

## Management of Stroke in Infants and Children: A Scientific Statement From a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young

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*Stroke*. 2008;39:2644-2691; originally published online July 17, 2008;

doi: 10.1161/STROKEAHA.108.189696

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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## Management of Stroke in Infants and Children A Scientific Statement From a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young

E. Steve Roach, MD, FAHA, Chair; Meredith R. Golomb, MD, MSc; Robert Adams, MD, MS, FAHA; Jose Biller, MD, FAHA; Stephen Daniels, MD, PhD, FAHA; Gabrielle deVeber, MD; Donna Ferriero, MD; Blaise V. Jones, MD; Fenella J. Kirkham, MB, MD; R. Michael Scott, MD, FAHA; Edward R. Smith, MD

**Purpose**—The purpose of this statement is to review the literature on childhood stroke and to provide recommendations for optimal diagnosis and treatment. This statement is intended for physicians who are responsible for diagnosing and treating infants, children, and adolescents with cerebrovascular disease.

**Methods**—The Writing Group members were appointed by the American Heart Association Stroke Council's Scientific Statement Oversight Committee. The panel included members with several different areas of expertise. Each of the panel's recommendations was weighted by applying the American Heart Association Stroke Council's Levels of Evidence grading algorithm. After being reviewed by panel members, the manuscript was reviewed by 4 expert peer reviewers and by members of the Stroke Council Leadership Committee and was approved by the American Heart Association Science Advisory and Coordinating Committee. We anticipate that this statement will need to be updated in 4 years.

**Results**—Evidence-based recommendations are provided for the prevention of ischemic stroke caused by sickle cell disease, moyamoya disease, cervicocephalic arterial dissection, and cardiogenic embolism. Recommendations on the evaluation and management of hemorrhagic stroke also are provided. Protocols for dosing of heparin and warfarin in children are suggested. Also included are recommendations on the evaluation and management of perinatal stroke and cerebral sinovenous thrombosis in children. (*Stroke*. 2008;39:2644-2691.)

**Key Words:** AHA Scientific Statements ■ children ■ stroke

Stroke has been increasingly recognized in children in recent years, but diagnosis and management can be difficult because of the diversity of underlying risk factors and the absence of a uniform treatment approach. Children and adolescents with stroke have remarkable differences in presentation compared with older patients. Stroke type also varies according to age. In Western countries, 80% to 85% of strokes among adults are ischemic, and the rest are hemorrhagic. In children, ≈55% of strokes are ischemic, and the remainder are hemorrhagic.

The World Health Organization definition of stroke (a clinical syndrome of rapidly developing focal or global

disturbance of brain function lasting >24 hours or leading to death with no obvious nonvascular cause) is far from ideal for children. Children with symptoms compatible with a transient ischemic attack (TIA), for example, commonly have a brain infarction shown by brain imaging despite the transient nature of their symptoms. Children with cerebral venous sinus thrombosis (CVST) commonly present with headache or seizures. "Stroke-like episodes" without an obvious vascular cause may occur in migraine or metabolic disease but may require specific treatment. Prior illness (eg, infection) or events (eg, head trauma) need not preclude a diagnosis of stroke. Although extra-axial hema-

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on April 4, 2008. A single reprint is available by calling 800-242-8721 (US only) or by writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0451. A copy of the statement is also available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the "topic list" link or the "chronological list" link. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

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DOI: 10.1161/STROKEAHA.108.189696

**Table 1. Definition of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations**

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
<b>Therapeutic recommendations</b>	
Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts
<b>Diagnostic recommendations</b>	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, $\geq 1$ case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

tomas, neonatal intraventricular hemorrhages (IVHs), and periventricular leukomalacia arise from cerebrovascular dysfunction in a broad sense, they are not considered in detail here.

Our purpose is to review the literature on stroke in children and, whenever possible, to make recommendations for the diagnosis and management of these children. Writing Group members were appointed by the American Heart Association Stroke Council's Scientific Statement Oversight Committee. The panel included members with several different areas of expertise. The panel reviewed relevant articles on stroke in children using a computerized search of the medical literature through 2006. These articles were supplemented by other articles known to the authors. Each recommendation was weighted by applying the American Heart Association Stroke Council's Levels of Evidence grading algorithm (Table 1 and the Figure). After being reviewed by the panel members, the manuscript was reviewed by 4 expert peer reviewers and members of the Stroke Council Leadership Committee and was subsequently approved by the American Heart Association's Science Advisory and Coordinating Committee.

Although some information about the cause and clinical manifestations of childhood stroke is included for the convenience of readers who may be unfamiliar with these topics,

the group's recommendations emphasize issues regarding treatment. The recommendations in this article represent a consensus of the authors. Because some aspects of stroke in children have been studied more thoroughly than others, some topics receive more attention than others. Despite major progress in the study of stroke in children in recent years, much of the literature remains descriptive. Continued research is essential if we are to better understand the diagnosis and treatment of stroke in children.

### Overview of the Cause of Childhood Stroke

About half of the children presenting with an acute focal neurological deficit have a previously identified risk factor, and  $\geq 1$  additional risk factors often are uncovered in the remaining patients.<sup>1</sup> For arterial ischemic stroke, the most common underlying conditions are sickle cell disease (SCD) and congenital or acquired heart disease. Heart disease and chronic anemia (including SCD and  $\beta$ -thalassemia) also are risk factors for CVST, but the list of associated conditions ranges from head and neck infections to systemic conditions such as inflammatory bowel disease and autoimmune disorders.<sup>2</sup> Head trauma appears to be a trigger for arterial stroke<sup>1,3</sup> and dehydration for venous stroke,<sup>4-6</sup> whereas infections, including varicella, meningitis, tonsillitis, and otitis media,<sup>1</sup> and anemia, leukocytosis, and prothrombotic disorders are probably risk factors for both.<sup>1,5-7</sup> It is increasingly evident that many children have multiple risk factors that together determine the risk of stroke or stroke recurrence.

Various factors influencing stroke recurrence risk have been documented in individuals with both symptomatic and idiopathic stroke.<sup>5</sup> Some arteriopathies are transient,<sup>8</sup> and occluded venous sinuses often recanalize.<sup>5,6</sup> An estimated 10% of intracranial hemorrhages (ICHs) in the young result from CVST.

### Epidemiology of Childhood Stroke

After excluding neonatal strokes and strokes related to trauma and infection, Schoenberg et al<sup>9</sup> found 3 hemorrhagic strokes and 1 ischemic stroke among 15 834 children in Rochester, Minn, between 1965 and 1974. Their estimated annual stroke incidence rate for children  $<15$  years of age was 2.52 per 100 000 per year or 1.89 per 100 000 per year and 0.63 per 100 000 per year for hemorrhagic and ischemic strokes, respectively. In this population, hemorrhagic strokes occurred more often than ischemic strokes, whereas in the Mayo Clinic referral population, ischemic strokes were more common. Another study found a similar overall stroke incidence of 2.7 cases per 100 000 per year in the greater Cincinnati, Ohio, area,<sup>10</sup> although their combined incidence rate for intraparenchymal brain hemorrhage and subarachnoid hemorrhage (SAH), 1.5 cases per 100 000 per year, was similar to the incidence of ischemic infarction (1.2 cases in 100 000 per year).<sup>10</sup>

More recent US studies have found a similar incidence,<sup>11</sup> although a few studies report higher rates.<sup>12</sup> Analyzing California hospital discharge data for a 10-year interval for children 1 month through 19 years of age, Fullerton and colleagues<sup>11</sup> estimated the stroke incidence to be 2.3 per 100 000 children per year (1.2 per 100 000 per year for

"Estimate of Certainty (Precision) of Treatment Effect"	"Size of Treatment Effect"				
	Class I <i>Benefit &gt;&gt;&gt; Risk</i>	Class IIa <i>Benefit &gt;&gt; Risk Additional studies with focused objectives needed</i>	Class IIb <i>Benefit ≥ Risk Additional studies with broad objectives needed; Additional registry data would be helpful</i>	Class III <i>Risk ≥ Benefit No additional studies needed</i>	
Level A <i>Multiple (3-5) population risk strata evaluated*</i>  <i>General consistency of direction and magnitude of effect</i>	Procedure/Treatment SHOULD be performed/administered	IT IS REASONABLE to perform procedure/administer treatment	Procedure/Treatment MAY BE CONSIDERED	Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL	
Level B <i>Limited (2-3) population risk strata evaluated*</i>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
Level C <i>Very limited (1-2) population risk strata evaluated*</i>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard-of-care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard-of-care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard-of-care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard-of-care</li> </ul>	
<b>Suggested phrases for writing recommendations †</b>	should be recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/ beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown /unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful	

\*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

Figure. Applying classification of recommendations and level of evidence.

ischemic lesions and 1.1 per 100 000 per year for hemorrhagic lesions). Boys were at higher risk than girls, and black children were at higher risk than white and Asian children, even after adjustment for trauma and the presence of SCD.<sup>11</sup> A study of Chinese children in Hong Kong found a similar overall stroke risk (2.1 per 100 000 per year), but only 28% of those children had hemorrhagic strokes.<sup>13</sup> Peak age for both ischemic stroke and intraparenchymal brain hemorrhage is the first year of life, with a third of the cases presenting in this age group, whereas SAH is more common among teenagers.<sup>11</sup> There also appears to be an excess of strokes in boys and in those of black ethnicity; this excess is not fully explained by the prevalence of SCD in this population.<sup>14</sup>

The frequency of ischemic stroke may be greater than previously suggested. Giroud and colleagues<sup>15</sup> calculated the stroke risk among individuals <16 years of age to be 13 per 100 000 per year. Their estimated incidence of hemorrhagic lesions in children, however, was only slightly higher than in earlier reports. Data from the National Hospital Discharge Survey from 1980 to 1998 indicate that the risk of ischemic stroke in individuals from birth through 18 years of age is 7.8 per 100 000, with a hemorrhagic stroke risk of 2.9 per 100 000.<sup>16</sup>

Recent estimates suggest that ischemic stroke occurs in ≈1 per 4000 live births,<sup>17</sup> clearly a much higher rate than in older children. Approximately 80% of these are ischemic, and the

rest are due to CVST or hemorrhage (excluding SAH and IVH in premature babies). Schoenberg<sup>18</sup> estimated that the incidence of nontraumatic perinatal ICH in neonates was 1.1 per 1000 live births. However, this study was done before the widespread use of computed tomography (CT), cranial ultrasound, and magnetic resonance imaging (MRI); the fact that all 12 identified babies had an autopsy suggests that only the most severe hemorrhages were identified. However, more recent (1980 to 1998) data from the National Hospital Discharge Survey indicate that the rate of hemorrhagic stroke for term infants is 6.7 per 100 000 per year.<sup>16</sup>

The incidence of childhood CVST is 0.3 per 100 000 children per year for term birth to 18 years of age, and neonates make up 43% of the patients.<sup>4</sup>

## Arterial Ischemic Stroke

### Perinatal Stroke

#### Definitions and Risk Factors

Neonatal stroke encompasses both ischemic and hemorrhagic events resulting from disruption of either arteries or veins from early gestation through the first month of life. The term perinatal stroke describes cerebrovascular lesions that occur from 28 weeks' gestation through the first 7 days of life, although some authors broaden this range from 20 weeks' gestation to 28 days after birth, and lesions occurring even

before 20 weeks have been documented.<sup>17,19</sup> Approximately 80% of these are ischemic, and the remainder are due to CVST or hemorrhage. Risk factors for neonatal stroke include cardiac disorders, coagulation disorders, infection, trauma, drugs, maternal and placental disorders, and perinatal asphyxia.<sup>17</sup> Multiple risk factors have been documented, especially blood disorders with asphyxial stress.<sup>20–22</sup> Suspected maternal risk factors for perinatal arterial ischemic stroke include a history of infertility, chorioamnionitis, premature rupture of membranes, and preeclampsia.<sup>23</sup> In fact, the rate of perinatal arterial ischemic stroke increased dramatically with the increasing number of risk factors in population-based studies.

### **Clinical Presentation**

Both neonatal arterial and venous strokes often present with seizures, typically focal motor seizures involving only 1 extremity. Stroke accounts for an estimated 10% of the seizures in term neonates. Some children with perinatal stroke do not present in the neonatal period and appear quite normal at this stage. These children usually present with early handedness or developmental delay, suggesting a process that began the first few months of life.

