Serra et al,(^67) 1987</td>
<td>V</td>
<td>24</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>McGrath et al,(^55) 1987</td>
<td>V</td>
<td>30</td>
<td>4-20 yr</td>
<td>St. Jude</td>
<td>M, Ao</td>
<td>19</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>El Mahlouf et al,(^44) 1987</td>
<td>V</td>
<td>150</td>
<td>2-16 yr</td>
<td>Various</td>
<td>M, Ao</td>
<td>32</td>
<td>0(!)</td>
<td>0</td>
</tr>
<tr>
<td>Bradley et al,(^56) 1985</td>
<td>V</td>
<td>10</td>
<td>&lt;19 yr</td>
<td>Various</td>
<td>A, Ao</td>
<td>2.3</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Solymar et al,(^81) 1991</td>
<td>V (186)(!)</td>
<td>12</td>
<td>1-20 yr</td>
<td>Various</td>
<td>M, Ao</td>
<td>1.8</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Borkon et al,(^52) 1986</td>
<td>V</td>
<td>8</td>
<td>3 wk-17 yr</td>
<td>Various</td>
<td>M, Ao</td>
<td>1.1</td>
<td>0.1(!)</td>
<td>0</td>
</tr>
<tr>
<td>LeBlanc et al,(^53) 1993</td>
<td>V</td>
<td>20</td>
<td>1-17 yr</td>
<td>Various</td>
<td>M, Ao</td>
<td>1.7</td>
<td>0.1(!)</td>
<td>0</td>
</tr>
<tr>
<td>Bradley et al,(^54) 1997</td>
<td>III</td>
<td>16</td>
<td>3-16 yr</td>
<td>St. Jude</td>
<td>M, Ao</td>
<td>1.7</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*DIP = dipyridamole; Ao = aortic; ASA = aspirin; M = mitral; TE = thromboembolic event; HEM = hemorrhage; CVA = cerebral vascular accident. Solymar et al\(^81\) is an updated version of Rao et al.\(^50\) 1989.*

†NR = not reported.

\(\!\)No hemorrhage. The number of patients treated with antiplatelet agents could not be determined. (186) refers to the entire patient population of the study.\(^81\)

\(\!\)Secondary to a mitral valve thrombosis.

\(\!\)Parentheses indicate estimated number.
tricorporeal membrane oxygenation,238–240 and continuous
veno-venous hemofiltration.241–243

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.244

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¬
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 level V studies,245,246
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 study247 failed to confirm this
hypothesis. Furthermore, there is no evidence that aspirin
and dipyridamole favorably affect other outcome variables
in HUS. A level I study248 showed no benefit of dipyri¬
amole and heparin treatment over symptomatic therapy
alone. Similarly, antiplatelet agents have not been shown
to be useful in the related disorder of childhood thromb¬
ocytic thrombocytopenia purpura.

Homocystinuria: In a level V study,249 aspirin and
dipyridamole were hypothesized to diminish the throm¬
boembolic complications of homocystinuria in patients
who are unresponsive to pyridoxine. However, two other
level V studies250,251 did not support this hypothesis.

CLINICAL TRIALS CURRENTLY BEING
CONducted

In general, the levels of evidence supporting guidelines
for anticoagulation in children are suboptimal. The re¬
duced incidence of thromboembolic disease in children
compared to adults limits the value of single institution
studies. The rapid emergence of thromboembolic complica¬
tions as a major problem in tertiary pediatric health care
over the last decade has led to the development of

| Table 16—Thromboembolic and Hemorrhagic Complications of Mechanical Prosthetic Heart Valves Treated With
<p>| Warfarin* |</p>
<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Level</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 al,69 1985</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>1</td>
</tr>
<tr>
<td>el Makhlouf et al,64 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>1</td>
</tr>
<tr>
<td>Harada et al,70 1990</td>
<td>V</td>
<td>40</td>
<td>4 mo–15 yr</td>
<td>St. Jude</td>
<td>Ao</td>
<td>1.3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stewart et al,63 1987</td>
<td>V</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>1</td>
</tr>
<tr>
<td>Bradley et al,60 1985</td>
<td>V</td>
<td>20</td>
<td>&lt;19 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0</td>
<td>8.2</td>
<td>1</td>
</tr>
<tr>
<td>Milano et al,254 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>1</td>
</tr>
<tr>
<td>Schaff et al,252 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>1</td>
</tr>
<tr>
<td>Solymar et al,81 1991</td>
<td>V</td>
<td>(186)¶</td>
<td>1–20 yr</td>
<td>Various</td>
<td>M</td>
<td>2.1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Schaff et al,80 1984</td>
<td>V</td>
<td>48</td>
<td>6 mo–18 yr</td>
<td>Starr-Edwards</td>
<td>Ao</td>
<td>5.3</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Borkon et al,62 1986</td>
<td>V</td>
<td>22</td>
<td>3 wk–17 yr</td>
<td>St. Jude</td>
<td>M</td>
<td>2.0</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Human et al,253 1982</td>
<td>V</td>
<td>56</td>
<td>2–12 yr</td>
<td>Various</td>
<td>M</td>
<td>3.2</td>
<td>3.2</td>
<td>1</td>
</tr>
<tr>
<td>Antunes et al,254 1989</td>
<td>V</td>
<td>352</td>
<td>≤20 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0.5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Woods et al,66 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>
<tr>
<td>Champsur et al,222 1997</td>
<td>V</td>
<td>54</td>
<td>1–17 yr</td>
<td>Various</td>
<td>Ao</td>
<td>0.3</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Bradley et al,64 1997</td>
<td>III</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</td>
</tr>
</tbody>
</table>