### **Diagnostic Evaluation**

The optimal imaging study is somewhat dependent on the child's clinical stability. Cranial ultrasound is safe and readily available, but it may miss superficial and ischemic lesions.<sup>24</sup> CT is relatively quick, accurately depicts superficial or hemorrhagic lesions, and confirms the lesion location. However, venous thrombosis and early arterial ischemic stroke (AIS) are easily missed with CT.

Like ultrasound, MRI techniques do not expose the neonate to the potentially harmful effects of ionizing radiation. MRI, magnetic resonance angiography (MRA), and magnetic resonance venography (MRV) may more accurately define the site of an arterial or venous occlusion. Additionally, MR studies often demonstrate associated parenchymal abnormalities more clearly, including nonischemic lesions that clinically mimic arterial or venous stroke. Diffusion-weighted imaging can confirm the presence and location of an infarction earlier than other MRI sequences or CT.<sup>21</sup> CT angiography (CTA) is an accurate means of identifying primary vascular abnormalities when there is an unexplained hemorrhagic lesion. Catheter angiography (CA) is technically more difficult in babies and tends to be done only when endovascular surgical intervention is anticipated.

### **Residual Effects of Perinatal Stroke**

Children frequently have significant long-term disabilities after a perinatal stroke, including cognitive and sensory impairments, cerebral palsy, and epilepsy. The few studies of perinatal stroke outcome tend to be limited by small sample size, heterogeneity of age of onset (eg, neonates with perinatal stroke frequently are combined with older children with stroke), or confounding by other conditions such as hypoxic-ischemic encephalopathy. Only studies that include neonates with clearly defined AIS, CVST, or ICH and outcome data are discussed here.

Cognitive impairment after perinatal AIS ranges from 0% to 55%.<sup>20,25–29</sup> One study of 40 children with perinatal stroke found language delay in 25%.<sup>29</sup> A study of 29 children with unilateral perinatal stroke reported that all children >2 years of age had “normal” IQ scores.<sup>26</sup> Estimates of generalized “developmental delay” after neonatal CVST range from 28%<sup>30</sup> to 58%.<sup>31</sup> A study of 19 children with neonatal CVST reported a learning disability in only 1 child (5.3%).<sup>31</sup> One report of 27 children with neonatal sinovenous thrombosis found cognitive impairment in 16 (59%), and 9 of the 27 had moderate to severe dysfunction.<sup>32</sup> Another study of 11 children with spontaneous ICH reported cognitive delay or speech impairment in 4 (36%).<sup>33</sup>

Sensory function in young children is difficult to assess. Children with neonatal middle cerebral artery (MCA) territory infarction may develop thalamic atrophy, but whether this has long-term implications for sensory perception is unclear.<sup>34</sup> In a study of 12 children and young adults with unilateral perinatal stroke, 4 had abnormal somatosensory-evoked potentials, but these children were unable to cooperate for further evaluation of sensory function.<sup>35</sup> In a study of 16 school-aged children with perinatal stroke, 6 (28%) had impaired visual function.<sup>36</sup> Several studies of children with unilateral prenatal or perinatal strokes have described increased difficulty with facial recognition<sup>37</sup> and other visuospatial tasks in small cohorts.<sup>38–40</sup>

Estimates of the incidence of cerebral palsy after perinatal stroke vary widely: 9% to 88% after perinatal AIS<sup>26,29,41–47</sup> and 6% to 67% after perinatal CVST.<sup>4,30,32,44</sup> Outcome of children with perinatal stroke ranges from normal to subtle hemiplegia to severe quadriplegia. However, most children with neonatal AIS and CVST learn to walk independently, usually before 2 years of age.<sup>48</sup> Although many neonates with AIS, CVST, or ICH present with seizures,<sup>4,30</sup> most do not have epilepsy after the neonatal period. Estimates of the incidence of epilepsy past the neonatal period range from 0% to 46% for neonatal AIS<sup>20,25,27,29,43</sup> and 6% to 41% for neonatal CVST.<sup>4,32,49</sup> A small portion of perinatal stroke patients undergo surgery because of severe epilepsy syndromes such as infantile spasms<sup>50</sup> or intractable epilepsy.<sup>51</sup>

### **Outcome**

There are few studies of stroke recurrence risk after neonatal stroke. One study followed 215 children with neonatal AIS for a median of 3.5 years. Recurrent symptomatic thromboembolism occurred in 7, AIS in 4, CVST in 2, and deep venous thrombosis in 1 individual. Factors associated with an increased recurrence rate included thrombophilic states and the presence of additional comorbidities such as complex congenital heart disease or dehydration.<sup>52</sup> Few data exist on the risk of recurrent thromboembolism after neonatal CVST. In the Canadian Registry, 5 of 61 neonates (8%) had recurrence.<sup>4</sup> Prothrombotic risk factors may modify presentation and severity in children with bleeding disorders. Children who have both hemophilia A and a thrombophilic state may have a lower risk of hemorrhage as a neonate and less likelihood of recurrent ICH.<sup>53</sup>

One study of 46 neonates with AIS noted that vascular territory is not closely correlated with outcome.<sup>27</sup> Another

study of 24 children with perinatal stroke found that lesions involving the cortex, basal ganglia, and internal capsule on MRI were more likely to cause hemiplegia than strokes involving only one of these regions.<sup>42</sup> A study of 40 children with perinatal stroke found that large stroke size and injury to Broca's area, the internal capsule, Wernicke's area, or basal ganglia were associated with cerebral palsy.<sup>29</sup> In another cohort of 23 preterm and term neonates with perinatal AIS, infarction of an area supplied by a main branch of the MCA predicted subsequent hemiplegia.<sup>46</sup> A report of 62 children with neonatal AIS and 25 children with neonatal CVST noted that bilateral infarctions decreased the likelihood of walking.<sup>48</sup> Neonates with CVST without infarction have a better outcome than those with both CVST and infarction.<sup>4,32,48,54</sup>

Although most neonates with stroke do not subsequently develop epilepsy, those who present with seizures may be at a higher risk of an abnormal neurodevelopmental outcome. In 1 cohort of 46 neonates with AIS, the presence of seizures in the neonatal period predicted the development of  $\geq 1$  disabilities in the first years of life.<sup>27</sup> Another study of 24 children with perinatal AIS found that an abnormal electroencephalography background predicted childhood hemiplegia.<sup>42,55</sup>

Neonatal encephalopathy may predict poor outcome after AIS.<sup>56</sup> However, children who appear normal in the neonatal period but develop a hand preference or seizures after 2 months of age resulting from perinatal AIS may have a worse prognosis than children who have neurological signs as neonates. The presenting findings (hemiparesis or seizures) may be more likely to persist.<sup>20,29</sup> Prothrombotic disorders may lead to poorer outcome after neonatal AIS.<sup>55</sup> Not surprisingly, term neonates who develop idiopathic ICH or IVH appear to have a better prognosis than those with ICH associated with hypoxic-ischemic insults or trauma.<sup>57</sup>

## Management

### Acute

Supportive care is important for all types of perinatal stroke. Anecdotal reports suggest that surgical evacuation of a hematoma may reduce extremely high intracranial pressure, but it is not clear whether surgery improves the eventual outcome. Ventricular drainage and, if indicated, later shunting for progressive hydrocephalus caused by IVH is appropriate.<sup>33</sup>

The optimal therapy for neonates with AIS or CVST has not been determined. Thrombolytic therapy has been used for peripheral thrombi in neonates but rarely for neonatal CVST, so neither its safety nor its effectiveness has been ascertained in these patients. Neither unfractionated heparin (UFH) nor low-molecular-weight heparin (LMWH) is used widely in children with perinatal AIS, although children with severe prothrombotic disorders or with cardiac or multiple systemic thrombi may benefit. No major complications occurred in preliminary studies of LMWH in neonates with CVST,<sup>58</sup> but it is not clear whether anticoagulation is beneficial in these neonates, except in the setting of multiple thrombosed sinuses and radiological evidence of propagating thrombosis despite supportive therapy. Case reports also have described the use of antithrombin concentrate<sup>59,60</sup> and protein C concentrate<sup>61</sup>

to prevent venous thrombosis in neonates with congenital or iatrogenic coagulation factor deficiencies.

Markedly low platelet counts and factor deficiencies should be corrected. Vitamin K deficiency may be an issue in areas of the world where vitamin K is not routinely administered to newborns,<sup>62</sup> in infants with biliary atresia, or in babies whose mothers ingested warfarin, phenytoin, or barbiturates during pregnancy. Large doses of vitamin K may be needed to correct factor deficiencies induced by maternal medications.<sup>63,64</sup>

### Chronic

Many studies have documented a positive effect of rehabilitation on outcomes in children with cerebral palsy,<sup>65–70</sup> but these studies have not specifically described the subset of children with perinatal stroke. Children who need rehabilitation may be at higher risk of poor outcome.<sup>27,44</sup> A study of 18 children with hemiplegic cerebral palsy from several causes suggested that constraint of the normal arm led to increased use of the weak arm.<sup>71</sup>

There is little information about the long-term use of prophylactic therapies such as LMWH in neonates. Although recurrent stroke is uncommon in these patients, individuals with prothrombotic conditions plus other risk factors (eg, complex congenital heart disease, dehydration, or prolonged bed rest) may have a higher likelihood of recurrent venous and arterial thrombosis, and prophylaxis may be considered in these individuals.<sup>52</sup> It is reasonable to supplement folate and B vitamins for children with a methylenetetrahydrofolate reductase (MTHFR) mutation in an effort to normalize homocysteine levels.

Similar uncertainties arise in the long-term treatment of children with neonatal CVST. It is reasonable to try to prevent dehydration and anemia, 2 known precipitants of sinovenous thrombosis.<sup>4</sup> Individuals with ICH caused by bleeding disorders may require prophylactic replacement of coagulation factors.<sup>72</sup>

## Recommendations for Perinatal Stroke

### Class I Recommendations

1. Markedly low platelet counts should be corrected in individuals with ICH (Class I, Level of Evidence B).
2. Neonates with ICH resulting from coagulation factor deficiency require replacement of the deficient coagulation factors (Class I, Level of Evidence B).
3. Vitamin K should be administered to individuals with vitamin K–dependent coagulation disorders (Class I, Level of Evidence B). Higher doses of vitamin K may be required in neonates with factor deficiencies resulting from maternal medications.
4. Patients who develop hydrocephalus after an ICH should undergo ventricular drainage and later shunting if significant hydrocephalus persists (Class I, Level of Evidence B).

### Class II Recommendations

1. It is reasonable to treat dehydration and anemia in neonates with stroke (Class IIa, Level of Evidence C).
2. It is reasonable to use rehabilitation and ongoing physical therapy in an effort to reduce neurological dysfunction.

tion in individuals with perinatal stroke (Class IIa, Level of Evidence B).

- It is reasonable to give folate and B vitamins to individuals with an MTHFR mutation in an effort to normalize homocysteine levels (Class IIa, Level of Evidence C).
- It is reasonable to evacuate an intraparenchymal brain hematoma to reduce very high intracranial pressure, although it is not clear whether this approach always improves the outcome (Class IIa, Level of Evidence C).
- Anticoagulation with LMWH or UFH may be considered in selected neonates with severe thrombophilic disorders, multiple cerebral or systemic emboli, or clinical or radiological evidence of propagating CVST despite supportive therapy (Class IIb, Level of Evidence C). Until additional information on its safety and efficacy is available, a recommendation on the use of anticoagulation in other neonates with CVST is not possible.

### Class III Recommendations

- Thrombolytic agents are not recommended in neonates until more information about the safety and effectiveness of these agents is known (Class III, Level of Evidence C).

## AIS in Infants and Older Children

### Risk Factors for First Stroke

Almost half of children with AIS are known to have a stroke risk factor at the time of infarction, and  $\geq 1$  vascular risk factors can be identified in at least two thirds of children after a thorough evaluation.<sup>1,7</sup> A detailed family history will document cerebrovascular disease among first-degree relatives, and a thorough physical examination will help to identify systemic diseases that increase stroke risk. Even after extensive investigations, however, no cause can be discovered in up to 30% of children with AIS. A discussion of all potential stroke risk factors is beyond the scope of this article, but pediatric stroke risk factors have been reviewed extensively.<sup>73</sup>

Some patients have  $>1$  risk factor, but the presence of multiple risk factors may compound the stroke risk for some children. It may be impractical to investigate every conceivable stroke risk factor in each child, and some physicians try first assessing for the common causes of stroke and then eliminating less common stroke risk factors (Tables 2 through 5) on the basis of the patient's clinical findings. The evaluation of stroke in children is presented in more detail in Diagnostic Evaluation of Children With Stroke.