*Ao = aortic; M = mitral, pulm = pulmonary; TE = thromboembolic event; HEM = hemorrhage.
¶The anticoagulant used could not be determined.
†The death was due to a mitral valve thrombosis.
‡Parentheses indicate estimated number.
collaborative clinical trial groups. Current and future multicenter trials will provide the best evidence from which to formulate specific guidelines for the management of thromboembolic disease in children.

There are currently five ongoing multicenter, multinational, randomized, controlled trials assessing the optimal use of anticoagulants in children with or at risk for specific thromboembolic complications. The following section briefly describes these trials.

**REVIVE:** This study (Reviparin in Venous Thromboembolism) is a randomized, controlled trial comparing LMWH (Reviparin) to standard heparin and warfarin for the treatment of DVT in children.

**PROTEKT:** This study (Prophylaxis of Thromboembolism in Kids Trial) is a randomized, controlled trial comparing LMWH (Reviparin) to standard of care primary prophylaxis for the prevention of DVT in children with CVLs.

**FONTAN A:** This is a randomized, controlled trial comparing aspirin to heparin/warfarin as primary prophylaxis against thromboembolic complications following Fontan surgery.

**SLE study:** This is a randomized, placebo-controlled trial of warfarin anticoagulation (INR 2.0 to 2.5) for primary thromboembolic prophylaxis in children with systemic lupus erythematosus and antiphospholipid antibodies.

**PARKAA:** This study (Prophylactic Antithrombin Replacement in Kids with Acute lymphoblastic leukaemia treated with Asparaginase) is a randomized controlled trial of AT replacement as thromboembolic prophylaxis for children with acute lymphoblastic leukaemia during L-asparaginase therapy.

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**Recommendations**

**Treatment of VTE in Children**

1. Children (≥2 months of age) with DVT or pulmonary embolism should be treated with IV heparin sufficient to prolong the APTT to a range that corresponds to an anti-factor Xa level of 0.3 to 0.7 U/mL. This grade C1 recommendation is based on grade A recommendations for adults and one level IV study in children. LMWH sufficient to achieve an anti-factor Xa level of 0.5 to 1.0 U/mL 4 to 6 h after an injection is an alternative to initial therapy with heparin. This grade C2 recommendation is based on grade A recommendations for adults and two level IV studies in children.

2. It is recommended that treatment with heparin or LMWH should be continued for 5 to 10 days and that oral anticoagulation should be overlapped with heparin for 4 to 5 days. For many patients, heparin and warfarin can be started together and heparin discontinued on day 6 if the prothrombin time (INR) is therapeutic. For massive PE or extensive DVT, a longer period of heparin therapy should be considered. This grade C1 recommendation is based on grade A1 recommendations for adults and two level IV studies 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 C2 recommendation is based on grade A recommendations for adults and one level IV and six level V studies in children. Alternatively, LMWH is an option in children in whom long-term oral anticoagulant therapy is problematic. If LMWH is chosen for long-term use, studies of bone density should be considered to detect osteoporosis at an early stage.

4. Either indefinite oral anticoagulant therapy with an INR of 2 to 3, low-dose anticoagulant therapy (INR <2.0), low-dose LMWH, or close monitoring should be considered for children with a first recurrence of venous thrombosis or an initial venous thrombosis and a continuing risk factor, such as a CVL, AT deficiency, PC or PS deficiency, activated PC resistance, prothrombin gene 20210, lupus anticoagulants in the antiphospholipid antibody syndrome, or systemic lupus erythematosus. This grade C recommendation is based on grade C2 recommendations for adults and one level V study in children.