### Risk of Recurrent Stroke

Clinical and radiological recurrence of AIS is seen in 6% to 14% of children with a new infarction,<sup>74,75</sup> but many more have TIAs or silent reinfarctions. There are data suggesting that a vascular lesion plus prothrombotic risk factors predict recurrence risk. A large German population-based cohort<sup>74</sup> found that a vascular origin was a risk factor for recurrence, as were elevated lipoprotein(a) and protein C deficiencies. In another series of 212 children from the United Kingdom, the most important predictors of clinical recurrence were moyamoya syndrome and low birth weight.<sup>75</sup> The presence of at

**Table 2. Miscellaneous and Genetic Risk Factors for Stroke**

Hereditary dyslipoproteinemia
Familial hypoalphalipoproteinemia
Familial hypercholesterolemia
Type IV, type III hyperlipoproteinemia
Tangier disease
Progeria
Heritable disorders of connective tissue
Ehlers-Danlos syndrome (type IV)
Marfan syndrome
Pseudoxanthoma elasticum
Homocystinuria (cystathionine $\beta$ -synthase deficiency, or 5, 20-MTHFR)
Menkes syndrome
Organic acidemias
Methylmalonic acidemia
Propionic acidemia
Isovaleric acidemia
Glutaric aciduria type II
Mitochondrial encephalomyopathies
MELAS
MERRF
MERRF/MELAS overlap syndrome
Kearns-Sayre syndrome
Fabry disease ( $\alpha$ -galactosidase-A deficiency)
Subacute necrotizing encephalomyelopathy (Leigh disease)
Sulfite oxide deficiency
11- $\beta$ -ketoreductase deficiency
17- $\alpha$ -hydroxylase deficiency
Purine nucleoside phosphorylase deficiency
Ornithine transcarbamylase deficiency
Neurofibromatosis type 1
HERNS

MERRF indicates myoclonic epilepsy with ragged-red fibers; HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke. Adapted from Biller et al,<sup>523</sup> with permission from Elsevier.

least 1 genetic thrombophilic state was associated with a higher risk of recurrence, as were previous TIAs and bilateral infarctions at initial presentation.

### Vascular and Nonvascular Risk Factors for Arterial Ischemic Stroke

There are many risk factors for ischemic stroke in infants and children, including preexisting illnesses such as congenital cardiac disease, SCD, infections (eg, meningitis or varicella), and various prothrombotic states (Table 3). Other patients have cervicocephalic arterial dissection (CCAD), fibromuscular dysplasia (FMD), vasculitis (Table 5), moyamoya disease, or other vasculopathies (Table 4).<sup>76</sup> Yet, the cause of stroke in up to one third of children with AIS goes undetermined. What follows is a summary of some of the more important risk factors for childhood ischemic stroke.

### Sickle Cell Disease

Stroke is one of the major complications of SCD.<sup>77</sup> Rates of stroke in SCD are much higher than rates of stroke in children

**Table 3. Reported Causes of Hypercoagulable States**

Primary (hereditary) hypercoagulable states
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Activated protein C resistance with or without factor V Leiden mutation
Prothrombin gene mutation <i>G20210A</i>
Thermolabile variant of MTHFR
Disorders of fibrinogen
Disorders of plasminogen activator inhibitor
Anticardiolipin antibodies and lupus anticoagulant
Factor VII elevation
Factor VIII elevation
Factor XII deficiency
Protein C deficiency
Antithrombin deficiency
Protein S deficiency
Selected secondary (acquired) hypercoagulable states
Malignancy
Pregnancy (especially postpartum period)
Oral contraceptives
Ovarian hyperstimulation syndrome
Other hormonal treatments (eg, anabolic steroids, erythropoietin)
Nephrotic syndrome
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Diabetes mellitus
Hypertlipidemia
Elevated lipoprotein(a)
Heparin-induced thrombocytopenia
Homocystinuria
Hyperviscosity
Congestive heart failure
Sickle cell disease
Thrombotic thrombocytopenic purpura
Chemotherapeutic agents (ie, L-asparaginase, mitomycin, adjuvant breast cancer therapy)

Adapted from Biller et al,<sup>523</sup> with permission from Elsevier.

in general. The Baltimore-Washington Cooperative Young Stroke Study was a retrospective study that identified all cases of ischemic and hemorrhagic stroke among children and young adults within a catchment area that totaled 46 hospitals over a 3-year period between 1988 and 1991.<sup>14</sup> The total population of the region was based on 1990 census data. The population of children with SCD was estimated from the *National Newborn Screening Report*. A total of 35 strokes, 18 ischemic infarcts and 17 ICHs were identified. The overall incidence of childhood stroke was calculated at 1.29 per 100 000 per year in the Baltimore-Washington area, but for those with SCD, the incidence rate was 285 per 100 000 per year (0.28% per year). The risk of both ischemic infarction and hemorrhage was increased. The overall incidence of AIS

**Table 4. Cerebral Vasculopathies in Children**

Cervicocephalic arterial dissections
Moyamoya disease and moyamoya syndrome
FMD
Vasculitis
Transient cerebral arteriopathy
Postvaricella angiopathy
Migrainous infarction
Ergotism
Traumatic cerebrovascular disease
Radiation-induced arteriopathy
Tumoral encasement of cervicocephalic vessels
Hypoplasia and agenesis of cervicocephalic vessels
Congenital arterial fenestration

Adapted from Biller et al,<sup>523</sup> with permission from Elsevier.

was 0.58 per 100 000 and ICH was 0.71 per 100 000. Conversely, for children with SCD, the incidence rates per 100 000 were 238 and 47.5 for AIS and ICH, respectively.

Similar incidence rates in SCD were obtained in the Cooperative Study of Sickle Cell Disease (CSSCD).<sup>78</sup> The CSSCD collected data on 4082 patients with SCD at 23 clinical centers within the United States over a 10-year period from 1978 to 1988. In this study, TIA was included with infarction and ICH. The annual incidence of first stroke was 0.46% per year. Children homozygous for the sickle cell gene mutation (SCD-SS) had an even higher rate, 0.61% per year. The highest rate of first stroke was in children between 2 and 5 years of age, followed by those from 6 to 9 years of age, with incidences of 1.02% and 0.68% per year, respectively. In contrast, the incidence of ICH was highest in adults between 20 and 29 years of age.

**Acute Stroke in SCD.** SCD promotes different forms of cerebrovascular disease. The clinical presentation depends primarily on the size and location of the lesion, although many asymptomatic individuals have small infarctions on MRI. Individuals with carotid vasculopathy often present with an acute deficit resulting from a large ischemic infarction in the MCA territory. Some individuals develop progressive vasculopathy of the intracranial internal carotid artery (ICA) with distal collateral vessels or moyamoya syndrome (see below). Large infarctions within the anterior cerebral artery (ACA) or posterior cerebral artery territories occur less often. Small infarctions are common and typically involve the basal ganglia and deep white matter within the anterior circulation. Border-zone infarctions are not as common as large infarctions, but both are probably traceable to large-artery disease. Occasionally, individuals with SCD may develop sinovenous thrombosis or anterior spinal artery syndrome. SAH and intracerebral hemorrhage also occur in the context of sinovenous thrombosis and after rupture of aneurysms usually located at the bifurcations of major vessels, particularly in the vertebrobasilar circulation, or of fragile moyamoya vessels. Reversible posterior leukoencephalopathy has been described after acute chest syndrome<sup>79</sup> but may result in infarction, typically occipital.

**Table 5. Classification of Cerebral Vasculitis**

Infectious vasculitis
Bacterial, fungal, parasitic
Spirochetal (syphilis, Lyme disease, leptospirosis)
Viral, rickettsial, mycobacterial, free-living amoebae, cysticercosis, other helminths
Necrotizing vasculitides
Classic polyarteritis nodosa
Wegener granulomatosis
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
Necrotizing systemic vasculitis overlap syndrome
Lymphomatoid granulomatosis
Vasculitis associated with collagen vascular disease
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Sjögren syndrome
Vasculitis associated with other systemic diseases
Behçet's disease
Ulcerative colitis
Sarcoidosis
Relapsing polychondritis
Kohlmeier-Degos disease
Takayasu arteritis
Hypersensitivity vasculitides
Henoch-Schönlein purpura
Drug-induced vasculitides
Chemical vasculitides
Essential mixed cryoglobulinemia
Miscellaneous
Vasculitis associated with neoplasia
Vasculitis associated with radiation
Cogan syndrome
Dermatomyositis-polymyositis
X-linked lymphoproliferative syndrome
Kawasaki disease
Primary CNS vasculitis

Adapted from Biller et al,<sup>523</sup> with permission from Elsevier.

**Risk Factors for First Stroke in SCD.** Risk factors for stroke in individuals with SCD include high blood flow velocity on transcranial Doppler (TCD), low hemoglobin value, high white cell count, hypertension, silent brain infarction, and history of chest crisis.<sup>78</sup>

Identification by TCD of those at highest risk provided an opportunity to prevent first stroke.<sup>80</sup> Children with TCD ultrasound evidence of high cerebral blood flow velocity rates (time-averaged mean velocity  $\geq 200$  cm/s) have a stroke rate of at least 10% per year.<sup>81,82</sup> Although few strokes occur in the ACA distribution, there is some evidence that elevated blood flow velocity in the ACA predicts a higher stroke risk in individuals with SCD than would similar velocities in the ICA or MCA.<sup>83</sup>

There appears to be a familial predisposition to stroke in individuals with SCD,<sup>84</sup> and some genetic risk factors have been identified,<sup>85,86</sup> although siblings may also share adverse environmental conditions, including poverty, air pollution, and poor nutrition. Nocturnal hypoxemia also is a predictor of central nervous system (CNS) events in SCD<sup>87</sup> and might be a modifiable risk factor.

**Predictors of Stroke Recurrence in SCD.** Recurrence of stroke is high in SCD, but no population or clinical trial data are available. Pegelow et al<sup>88</sup> pooled retrospective data from 6 clinics and compared rates of recurrent stroke with and without regular transfusion and reported that at 50 months the recurrent stroke-free survival was only 30% without transfusion. In another multicenter cohort, Scothorn and colleagues<sup>89</sup> reported on data from 137 children who had had a first stroke between 1.4 and 14 years of age. Twenty-six individuals had an antecedent or concurrent event (hypertension, fever, chest syndrome, acute anemia, or exchange transfusion). Thirty-one of these patients (23%) had at least 1 recurrent stroke with a mean time to recurrence of  $\approx 4$  years and a recurrence rate of 2.2 per 100 patient-years. After 2 years, recurrence continued only in those with no antecedent events. Dobson et al<sup>90</sup> described the findings from a single center managing children with homozygous SCD with stroke who were <18 years of age from 1980 to 1999. Forty-one percent of the patients had recurrent stroke or TIAs. Recurrent stroke was more common in patients with moyamoya syndrome.

**Subclinical Brain Disease.** The CSSCD confirmed that  $\approx 20\%$  of children with SCD have “silent” brain lesions on MRI predominantly in frontal and parietal cortical, subcortical, and border-zone locations.<sup>91</sup> These so-called “silent infarcts” are important because they are associated with deterioration in cognitive function with effects on learning and behavior.<sup>92</sup> Further evidence from the CSSCD confirms that the risk of clinical stroke is increased if MRI is abnormal from the background rate of 0.5% to 1% to  $\approx 2\%$  per year.<sup>93</sup> Silent lesions are evidence of brain injury, and it is reasonable to reassess these patients’ histories for symptoms that were not previously recognized and to re-examine the patients’ clinical and laboratory risks for stroke. The rate of stroke in children with positive MRI but TCD findings that do not reach current treatment guidelines is not clear, and regular blood transfusions are not recommended on the basis of MRI alone. The risks and benefits of prophylactic transfusion based on silent MRI lesions are being tested in a randomized clinical trial (SITT: <http://www.clinicaltrials.gov/ct/show/NCT00072761?order=1>).

**ICH Resulting From SCD.** Children with SCD develop all types of ICH.<sup>77,78</sup> Intraparenchymal bleeding may be associated with large-vessel vasculopathy, especially if moyamoya formation is present. ICH also can occur as a result of CVST. IVH is unusual but may occur if moyamoya vessels are present near the ventricular wall. One retrospective study suggested that systemic hypertension, corticosteroid use, and recent transfusion increased the likelihood of an ICH in individuals with SCD.<sup>94</sup>

There are reports of epidural hematomas in the absence of significant head trauma in SCD.<sup>95</sup> The cause is not known, but epidural hematomas may be related to hypervascular areas of bone.

SAH is relatively common in individuals with SCD. Although the cause of many of these hemorrhages is unknown, an aneurysm often is present in adolescents and adults with SCD and an SAH.<sup>96</sup> Because of the potential for rebleeding in individuals with an aneurysm, it is reasonable to fully evaluate these individuals with CA. However, there is some concern that CA might facilitate sickling in individuals with SCD, and the typical approach is to defer the CA until after the percentage of sickle hemoglobin has been reduced with transfusions.

*Treatment of Acute Stroke Caused by SCD.* The usual acute treatment of acute ischemic infarction resulting from SCD is hydration and exchange transfusion, although there are no controlled studies to prove the value of this approach.<sup>97</sup> Exchange transfusion avoids the theoretical risk of increasing blood viscosity that could accompany a rapid increase in hematocrit. Hypoxemia and hypotension should be treated and normoglycemia maintained. Even though intracranial arterial vasculopathy characteristic of SCD is the most likely cause of stroke in this setting,<sup>98</sup> it may be appropriate to consider other disorders such as infection, cardiac embolism, and CVST.

*Primary and Secondary Prevention of Stroke Resulting From SCD.* Although no clinical trial has addressed this specific issue, regular blood transfusions have been used for several years in individuals with SCD for secondary stroke prevention.<sup>88</sup> The targeted reduction of the sickle hemoglobin to <30% of the total hemoglobin is based on in vitro viscosity experiments, has not been critically evaluated, but has become the standard therapeutic target.<sup>97</sup> Pegelow et al<sup>88</sup> estimated from retrospective clinical data that stroke-free survival with chronic transfusion was 80% at 50 months compared with 30% when no transfusion is given. Scothorn et al<sup>89</sup> estimated an annual rate of recurrent stroke of ≈2% despite ongoing transfusion. Several transfusion regimens are in use, including simple transfusions of 10 to 15 mL/kg of packed red blood cells every 3 to 4 weeks and the use of apheresis machines to remove blood while adding donor red cells. Chronic transfusion brings with it the requirement to manage iron overload, and the reader is referred to other reviews for more information and for a discussion of transfusion method options.<sup>97</sup> In the absence of more robust data, it has been recommended that transfusion should be continued for at least 5 years or at least until the child reaches 18 years of age.<sup>97</sup>

A randomized trial (Stroke Prevention Trial in Sickle Cell Anemia [STOP]) compared periodic blood transfusion with standard care in 130 children with SCD ranging from 2 to 16 years of age (mean age, 8 years) who were selected for high stroke risk with TCD. Blood transfusions were given an average of 14 times per year for >2 years in the treatment group, with a target reduction of sickle hemoglobin from a baseline of >90% to <30%. The trial was halted 16 months early after 11 strokes occurred in the standard-care arm

compared with 1 stroke in the transfusion-treated group. The risk of stroke was reduced from 10% to <1% per year. A Clinical Alert issued by the National Heart, Lung, and Blood Institute of the National Institutes of Health recommended screening all children with SCD who have no history of stroke, with consideration of transfusion for those with 2 abnormal TCD ultrasound studies. The rates of first stroke among children with SCD have declined in California since the STOP study and the Clinical Alert called for screening and treatment, suggesting that this approach may be having an impact.<sup>99</sup>

In STOP, there was no evidence of transfusion-related infection, but iron overload and alloimmunization remained important transfusion-related risks. A randomized controlled trial (STOP II) of withdrawal of transfusion was initiated in 2000 to test whether chronic transfusions for primary stroke prevention could be safely discontinued after at least 30 months in children who had not had an overt stroke and who had reversion to low-risk TCD on transfusion. In both treatment arms, children received close clinical and TCD surveillance for the first occurrence of reversion of TCD to abnormal, confirmed with ≥2 TCDs of ≥200 cm/s, indicating a return of high risk for overt stroke. Clinical stroke also was part of the composite end point. It was hoped that most end points would be TCD reversions rather than clinical stroke and that close monitoring with TCD, at least quarterly, would provide acceptable safety monitoring by signaling the return of high risk, allowing reinstatement of transfusion. The patients in the transfusion arm received periodic simple or exchange blood transfusions every 3 to 4 weeks in an effort to maintain the sickle hemoglobin level <30%. After 79 of a planned sample size of 100 children had been randomized, the Data and Safety Monitoring Board recommended closure of the study for safety concerns after an interim analysis showed a highly significant difference between the transfusion and nontransfusion treatment arms with respect to the composite end point of TCD reversion to high risk and overt stroke. Among the 41 individuals randomized to halt transfusion, there were 16 end points, 14 of which were TCD reversions to high-risk TCD (without stroke), and 2 were ischemic strokes that occurred shortly after the first TCD reverted to abnormal but before a confirmatory TCD could be obtained and transfusion therapy resumed. Six other subjects were returned to periodic transfusion therapy for other clinical reasons before end points took place. No strokes or reversions to high-risk TCD were observed in those subjects who were in the chronic transfusion treatment arm. The reversions to abnormal TCD velocity were seen only 4 to 9 months after randomization. Eight children (≈20%) tolerated removal from chronic transfusion therapy without apparent problems, but the National Heart, Lung, and Blood Institute does not recommend discontinuation of transfusion after 30 months based on STOP II because of the high TCD reversion rate and the small risk of overt stroke despite frequent TCD surveillance.<sup>100</sup>

There are no data to support the use of chronic transfusion to prevent recurrent ICH in SCD.

Hydroxyurea is used to reduce painful episodes in adults with SCD, but whether it reduces the risk of stroke in children

with SCD is unknown.<sup>101</sup> Data from nonrandomized clinical series suggest that hydroxyurea might be an alternative to transfusion for primary stroke prevention, but a definitive study has not been done.<sup>102</sup>

A single study has looked at stroke rates in children and young adults who were first transfused after stroke and then later switched to hydroxyurea in an open-label study with historical controls,<sup>103</sup> with encouraging results. Hydroxyurea with phlebotomy is being tested in a randomized clinical trial (the SWITCH study; see <http://www.clinicaltrials.gov/ct/show/NCT00122980?order=1>) on the basis of preliminary evidence that it may offer a comparable stroke risk reduction after transfusion has been given for several years.<sup>103</sup>

Bone marrow transplantation reportedly stabilizes the cerebrovascular disease caused by SCD,<sup>104</sup> but data are limited. Because of the unavailability of suitable donors and other issues, bone marrow transplantation is not always feasible.

A few patients with moyamoya syndrome resulting from SCD have undergone surgical bypass procedures in an effort to prevent stroke.<sup>105,106</sup> In the largest series, encephaloduro-arteriosynangiosis was performed in 6 children, 4 of whom had had a stroke (2 occurred while on a chronic transfusion program). One patient who was initially free of cerebrovascular symptoms had an infarction 2 weeks after surgery.<sup>106</sup> The natural history of children with SCD and moyamoya has not been well studied, and the risk and benefit of this procedure should be evaluated in a randomized trial. In the meantime, revascularization surgery may be considered as a last-resort option for SCD patients who cannot be treated otherwise or who continue to have brain infarctions despite medical therapy.

#### Screening Patients With SCD

It is reasonable to monitor younger children (2 to 10 years of age) and those with relatively high velocities with TCD more frequently.<sup>107</sup> On the basis of an analysis of the STOP TCD data, Wang<sup>108</sup> proposed that patients with a normal TCD ( $\leq 170$  cm/s) be restudied annually and that patients with an abnormal TCD ( $\geq 200$  cm/s) be restudied in 1 month. He suggested a repeat TCD in 3 months for individuals with a blood flow velocity of 185 to 199 cm/s and every 6 months for those with flow velocities in the range of 170 to 184 cm/s.<sup>108</sup>

#### Recommendations for Children With SCD

##### Class I Recommendations

1. Acute management of ischemic stroke resulting from SCD should include optimal hydration, correction of hypoxemia, and correction of systemic hypotension (Class I, Level of Evidence C).
2. Periodic transfusions to reduce the percentage of sickle hemoglobin are effective for reducing the risk of stroke in children 2 to 16 years of age with an abnormal TCD resulting from SCD and are recommended (Class I, Level of Evidence A).
3. Children with SCD and a confirmed cerebral infarction should be placed on a regular program of red cell transfusion in conjunction with measures to prevent iron overload (Class I, Level of Evidence B).

4. Reducing the percentage of sickle hemoglobin with transfusions before performing CA is indicated in an individual with SCD (Class I, Level of Evidence C).

##### Class II Recommendations

1. For acute cerebral infarction, exchange transfusion designed to reduce sickle hemoglobin to  $<30\%$  total hemoglobin is reasonable (Class IIa, Level of Evidence C).
2. In children with SCD and an ICH, it is reasonable to evaluate for a structural vascular lesion (Class IIa, Level of Evidence B).
3. In children with SCD, it is reasonable to repeat a normal TCD annually and to repeat an abnormal study in 1 month (Class IIa, Level of Evidence B). Borderline and mildly abnormal TCD studies may be repeated in 3 to 6 months.
4. Hydroxyurea may be considered in children and young adults with SCD and stroke who cannot continue on long-term transfusion (Class IIb, Level of Evidence B).
5. Bone marrow transplantation may be considered for children with SCD (Class IIb, Level of Evidence C).
6. Surgical revascularization procedures may be considered as a last resort in children with SCD who continue to have cerebrovascular dysfunction despite optimal medical management (Class IIb, Level of Evidence C).

#### Moyamoya Disease and Moyamoya Syndrome

Moyamoya syndrome is characterized by chronic progressive stenosis of the distal intracranial ICA and, less often, stenosis of the proximal ACA and MCA, the basilar artery, and the posterior cerebral arteries. The term moyamoya is a Japanese word meaning "hazy, like a cloud of smoke drifting through the air," referring to the often hazy angiographic appearance of the distal collateral network on angiography. Traditionally, individuals with a well-recognized associated condition are categorized as having moyamoya syndrome, and those with no known risk factors are said to have moyamoya disease.

The relative rarity of moyamoya disease (an estimated 0.086 per 100 000 children in the United States) has limited the studies on its diagnosis, treatment, and outcome in this country.<sup>109</sup> Although there is a vast literature on moyamoya, randomized clinical trials are not available to guide therapy. A recent meta-analysis of the surgical treatment of pediatric moyamoya syndrome offers the most complete review of the literature to date.<sup>110</sup>

**Clinical Features and Diagnosis.** A Japanese research committee issued the following guidelines for the diagnosis of moyamoya: (1) stenosis involving the region of the distal ICA bifurcation (C1) and proximal portions of the ACA (A1) and MCA (M1), (2) appearance of dilated basal collateral arteries, and (3) bilateral abnormalities. If any of the conditions listed above is present and the angiographic pattern is found on 1 side only, the diagnosis is probable.