5. Indefinite oral anticoagulant therapy with an INR of 2.0 to 3.0 should be considered for children with a second recurrence of venous thrombosis or a first recurrence of a venous thrombosis and a continuing risk factor, such as a CVL, AT deficiency, PC or PS deficiency, activated PC resistance, prothrombin gene 20210, lupus anticoagulants in the antiphospholipid antibody syndrome, or systemic lupus erythematosus. In circumstances in which oral anticoagulation therapy is problematic, LMWH is an option.

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

7. Children with congenital prothrombotic 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 definite 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 should be instituted.

3. If anticoagulation is used, a short course (10 to 14 days) of IV heparin, 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 is recommended. Alternatively, a short course of LMWH, 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. 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, oral anticoagulation therapy extended LMWH should be considered.

4. The use of thrombolytic agents in the treatment of VTE continues to be highly individualized. Further clinical investigation is needed before more definitive recommendations can be made. Supplementation with plasminogen (FFP) may be helpful.4,102

Prophylaxis for Cardiac Catheterization in Children and Newborns

Newborns and children requiring cardiac catheterization via an artery should be given prophylaxis with IV heparin in doses of 100 to 150 U/kg as a bolus. This grade B2 recommendation is based on level II study in children ≤10 years of age.196 Aspirin alone cannot be recommended (one level II study197).

Mechanical Prosthetic Heart Valves in Children

1. It is strongly recommended that children with mechanical prosthetic heart valves receive oral anticoagulation therapy. This grade C2 recommendation is based on grade C recommendations for adults and 13 level V studies in children.46,50,63,64,69,70,80–82,224,352–354

2. Levels of oral anticoagulation therapy that prolong the INR to 2.5 to 3.5 are recommended based on recommendations in adults.255

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).256 Dipyridamole, 2 to 5 mg/kg/d, in addition to oral anticoagulation therapy, is an alternative option (adult level I study257,258).

4. When full-dose oral anticoagulation therapy is contraindicated, long-term therapy with oral anticoagulation therapy sufficient to increase the INR 2.0 to 3.0, in combination with aspirin, 6 to 20 mg/kg/d, and dipyridamole, 2 to 5 mg/kg/d, may be used (grade C1). This recommendation is an extrapolation of a level I study in adults.256 There is one level V study in children.46

Treatment of Kawasaki’s Disease in Children

In addition to IV γ-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 or longer to prevent the formation of coronary aneurysm thrombosis. This grade C1 recommendation is based on two level III studies.194,195

Fontan Operations

Further clinical investigation is needed before definitive recommendations for primary postoperative prophylaxis can be made. Current options include either aspirin or therapeutic amounts of heparin that are followed by oral anticoagulation therapy to achieve an INR of 2 to 3. The optimal duration of prophylaxis is unknown. 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.

Homzygous PC- and PS-Deficient Patients

1. It is recommended that newborns with purpura fulminans due to a homzygous deficiency of PC or PS should be treated initially with replacement therapy (either fresh frozen plasma or PC concentrate) for approximately 6 to 8 weeks until the skin lesions have healed.

2. Following resolution of the skin lesions, and under cover 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 PC or PS.

3. For patients with homzygous PC and PS deficiency but with measurable plasma concentrations, LMWH is a therapeutic option.30

ACKNOWLEDGMENTS

We would like to acknowledge the assistance of Lu Ann Brooker for conducting literature searches and for editing the preliminary draft of this manuscript.

REFERENCES

11 Andrew M, Mitchell L, Vegh P, et al. Thrombin regulation...
35 Tait DP. Does low molecular weight heparin cause bleeding [abstract]? Thromb Haemost 1997; 78:1422
55 Shearer MJ, Rahim S, Barkhan P, et al. Plasma vitamin K₁ in
mothers and their newborn babies. Lancet 2 1982; 460–463
86 Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. Circulation 1995; 92:2373–2380
87 Coller BS. Monitoring platelet GPIIb/IIIa antagonist therapy. Circulation 1997; 96:3928–3932
97 Halpin T, Holtzhauser FJ, Campbell RJ, et al. Reye’s syn-
drome and medication use. JAMA 1982; 248:687–691
104 Leaker M, Superina B, Andrew M. Fibrin clot lysis by tissue plasminogen activator (tPA) is impaired from pediatric patients undergoing orthotopic liver transplantation. Transplantation 1995; 60:144–147

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Fifth ACCP Consensus Conference on Antithrombotic Therapy


Taussig HB. Long-time observations on the Blalock-Taussig operation IX. Single ventricle (with apex to the left). Johns Hopkins Med J 1976; 139:69–76


Magnani HN. Heparin-induced thrombocytopenia (HIT); an overview of 230 patients treated with Orgaran (Org 10172). Thromb Haemost 1993; 70:554–561