Moyamoya disease accounts for  $\approx 6\%$  of childhood strokes in Western countries. Half of the patients present before 10 years of age.<sup>111,112</sup> Some patients have rare, intermittent ischemic events or even extended periods of clinical stability; other individuals have a more fulminant rapid neurological decline.<sup>113,114</sup> Children with moyamoya typically present with ischemic stroke or TIAs. Ischemic episodes also occur in

older individuals, but adults are more likely than children to develop an ICH. Ischemic strokes often are multiple and recurrent, involving predominantly the carotid circulation. Infarctions may be superficial or deep and often are found in watershed territories. Ischemic symptoms may follow hyperventilation, crying, coughing, straining, or fever. A characteristic electroencephalographic finding is slowing of the background rhythm after cessation of hyperventilation (“re-buildup” phenomenon).<sup>2</sup>

**Epidemiology of Moyamoya Disease.** First described in Japan, moyamoya syndrome has now been observed throughout the world and affects individuals of many ethnic backgrounds, with increasing detection of this disease in American and European populations.<sup>115,116</sup> In Japan, it is the most common pediatric cerebrovascular disease, affecting girls almost twice as often as boys with a prevalence of  $\approx 3$  of 100 000.<sup>111,117</sup> In Europe, a recent study cited an incidence of 0.3 patients per center per year, which is  $\approx 1/10$  the incidence in Japan.<sup>118</sup> Results from a 2005 US study suggest an incidence of 0.086 of 100 000 persons. The ethnicity-specific incidence rate ratios compared with whites were 4.6 (95% CI, 3.4 to 6.3) for Asian Americans, 2.2 (95% CI, 1.3 to 2.4) for blacks, and 0.5 (95% CI, 0.3 to 0.8) for Hispanics.<sup>109</sup>

In the United States and Korea, reports have corroborated historical claims of a bimodal age distribution of moyamoya, 1 group in the pediatric age range (around the first decade of life) and a second group of adults in the 30- to 40-year-old range. Children appear to be more likely to present with ischemic events (either strokes or TIAs) and adults with hemorrhage, leading to more rapid diagnosis.<sup>119,120</sup> The significance of ischemic events in children usually proves more difficult to diagnose because of the patient’s age and limited communication skills, leading to delayed recognition of the underlying moyamoya condition.<sup>3</sup>

**Associated Conditions.** Although the cause and pathogenesis of moyamoya disease are poorly understood, genetic factors play a major role. The familial incidence of affected first-degree relatives in Japan is 7% to 12%, and a similar rate of  $\approx 6\%$  was found in the Children’s Hospital, Boston, series.<sup>113,121–123</sup> Moyamoya has been linked to several genetic loci.<sup>124–126</sup> Moyamoya has been associated with specific human leukocyte antigen (HLA) haplotypes, including the HLA-B40 antigen in patients <10 years of age and the HLA B52 antigen in those >10 years of age. Moyamoya also has been associated with the AW24, BW46, B51-DR4, and BW54 antigens. Elevated levels of fibroblast growth factor may play a role in its pathogenesis. Increased levels of fibroblast growth factor have been found in the cerebrospinal fluid, and a strong fibroblast growth factor receptor immunoreactivity has been demonstrated in superficial temporal vessels.

Several clinical conditions have been reported in conjunction with moyamoya syndrome, although for conditions with only 1 or 2 reported cases, the link is at best tenuous.<sup>114</sup> Frequently reported risk factors include cranial radiotherapy, Down syndrome, neurofibromatosis type 1, and SCD. Table 6 summarizes the clinical associations noted in several published series.<sup>127–131</sup>

**Table 6. Risk Factors for Moyamoya Syndrome<sup>119–131</sup>**

	Patients, n
No associated conditions (idiopathic)	66
Neurofibromatosis type 1	16
Asian heritage	16
Cranial therapeutic radiation	15
Hypothalamic-optic system glioma	8
Craniopharyngioma	4
Medulloblastoma, with Gorlin’s syndrome	1
Acute lymphocytic leukemia, intrathecal chemotherapy	2
Down syndrome	10
Congenital cardiac anomaly, previously operated	7
Renal artery stenosis	4
Hemoglobinopathy (2 sickle cell, 1 “Bryn Mawr”)	3
Other (hematologic: 1 spherocytosis, 1 ITP)	2
Giant cervicofacial hemangiomas	3
Shunted hydrocephalus	3
Idiopathic hypertension requiring medication	3
Hyperthyroidism (1 with Graves syndrome)	2

Other syndromes, 1 patient each: Reye’s (remote), Williams, Alagille, cloacal extrophy, renal artery FMD, and congenital cytomegalic inclusion virus infection (remote). Two patients had unclassified syndromic presentations. There were 4 blacks, 2 of whom had sickle cell disease.

**Natural History and Prognosis of Moyamoya.** The prognosis of moyamoya disease is difficult to predict because its natural history is not firmly established. By some estimates, 50% to 66% of untreated moyamoya patients have progressive neurological dysfunction and a poor outcome<sup>132–134</sup> compared with a 2.6% deterioration rate for children summarized in a more recent meta-analysis of 1156 surgically treated patients.<sup>110</sup>

The overall prognosis of patients with moyamoya syndrome depends on the rapidity and extent of vascular occlusion, the patient’s ability to develop effective collateral circulation, age at onset of symptoms, severity of presenting neurological deficits and degree of disability, and the extent of infarction on CT or MRI at presentation.<sup>135</sup> Some authors suggest that neurological status at the time of treatment, more than age of the patient, predicts long-term outcome.<sup>113,136</sup>

**Diagnostic Studies.** Diagnosis is based on a distinct arteriographic appearance characterized by bilateral stenosis of the distal ICA extending to the proximal ACA, MCA, and posterior cerebral artery with frequent involvement of the circle of Willis and development of an extensive collateral network at the base of the brain. The typical abnormal vessels of moyamoya disease are noted with 3-dimensional CTA, postcontrast MRI, and MRA. MRA may be useful for screening high-risk subjects. TCD has been used to assist with the diagnosis and postoperative follow-up of these patients. Small areas of hypodensity suggestive of stroke are commonly observed in cortical watershed zones, basal ganglia, deep white matter, or periventricular regions.<sup>137,138</sup>

There are no data to support routine vascular screening for moyamoya syndrome, but screening may be considered in

individuals with relatively common and high-risk disorders such as neurofibromatosis type 1, Down syndrome, and SCD.<sup>73,139–141</sup> There is little evidence to justify screening first-degree relatives of patients with moyamoya when a single individual in a family is affected.

Acute infarcts are best seen with diffusion-weighted imaging. Chronic infarcts are better demonstrated with T1 and T2 imaging. Cortical oligemia may be inferred from fluid-attenuated inversion recovery sequences, which demonstrate linear high signal following a sulcal pattern, thought to represent slow flow in poorly perfused cortical circulation.<sup>142</sup> Most suggestive of moyamoya on MRI is the absence of flow voids in the ICA, MCA, and ACA coupled with abnormally prominent flow voids from basal ganglia and thalamic collateral vessels. These imaging findings are virtually diagnostic of moyamoya syndrome.<sup>138,143–147</sup>

Because of its excellent diagnostic yield and noninvasiveness, MRA has largely supplanted CA as the primary diagnostic imaging modality for moyamoya syndrome.<sup>143,148–153</sup> However, although MRA affords the ability to detect stenosis of major intracranial vessels and to visualize the basal collateral vessels, MRA is less reliable when applied to smaller vessel occlusions. In a study of 190 angiograms from pediatric patients, the complication rate from angiography in children with moyamoya syndrome was no higher than the risk of angiography in nonmoyamoya populations with other forms of cerebrovascular disease.<sup>154</sup>

Techniques such as TCD, perfusion CT, xenon-enhanced CT, positron emission tomography (PET), MR perfusion imaging,<sup>155–157</sup> and single-photon emission CT (SPECT) with acetazolamide challenge have been used to evaluate moyamoya syndrome. TCD provides a noninvasive way to follow changes in blood flow velocities in larger cerebral vessels over time, whereas xenon-enhanced CT, PET, and SPECT can detect inadequate resting perfusion and poor blood flow reserve before treatment and can help determine the extent of the improvement in functional perfusion after therapy.<sup>158–166</sup> The role of SPECT and PET scans in the evaluation and management of moyamoya syndrome has increased over the past decade.<sup>164,166</sup>

Several reports suggest that periodic clinical and radiographic reexaminations of patients with moyamoya disease may be helpful in some clinical settings.<sup>110,167</sup> One study found that 27% (17 of 64) of the moyamoya patients with unilateral disease eventually developed bilateral involvement.<sup>168</sup> There is also evidence that disease progression is more likely to occur in younger patients.<sup>168</sup> Of those patients who had surgery (for either bilateral or unilateral disease), the need for reoperation as a result of refractory disease ranged from 1.8% to 18%.<sup>169</sup>

*Treatment of Moyamoya Disease and Moyamoya Syndrome.* Surgical revascularization procedures are widely used for moyamoya syndrome, particularly for patients with cognitive decline or recurrent or progressive symptoms.<sup>110</sup>

Direct anastomosis procedures, most commonly a superficial temporal artery to MCA anastomosis (bypass), often are technically difficult to perform in children because of the small size of scalp donor vessels or MCA recipient vessels.

Indirect revascularization procedures have included encephaloduroarteriosynangiosis and encephalomyoarteriosynangiosis.<sup>170–172</sup> There are multiple variations of these procedures, including simply drilling burr holes without vessel synangiosis<sup>173,174</sup> and craniotomy with inversion of the dura in hopes of enhancing new dural revascularization of the brain.<sup>175</sup> Some patients stabilize without intervention, but unfortunately this can occur after they have already sustained a debilitating neurological disability. Potential complications of surgery for moyamoya include postoperative ischemic stroke, spontaneous or traumatic subdural hematoma, and ICH.

A number of groups have reported improved results in the use of combined direct and indirect anastomoses.<sup>169,170,176,177</sup> A modification of the encephaloduroarteriosynangiosis procedure called pial synangiosis has been used with encouraging results.<sup>113</sup> A review of 143 children with moyamoya syndrome treated with pial synangiosis demonstrated marked reductions in their stroke frequency after surgery, especially after 1 month postoperatively. Sixty-seven percent had strokes preoperatively, 7.7% had strokes in the perioperative period, and only 3.2% had strokes after at least 1 year of follow-up. The long-term stroke rate was 4.3% (2 of 46 patients) in individuals with a minimum of 5 years of follow-up.<sup>113</sup> Despite extensive anecdotal evidence supporting the role for surgical treatment of moyamoya syndrome, there is a need for further research to validate these data.

Two large studies with long-term follow-up demonstrated a good safety profile for surgical treatment of moyamoya (4% risk of stroke within 30 days of surgery per hemisphere) with a 96% probability of remaining stroke free over a 5-year follow-up period.<sup>113,132</sup> A recent meta-analysis of 1156 pediatric moyamoya patients treated with surgery concluded that 87% (1003 patients) derived symptomatic benefit from surgical revascularization but that there was no difference between the indirect and direct/combined groups.<sup>110</sup> Some physicians believe that revascularization surgery is less useful in patients presenting with ICH,<sup>119</sup> although additional studies of patients presenting with hemorrhage are ongoing.

Moyamoya patients are at additional risk of ischemic events during the perioperative period. Crying and hyperventilation, common occurrences in children during hospitalization, can lower PaCO<sub>2</sub> and induce ischemia secondary to cerebral vasoconstriction. Any techniques to reduce pain—including the use of perioperative sedation, painless wound dressing techniques, and absorbable wound suture closures—may reduce the likelihood of stroke and shorten the hospitalization.<sup>178</sup> Similarly, it is good to avoid hypotension, hypovolemia, hyperthermia, and hypocarbia both intraoperatively and perioperatively.<sup>113</sup> Slight elevation of the systemic blood pressure may be beneficial, and postoperative patients may be given intravenous fluids at 1.5 times the normal maintenance rate based on weight for 48 to 72 hours.<sup>178</sup>

Few studies have compared medical and surgical therapies for moyamoya. A large survey from Japan in 1994 found no significant differences in outcome between medically and surgically treated moyamoya patients.<sup>179</sup> Another study indicated that 38.4% of 651 moyamoya patients who were not initially treated with surgery eventually came to surgery as a result of progressive symptoms.<sup>169</sup>

Platelet antiaggregants are sometimes given for moyamoya syndrome, particularly when the patient is considered a poor operative risk or has relatively mild disease, but there are few data demonstrating either short-term or long-term efficacy. Antiplatelet agents have been used in individuals whose ischemic symptoms seem to arise from emboli from microthrombus formation at sites of arterial stenosis and routinely for all patients in many operative series.<sup>113,114,127,180</sup> Anticoagulants such as warfarin are rarely used because of the difficulty of maintaining therapeutic levels in children and the risk of hemorrhage after inadvertent trauma, but low-dose LMWH has been used.<sup>181</sup> Calcium channel blockers<sup>180</sup> have been used in a few patients in an attempt to improve intractable headaches and to reduce the frequency and severity of refractory TIAs.

#### *Recommendations for Treatment of Moyamoya in Children*

##### *Class I Recommendations*

1. Different revascularization techniques are useful to effectively reduce the risk of stroke resulting from moyamoya disease (Class I, Level of Evidence B). However, despite a vast literature on moyamoya, there are no controlled clinical trials to guide the selection of therapy.
2. Indirect revascularization techniques are generally preferable and should be used in younger children whose small-caliber vessels make direct anastomosis difficult, whereas direct bypass techniques are preferable in older individuals (Class I, Level of Evidence C).
3. Revascularization surgery is useful for moyamoya (Class I, Level of Evidence B). Indications for revascularization surgery include progressive ischemic symptoms or evidence of inadequate blood flow or cerebral perfusion reserve in an individual without a contraindication to surgery (Class I, Level of Evidence B).

##### *Class II Recommendations*

1. TCD may be useful in the evaluation and follow-up of individuals with moyamoya (Class IIb, Level of Evidence C).
2. Techniques to minimize anxiety and pain during hospitalizations may reduce the likelihood of stroke caused by hyperventilation-induced vasoconstriction in individuals with moyamoya (Class IIb, Level of Evidence C).
3. Management of systemic hypotension, hypovolemia, hyperthermia, and hypocarbia during the intraoperative and perioperative periods may reduce the risk of perioperative stroke in individuals with moyamoya disease (Class IIb, Level of Evidence C).
4. Aspirin may be considered in individuals with moyamoya after revascularization surgery or in asymptomatic individuals for whom surgery is not anticipated (Class IIb, Level of Evidence C).
5. Techniques to measure cerebral perfusion and blood flow reserve may assist in the evaluation and follow-up of individuals with moyamoya disease (Class IIb, Level of Evidence C).

##### *Class III Recommendations*

1. Except in selected individuals with frequent TIAs or multiple infarctions despite antiplatelet therapy and

surgery, anticoagulants are not recommended for most individuals with moyamoya because of the risk of hemorrhage and the difficulty of maintaining therapeutic levels in children (Class III, Level of Evidence C).

2. In the absence of a strong family history of moyamoya disease or medical conditions that predispose to moyamoya syndrome, there is insufficient evidence to justify screening studies for moyamoya disease in asymptomatic individuals or in relatives of patients with moyamoya syndrome (Class III, Level of Evidence C).

##### *Cervicocephalic Arterial Dissection*

CCAD is an important but probably underrecognized cause of stroke in children, accounting for 16 of 213 children (7.5%) with ischemic stroke in 1 series.<sup>182-184</sup> Most dissections occur in the extracranial ICA, typically in the pharyngeal portion of the ICA. In children, the site of dissection is often intracranial.<sup>182</sup>

The recurrence rate of CCADs is  $\approx 1\%$  per year<sup>185</sup> and is greater among younger patients, in patients with a family history of arterial dissections, in patients with FMD, and in those with inherited arteriopathies such as Ehlers-Danlos syndrome type IV. Other disorders predisposing to CCAD include Marfan syndrome, coarctation of the aorta, cystic medial necrosis, autosomal-dominant polycystic kidney disease, osteogenesis imperfecta, atherosclerosis, extreme arterial tortuosity, moyamoya syndrome, and pharyngeal infections. CCADs occur both spontaneously and after blunt or penetrating trauma.

Arteriographic features of CCAD include the presence of a string sign; double-lumen sign; short, smooth, tapered stenosis; and vessel occlusion of a parent artery.<sup>186</sup> High-resolution MRI, particularly fat-saturated T1 imaging of the neck, and contrast-enhanced MRA provide valuable information and may eventually supplant conventional CA. Color flow duplex ultrasound studies are sometimes helpful in recognizing dissections and in monitoring their evolution. The role of CTA in the diagnosis of CCAD in children requires further evaluation.

Recanalization of the affected artery occurs in 60% of children with CCAD, and the risk of recurrent stroke or TIA is 12% (2 of 16 in a consecutive cohort study).<sup>184</sup> The main goal of therapy for CCAD is to prevent additional ischemic strokes until the vessel has healed. Potential medical treatments for CCAD, derived largely from adult series, include immediate anticoagulation with intravenous UFH or LMWH followed by a 3- to 6-month course of warfarin designed to maintain a target international normalized ratio of 2.0 to 3.0, continued LMWH, or platelet antiaggregant therapy. Platelet antiaggregants are sometimes continued longer than 6 months or started after a course of warfarin or LMWH.<sup>187</sup> Some physicians avoid using anticoagulants in patients with intracranial dissections because of the potential increased risk of SAH. For patients who do not respond to medical management, proximal ligation, trapping procedures, and extracranial-intracranial bypass procedures have sometimes been attempted. Although there is indirect evidence that anticoagulation for 3 to 6 months could reduce the likelihood of distal embolism from the abnormal arterial segment, the validity of such treatment remains unproven.

*Recommendations for CCAD in Children**Class II Recommendations*

1. In children with extracranial CCAD, it is reasonable to begin either UFH or LMWH as a bridge to oral anticoagulation (Class IIa, Level of Evidence C).
2. It is reasonable to treat a child with an extracranial CCAD with either subcutaneous LMWH or warfarin for 3 to 6 months (Class IIa, Level of Evidence C). Alternatively, an antiplatelet agent may be substituted for LMWH or warfarin. Extending anticoagulant therapy beyond 6 months is a reasonable option for individuals who develop recurrent symptoms (Class IIa, Level of Evidence C). It is reasonable to continue antiplatelet agents beyond 6 months, especially when there is radiographic evidence of a residual abnormality of the dissected artery (Class IIa, Level of Evidence C).
3. In patients who continue to have symptoms from a CCAD despite optimal medical therapy, surgical procedures may be considered (Class IIb, Level of Evidence C).

*Class III Recommendations*

1. Anticoagulation is not recommended for children with an intracranial dissection or those with SAH resulting from CCAD (Class III, Level of Evidence C).

*Other Traumatic Cerebrovascular Disorders*

In addition to CCAD and CVST (see Sinovenous Thrombosis), trauma also may result in arterial thrombosis, arterial rupture, pseudoaneurysm, or arteriovenous fistula. Basal ganglia infarction after relatively trivial trauma may be secondary to stretching of the deep arterial perforators.<sup>3</sup> Hanging or strangulation may result in injury to cervical arteries or veins. The carotid artery can be stretched over the transverse process of C2 or compressed by direct pressure over the transverse process of C6. The vertebral arteries may be affected at extremes of lateral flexion and rotation. Children may injure the ICA by direct trauma from a lollipop or pencil in the region of the tonsillar fossa with resultant thrombosis or dissection.<sup>188–190</sup>

*Fibromuscular Dysplasia*

FMD is a nonatherosclerotic segmental noninflammatory angiopathy that typically affects the renal arteries and extracranial segment of the ICA, typically 3 to 4 cm from its bifurcation. FMD most often presents in adults, but there are reports of affected children and adolescents. An estimated 20% to 30% of individuals with FMD have cerebrovascular involvement, but most remain asymptomatic. Brain infarction results from stenosis or dissection of the affected artery or from embolism arising from a stenotic major cerebral artery. Intracranial aneurysms have been reported in ≈7% of affected patients, but only a few children with both FMD and an aneurysm have been reported. Few children with symptomatic FMD have been described, and it is difficult to estimate the risk of an accompanying aneurysm.

*Vasculitis*

Vasculitis of the intracranial vessels can be difficult to diagnose with confidence. Not all individuals have clinical or laboratory signs of inflammation, and the classic angio-

graphic findings of arteritis (arterial beading and alternating areas of constriction and dilatation) are nonspecific. Different vasculitic disorders involve large, medium-sized, or small arteries and, in some instances, capillaries and veins (Table 5). Although some forms of vasculitis rarely occur in children, most types are documented from time to time. Infectious and multisystem noninfectious inflammatory diseases cause cerebral vasculitis.

Cerebral vasculitis may be considered in children with either ischemic or hemorrhagic stroke, patients with recurrent stroke, patients with ischemic or hemorrhagic stroke associated with encephalopathic changes, and patients with stroke accompanied by fever, multifocal neurological events, unexplained skin lesions, glomerulopathy, or elevated sedimentation rate.

Vasculitis occurs with most intracranial infections, and stroke seems to be particularly common with chronic infections such as tuberculous meningitis. Varicella virus may cause a necrotizing arteritis, and there is evidence of intracranial vasculopathy after chickenpox in children.<sup>191</sup> In some series, ischemic stroke occurred in a fourth of children with acute purulent meningitis. Among children 2 to 10 years of age with AIS, up to a third of the patients have postvaricella angiopathy occurring weeks to months after uncomplicated chickenpox, manifesting with unilateral stenosis involving the distal ICA, proximal ACA or MCA, and basal ganglia infarction.<sup>192</sup> Unilateral or bilateral ICA occlusion can complicate necrotizing fasciitis of the lateral parapharyngeal space. Mycotic infections, often seen in immunocompromised hosts, can cause arteritis, aneurysms, thrombosis, and cerebral infarction. Stroke also may occur with various other CNS infections, including aspergillosis, *Mycoplasma pneumoniae*, Coxsackie-9 virus, California encephalitis virus, mumps, paramyxovirus, *Borrelia burgdorferi*, cat-scratch disease, brucellosis, and neurocystercercosis. Lyme neuroborreliosis is an unusual cause of cerebral vasculitis or arterial stenosis. Although a rare cause of stroke, rickettsial infections can involve the cerebral vasculature, leading to cerebral infarcts. Malaria-associated cerebral vasculitis can cause small, punctate brain hemorrhages.

Cerebral infarction is a complication of the acquired immunodeficiency syndrome and may occur with secondary *V zoster* virus or meningovascular syphilis and with infective endocarditis, aneurysmal dilatation of major cerebral arteries, nonbacterial thrombotic endocarditis, antiphospholipid-antibody syndrome, or other hypercoagulable states. Hemorrhagic strokes in children with acquired immunodeficiency syndrome usually are seen in the setting of thrombocytopenia.

Stroke in patients with systemic lupus erythematosus has several different mechanisms; arguably the least common of these is immune-mediated vasculitis. In addition, stroke caused by systemic lupus erythematosus can result from cardiogenic embolism (Libman-Sacks endocarditis), antiphospholipid antibodies, and underlying vasculopathy. Valvular vegetations are generally located on the atrial side of the mitral valve or on the arterial side of the aortic valve. Takayasu arteritis may be considered in adolescents, especially in women of Mexican or Asian ancestry with absent

carotid or radial pulses, cervical bruits, asymmetrical blood pressure measurements, fever, and elevated erythrocyte sedimentation rate. Diagnosis can be supported by MRA, but the most accurate assessment requires aortography.

Primary CNS vasculitis is a rare, noninfectious, granulomatous, necrotizing angiopathy characterized by predominant or exclusive involvement of the CNS. Typical symptoms include headaches and altered consciousness. Occasionally, small-vessel involvement may present as a mass lesion or as a multifocal encephalopathy with normal angiograms.<sup>193</sup> Small-vessel strokes may occur over weeks to many months. The erythrocyte sedimentation rate is usually normal or only minimally elevated, and other acute-phase reactants are characteristically normal. The cerebrospinal fluid can be abnormal as a result of increased opening pressure, elevated protein values, or a lymphocytic pleocytosis (rarely exceeding 250 cells/mm<sup>3</sup>). Contrast-enhanced MRI studies are abnormal in >90% of cases. Arteriography may show segmental arterial narrowing, vascular occlusions, peripheral aneurysms, vascular shifts, or avascular areas or may be entirely unremarkable.

For diffuse or multifocal CNS vasculitis, cortical-leptomeningeal biopsy is the most specific diagnostic test, but because of the focal nature of primary cerebral arteritis, a negative biopsy result does not preclude the diagnosis. The yield of such a biopsy increases if it can be carried out in an area that is demonstrably abnormal on imaging studies, including MRI and CA.

Some children with arteritis stabilize or improve even without specific treatment, often in the context of a self-limiting or treated infection. Other examples include post-varicella angiopathy and transient cerebral arteriopathy or nonprogressive primary angiitis of the CNS. In most of the systemic vasculitides, rheumatological vasculitic syndromes, and primary CNS vasculitis, treatment involves the use of corticosteroids and cytotoxic agents. Distinguishing between transient or nonprogressive and progressive arteriopathies at presentation is not straightforward<sup>194,195</sup> and currently is the subject of active research.<sup>196–198</sup> Pulse cyclophosphamide has been used successfully to treat isolated angiitis of the CNS in children. Immunosuppressive agents have a substantial risk of side effects; a full discussion of these complications is beyond the scope of this review. Surgery has been used to relieve chronic vascular insufficiency resulting from Takayasu arteritis.

### *Migraine*

The exact contribution of migraine to the risk of stroke among children is unknown. Migraine with aura seems to increase the risk of ischemic stroke among young individuals, particularly those of childbearing age and those taking oral contraceptives. Common migraine alone is unlikely to cause an ischemic stroke, although there may be more reason for concern when migraine with aura is coupled with other risk factors such as smoking, pregnancy, or oral contraceptive use.<sup>199</sup> Thus, it seems prudent to evaluate a young patient with cerebral infarction and a history of migraines for other stroke risk factors, paying special attention to disorders that often feature migraine-like headache such as CCAD,<sup>200</sup> cere-

bral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), moyamoya, and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).

Three genes that promote familial hemiplegic migraine have now been identified, each affecting a subunit of a different ion channel.<sup>201</sup> Some children with a familial hemiplegic migraine mutation develop persistent neurological deficits,<sup>202</sup> suggesting that their risk of stroke might be greater than the risk in individuals with other forms of migraine.

Given the potential for oral contraceptive agents to exacerbate migraine and to alter coagulation, it might be prudent for individuals with migraine and AIS who are taking oral contraceptives to switch to another form of birth control. Although the stroke risk, if any, from the use of triptans in children is unknown, it is reasonable to minimize the use of these agents in children with hemiplegic migraine, basilar migraine, known vascular risk factors, or prior cardiac or cerebral ischemia pending the availability of more detailed information. Similarly, it is reasonable to avoid triptan agents in individuals with renal or hepatic disease and in adolescents who are pregnant or lactating. Limiting  $\beta$ -blocking drugs in individuals who developed an infarction while taking a prophylactic regimen may be appropriate because these agents might worsen intracranial vasoconstriction. Options for prophylactic therapy include amitriptyline, sodium valproate, cyproheptadine, or a combination of short-acting verapamil hydrochloride or other calcium channel antagonists and aspirin if there are no contraindications.<sup>203,204</sup> No specific treatment is currently available for patients with CADASIL; antiplatelet agents may be tried.

### *Recommendations for Migraine as a Stroke Risk Factor*

#### *Class II Recommendations*

1. Individuals with AIS and symptoms of migraine may be evaluated for other stroke risk factors (Class IIb, Level of Evidence C).
2. It is reasonable to advise individuals with migraine and AIS who are taking oral contraceptives to switch to another form of birth control (Class IIa, Level of Evidence C).
3. It is reasonable to avoid triptan agents in children with hemiplegic migraine, basilar migraine, known vascular risk factors, or prior cardiac or cerebral ischemia, at least pending the availability of more information (Class IIa, Level of Evidence C).

#### *Cardiac Disease*

Up to a fourth of ischemic strokes in children result from cardiac disease, and most of these children are already known to have a cardiac lesion at the time of their stroke. Complex congenital heart lesions with right-to-left shunting and cyanosis are particularly prone to cause stroke, but stroke has been described with most types of cardiac lesions (Table 7). Stroke is more common among children with uncorrected congenital heart disease.<sup>205</sup> Emboli can arise at the atrial level (eg, atrial septal defect with pulmonary hypertension), at the ventricular level (eg, ventricular septal defect with pulmonary

hypertension), or at the arterial level (eg, pulmonary arteriovenous fistula).

Occasionally, children develop a stroke as a result of acquired disorders of the myocardium or cardiac valves. Valvular heart disease may result from rheumatic, prosthetic, myxomatous, inflammatory, infective, marantic, traumatic, degenerative, or congenital disorders. Rheumatic heart disease is less common since the advent of antibiotics, but the lifetime risk of systemic thromboembolism from untreated rheumatic mitral stenosis is 20%. Case reports document rare strokes resulting from embolism of particulate matter or air.

Patients with prosthetic heart valves are at risk for endocarditis and stroke. Despite the high prevalence of mitral valve prolapse in the general population, it is a rare cause of embolic stroke in adults and an even rarer cause in children.

Thromboembolic stroke can complicate cardiac catheterization and cardiac surgery. Surgical repair of congenital cardiac defects reduces but does not always eliminate the long-term risk of thromboembolism. Neurological injury during cardiac surgery also can result from global ischemia and reperfusion.<sup>206</sup>

Children with heart disease who have a low hemoglobin concentration resulting from iron deficiency appear to have a higher risk of arterial stroke, although the precise mechanism for this risk is not known. In contrast, individuals with a markedly elevated hematocrit may be at more risk for cerebral venous thrombosis.<sup>207,208</sup>

The foramen ovale usually closes at birth, but it remains patent in up to 35% of people between 1 and 29 years of age, providing an opportunity for right-to-left shunting during transient increases in the right atrial pressure.<sup>209</sup> In some series, the prevalence of a patent foramen ovale (PFO) is greater in young adults with unexplained ischemic stroke than in normal individuals,<sup>210</sup> and the significance of a PFO in a child with stroke is even less certain. Optimal treatment of paradoxical embolism associated with PFO is not known,<sup>211</sup> but ongoing adult studies of transcatheter PFO closure may provide additional evidence that might apply to children.<sup>212,213</sup>

Paradoxical emboli result when thrombi bypass the pulmonary circulation during right-to-left shunting. Paradoxical embolism also occurs in individuals with pulmonary arteriovenous fistula, which occurs with increased frequency in patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).

Neurological complications occur in 20% to 40% of individuals with infective endocarditis involving the left side of the heart. Strokes account for about half of the neurological manifestations, and they most often involve the MCA territory or its branches. ICH, TIAs, and seizures also occur. Pathophysiological mechanisms include septic embolism, infective aneurysm formation, and vasculitis. There are few data to govern the management of patients with prosthetic valve endocarditis, but it may be reasonable to continue maintenance anticoagulation in individuals who are already taking it.

Although cardiac arrhythmias do not often cause stroke in children, various types of arrhythmias have been described in children with stroke. Atrial fibrillation occurs with increased frequency in children with hyperthyroidism or rheumatic

**Table 7. Cardiac Disorders Reported With Pediatric Stroke**

Congenital heart disease	
	Transposition of the great vessels
	Ventricular septal defect
	Atrial septal defect
	PFO with paradoxical embolism
	Pulmonary stenosis
	Tetralogy of Fallot
	Eisenmenger complex
	Truncus arteriosus with decreased flow
	Patent ductus arteriosus
	Endocardial cushion defect
	Hypoplastic left ventricle
	Ebstein anomaly
	Pulmonary atresia
	Coarctation of the aorta
Valvular heart disease	
	Congenital
	Rheumatic
	Prosthetic heart valves
	Mitral valve prolapse
	Infective endocarditis
	Nonbacterial thrombotic endocarditis
	Libman-Sacks endocarditis
	Calcific heart valves
	Mitral valve strands
	Aneurysms of the sinus of Valsalva
Cardiac arrhythmias	
	Atrial fibrillation
	Supraventricular tachycardia
	Sick sinus syndrome
Cardiomyopathy	
	Kearns-Sayre syndrome
	Myocardial infarction
	Left ventricular aneurysm
	Intracardiac tumors: atrial myxomas, rhabdomyomas, cardiac papillary fibroelastoma
	Muscular dystrophy
	Myocarditis
	Friedreich ataxia
Cardiac surgery and catheterization	
Extracorporeal membrane oxygenation	
Kawasaki disease	

Adapted from Biller et al.<sup>523</sup>

heart disease and after surgery for congenital heart disease. Individuals with sick sinus syndrome may develop systemic embolism, even after pacemaker insertion. Heart block is common in patients with Kearns-Sayre syndrome.

Regardless of the cause, congestive heart failure with reduced ejection fraction increases the risk of embolism. Cardiomyopathy or myocardial infarction from various causes can lead to cardiac arrhythmia or to cerebral embo-

lism. Cardiomyopathy has been documented with mitochondrial disorders, various forms of muscular dystrophy, Friedreich's ataxia, some congenital myopathies, and Fabry's disease ( $\alpha$ -galactosidase deficiency). Cardiomyopathy is a frequent manifestation of the latent and chronic phase of Chagas' disease (caused by *Trypanosoma cruzi*), a condition that is highly prevalent in some regions of South and Central America. Myocardial infarction in children most often occurs in the setting of childhood polyarteritis nodosa, homozygous type II hyperlipoproteinemia, or Kawasaki disease.

Cardiac myxomas are the most common primary cardiac tumors in adults, but in children, rhabdomyomas are more common. Although cardiac rhabdomyomas occur in two thirds of children with tuberous sclerosis complex and occasionally as an isolated lesion, only a few of these children have developed a stroke.<sup>214</sup> Atrial myxomas occur with increased frequency in patients with familial multiple neoplasia and lentiginosis syndrome. In addition to cerebral embolism, individuals with atrial myxoma are at risk for peripheral and cerebral arterial aneurysms, which are sometimes discovered years after the myxomatous embolism.

There are no age-specific data to guide the use of anticoagulant therapy in children, but the common approach is to use these agents in patients who are, for whatever reason, believed to have a high risk of embolism or have CCAD (see Cervicocephalic Arterial Dissection). Anticoagulant therapy usually is not recommended in individuals with native valve infective endocarditis (because of the potential to exacerbate hemorrhage in people with a septic aneurysm or septic arteritis). Prolonged parenteral bactericidal antibiotics are the mainstay of treatment of infective endocarditis; cardiac surgery may be appropriate in selected instances. The guidelines for antibacterial prophylaxis were recently updated.<sup>215</sup>

Surgical resection is undertaken typically for patients with atrial myxomas, although tuberous sclerosis patients with a cardiac rhabdomyoma have such a low risk of embolism that neither surgery nor anticoagulation is usually warranted. Surgical repair or transcatheter closure is indicated for major atrial septal defect both to reduce the stroke risk and to prevent long-term cardiac complications.

#### *Recommendations for Children With Stroke and Heart Disease*

##### *Class I Recommendations*

1. Therapy for congestive heart failure is indicated and may reduce the likelihood of cardiogenic embolism (Class I, Level of Evidence C).
2. When feasible, congenital heart lesions, especially complex heart lesions with a high stroke risk, should be repaired both to improve cardiac function and to reduce the subsequent risk of stroke (Class I, Level of Evidence C). This recommendation does not yet apply to PFOs.
3. Resection of an atrial myxoma is indicated given its ongoing risk of cerebrovascular complications (Class I, Level of Evidence C).

##### *Class II Recommendations*

1. For children with a cardiac embolism unrelated to a PFO who are judged to have a high risk of recurrent

embolism, it is reasonable to initially introduce UFH or LMWH while warfarin therapy is initiated and adjusted (Class IIa, Level of Evidence B). Alternatively, it is reasonable to use LMWH initially in this situation and to continue it instead of warfarin (Class IIa, Level of Evidence C).

2. In children with a risk of cardiac embolism, it is reasonable to continue either LMWH or warfarin for at least 1 year or until the lesion responsible for the risk has been corrected (Class IIa, Level of Evidence C). If the risk of recurrent embolism is judged to be high, it is reasonable to continue anticoagulation indefinitely as long as it is well tolerated (Class IIa, Level of Evidence C).
3. For children with a suspected cardiac embolism unrelated to a PFO with a lower or unknown risk of stroke, it is reasonable to begin aspirin and to continue it for at least 1 year (Class IIa, Level of Evidence C).
4. Surgical repair or transcatheter closure is reasonable in individuals with a major atrial septal defect both to reduce the stroke risk and to prevent long-term cardiac complications (Class IIa, Level of Evidence C). This recommendation does not apply to individuals with a PFO pending additional data.
5. There are few data to govern the management of patients with prosthetic valve endocarditis, but it may be reasonable to continue maintenance anticoagulation in individuals who are already taking it (Class IIb, Level of Evidence C).

##### *Class III Recommendations*

1. Anticoagulant therapy is not recommended for individuals with native valve endocarditis (Class III, Level of Evidence C).
2. Surgical removal of a cardiac rhabdomyoma is not necessary in asymptomatic individuals with no stroke history (Class III, Level of Evidence C).

##### *Hypercoagulable Disorders*

Various hypercoagulable disorders have been documented in children (Table 3). One or more prothrombotic states have been identified in 20% to 50% of children presenting with AIS and 33% to 99% of children with CVST.<sup>216</sup> A prothrombotic state may be suspected in individuals with recurrent episodes of deep vein thrombosis, recurrent pulmonary emboli, or a family history of thrombotic events or if thrombotic events occur during childhood, adolescence, or early adulthood. The likelihood of stroke from most prothrombotic states seems to be relatively low, but the stroke risk increases when a prothrombotic disorder occurs in children with other risk factors. Thus, it is reasonable to evaluate for at least the more common prothrombotic states even when another stroke risk factor has been identified.

Several coagulation abnormalities have been identified in children with stroke, including antithrombin III, protein C or protein S deficiencies, activated protein C resistance, factor V Leiden mutation, prothrombin gene mutation (*G20210A*), and antiphospholipid antibody syndrome. Most of these conditions are rare in pediatric series, and it is difficult to demonstrate an increased stroke risk for each condition,<sup>1</sup> but protein C deficiency and the genetic polymorphisms collectively (factor V Leiden, prothrombin gene mutation, thermo-

labile form of the MTHFR gene) may be independent risk factors in children for recurrent arterial stroke.<sup>74,75</sup> Elevated levels of lipoprotein(a) and homocysteine are known risk factors for stroke in childhood, which act in part by causing a hypercoagulable state.

The antiphospholipid antibody syndrome may be primary (ie, not associated with another disorder) or secondary (ie, associated with conditions such as systemic lupus erythematosus or other rheumatological disorders), but current evidence suggests that antiphospholipid antibodies increase stroke risk little if any in children.<sup>217</sup> The pathophysiological process associated with antiphospholipid antibody syndrome remains uncertain, but it evidently includes inhibition of prostacyclin formation or protein C activation. In addition, these antibodies may affect platelets, limit the production of endothelium-derived relaxing factor, and possibly inhibit the prekallikrein-mediated intrinsic pathway of fibrinolysis. Antiphospholipid antibodies are associated with recurrent fetal loss (typically second- or third-trimester miscarriages), thrombocytopenia, false-positive Venereal Disease Research Laboratory test results, painful leg ulcerations, cardiac valve alterations, and livedo reticularis. Although antiphospholipid antibody syndrome may promote cerebral ischemia, its link with stroke is at best tenuous, and the optimal treatment for the thrombotic complications of antiphospholipid antibody syndrome has not been elucidated.<sup>218</sup>

Children with hemolytic-uremic syndrome develop an array of neurological manifestations, including seizures, hemiparesis, aphasia, and visual field defects.<sup>219</sup> Focal neurological deficits caused by hemolytic-uremic syndrome result from ischemic infarction, although at least 1 child developed a hemorrhagic infarction.<sup>220</sup> Coma at the time of presentation and elevated cerebrospinal fluid protein predict a poor outcome in children with hemolytic-uremic syndrome, and children with neurological dysfunction have more severe azotemia and are more likely to need dialysis.<sup>219</sup>

Fever, microangiopathic hemolytic anemia, renal dysfunction, and fluctuating neurological signs characterize thrombotic thrombocytopenic purpura. Neurological manifestations include confusion, coma, seizures, aphasia, hemiplegia, and papilledema. Pathological findings of thrombotic thrombocytopenic purpura include diffuse hyaline microthrombi affecting the small vessels in the brain and various degrees of ischemic change, parenchymal hemorrhage, and SAH. Cerebral venous and, less often, cerebral arterial thromboses may occur in patients with paroxysmal nocturnal hemoglobinuria.

Polycythemia rubra vera, essential thrombocythemia, and disseminated intravascular coagulation may lead to cerebral infarction or ICH. Major symptoms in patients with polycythemia are related to arterial hypertension and arterial/venous thrombosis. Strokes may be the first manifestation. Patients <20 years of age are rare. Essential thrombocythemia is a clonal myeloproliferative disease that involves primarily the megakaryocytic lineage. Microvascular occlusion may lead to TIAs; thrombosis of major arteries and veins also may occur.

Homocystinuria is an uncommon but well-recognized cause of both arterial and venous occlusion.<sup>221</sup> Three enzyme deficiencies cause homocystinuria: cystathionine  $\beta$ -synthetase, homocysteine methyltransferase, and MTHFR.

Manifestations of homocystinuria include a marfanoid appearance, malar flushing, ectopia lentis, mental retardation, seizures, and rapidly progressive arteriosclerotic vascular disease. Hyperhomocysteinemia is an independent risk factor for cerebral arterial or venous thrombosis in children<sup>7,222,223</sup> and for coronary artery and peripheral arterial occlusive disease.

In about half of the individuals with homocystinuria, the homocysteine level improves or normalizes in response to pharmacological doses of pyridoxine, a coenzyme of cystathionine synthase.<sup>224</sup> Some patients also improve with folate, a restricted methionine diet, or betaine supplementation.<sup>225</sup> However, except in individuals with homozygous homocystinuria, there is little evidence that these methods are clinically useful. Toole and colleagues<sup>226</sup> demonstrated a reduction in plasma folate levels in adult stroke patients, but the risk of subsequent infarctions was unchanged.

Because of its frequency among teenaged girls, pregnancy must be included as a stroke risk factor in adolescents. The risk of both brain infarction and ICH is increased during the 6 weeks after delivery but not during pregnancy. Although the incidence is relatively low, ischemic stroke and ICH account for at least 4% to 8.5% of maternal mortality in the United States, and SAH is estimated to be responsible for 5% to 12% of maternal deaths during pregnancy. Alterations of multiple coagulation factors occur during pregnancy (eg, increased platelet adhesion; increased fibrinogen; increased factors VII, VIII, IX, X, and XII; decreased fibrinolysis; and reduced levels of available circulating plasminogen activator). The levels of protein S and protein C fall. Resistance to activated protein C increases in the second and third trimesters, and activity of the fibrinolytic inhibitors plasminogen activator inhibitor-1 and -2 and thrombin-activatable fibrinolytic inhibitor increases as well. During the last trimester, plasma levels of fibrinopeptide A are slightly elevated. One of the most significant changes is the rise in fibrinogen, which reaches its highest levels in the first weeks of pregnancy.

Characteristically, arterial strokes are more common during pregnancy, whereas venous occlusion is more common during the puerperium. Eclampsia remains the leading cause of both ICH and nonhemorrhagic stroke. Because warfarin-induced embryopathy is a major risk during the first trimester, therapy for thrombosis or embolism is always with heparin, at least during the first trimester.

There is a dose-related increase in the risk of cerebral thrombosis among users of oral contraceptives.<sup>227,228</sup> Preparations containing >50  $\mu\text{g}$  of estrogen carry the greatest stroke risk, but 96% of the current formulations of oral contraceptives contain lower estrogen doses. There is also concern about individuals who smoke cigarettes and those with arterial hypertension or hyperlipidemia, any of which might occur in teenagers taking oral contraceptives.<sup>229</sup>

### *Recommendations for Hypercoagulable States*

#### *Class II Recommendations*

1. Although the risk of stroke from most prothrombotic states is relatively low, the risk tends to increase when

a prothrombotic disorder occurs in children with other risk factors. Thus, it is reasonable to evaluate for the more common prothrombotic states even when another stroke risk factor has been identified (Class IIa, Level of Evidence C).

2. It is reasonable to discontinue oral contraceptives in adolescents with AIS or CVST (Class IIa, Level of Evidence C).
3. It is reasonable to measure the serum homocysteine level of children with CVST or AIS (Class IIa, Level of Evidence B) and to institute measures to lower the homocysteine level when it is higher than normal (Class IIa, Level of Evidence B). Measures to lower the homocysteine level might include diet or supplementation of folate, vitamin B6, or vitamin B12.

#### *Metabolic Disorders and Miscellaneous Conditions*

Mitochondrial encephalomyopathies may be suspected in patients with intractable seizures, failure to grow normally, recurrent strokes, lactic acidosis, or respiratory failure. The cardinal features of MELAS include exercise intolerance, onset before 40 years of age, seizures, ragged-red fibers, lactic acidosis, and stroke-like manifestations. Many individuals have migraine-like headaches. Ischemic lesions caused by MELAS preferentially involve the posterior cerebral hemispheres but usually do not conform to specific arterial territories. It is likely that the stroke-like syndrome found in MELAS patients is the result of altered cellular metabolism resulting in small cerebral vessels that impede blood flow to the affected cortex or indirectly owing to dysfunction of autoregulatory mechanisms. Whether mitochondrial dysfunction within neurons plays a role in the ischemic events is unclear. The blood leukocyte DNA reveals the A3243G mutation in  $\approx 80\%$  of MELAS patients. Stroke in Kearns-Sayre syndrome is probably due to cardiac embolism.

Various interventions have been tried for MELAS (ie, coenzyme Q10, L-carnitine, idebenone, dichloroacetate, vitamin C, riboflavins, and corticosteroids), but none of these is clearly effective. A recent study<sup>230</sup> suggested that the nitric oxide precursor L-arginine improves endothelial function in individuals with MELAS by flow-mediated vasodilatation. These intriguing data are promising, but their clinical significance, if any, remains to be determined.

Fabry's disease (Anderson-Fabry disease or angiokeratoma corporis diffusum) is an X-linked deficiency of  $\alpha$ -galactosidase that is characterized by cutaneous angiokeratomas, corneal and lenticular opacities, and painful paresthesias. Vascular complications (renal failure, arterial hypertension, myocardial infarction, and cerebral ischemia) are relatively common among young and middle-aged men with Fabry disease. Brain infarction resulting from Fabry disease tends to occur more often in the posterior circulation.<sup>231</sup> The frequency of Fabry disease in young individuals with unexplained stroke ranges from 0% to 1.2%.<sup>231,232</sup> Enzyme replacement therapy with genetically engineered galactosidase A (agalactidase  $\alpha$ ) effectively reduces both symptoms and the frequency of vascular complications.<sup>233,234</sup>

Microangiopathy of the brain, retina, and inner ear (Susac's syndrome or retinocochlear vasculopathy) is a rare

microcirculatory disorder that seems to be even more uncommon in children than in adults. It is characterized by multiple bilateral arteriolar branch occlusions of the brain, retina, and inner ear with resultant encephalopathy, visual loss, vestibular dysfunction, and asymmetrical sensorineural hearing loss.<sup>235,236</sup> Brain biopsy may show multifocal microinfarcts in both gray and white matter. The pathogenesis is poorly understood, but it has been attributed to vasospasm, abnormal coagulation, and microembolism.<sup>236</sup> Anecdotal reports suggest possible benefit from corticosteroids, cyclophosphamide, antiplatelet agents, anticoagulants, calcium channel blockers, plasmapheresis, and hyperbaric oxygen therapy.<sup>236–238</sup>

CADASIL results from a mutation of the *NOTCH3* gene at chromosome 19q12.<sup>239</sup> CADASIL has been described in a few children and adolescents but typically is recognized in adults.<sup>240</sup> Many CADASIL patients often have a history of complicated migraine attacks; over time, they develop increasing numbers of small, deep white matter infarctions that are evident as high signal lesions on MRI, often culminating in subcortical dementia.<sup>241,242</sup> Younger patients often have subtle or atypical findings. DNA testing for CADASIL is commercially available.

Both ischemic and hemorrhagic strokes have been reported in individuals who use cocaine. Stroke has been described in individuals using amphetamines, ecstasy (3,4-methylenedioxymethamphetamine), and drugs such as phentermine (used as appetite suppressants), although most of these reports involve adults rather than children. Phencyclidine (PCP or "angel dust") may increase the risk of ICH, and anabolic steroids could potentially lead to systemic hypertension and thrombogenesis. Case reports describe stroke in individuals using over-the-counter ephedrine and pseudoephedrine. A case-control study found no increase in stroke risk as a result of ephedra, and a similar study of phenylpropanolamine found an increased risk of hemorrhage in women taking the drug for weight reduction but not for upper respiratory symptoms (children were not included in either study).<sup>243,244</sup>

A relatively common pattern of focal cerebrovascular dysfunction in children is "transient cerebral arteriopathy" or "nonprogressive primary angiitis of the CNS." The pathogenesis of this disorder is uncertain. It mimics the radiographic features of postvaricella angiopathy, but there is an absence of preceding varicella infection. Unilateral, focal stenosis of the distal ICA and proximal ACA or MCA with secondary basal ganglia infarction is a hallmark of this self-arresting arteriopathy.<sup>195,198</sup>

Hereditary endotheliopathy with retinopathy, nephropathy, and stroke is an autosomal-dominant vasculopathy linked to chromosome 3p21. Clinical manifestations include progressive visual loss, macular edema, perifoveal microangiopathic telangiectasias, migraine-like headaches, focal neurological deficits, recurrent strokes, dementia, and renal insufficiency.<sup>245,246</sup> No effective therapy is available for patients with hereditary endotheliopathy with retinopathy, nephropathy, and stroke.

### Miscellaneous Recommendations for Modifying Stroke Risk Factors

#### Class I Recommendations

1. Individuals with Fabry disease should receive  $\alpha$ -galactosidase replacement therapy (Class I, Level of Evidence B).
2. If a treatable stroke risk factor is discovered in a child who has had a stroke, the underlying condition should be treated (Class I, Level of Evidence C).

#### Class II Recommendations

1. It is reasonable to seek and to treat iron deficiency because it may increase the risk of AIS in conjunction with other risk factors (Class IIa, Level of Evidence C). Drinking cow's milk has been known to promote iron deficiency, so limiting its consumption may be considered (Class IIb, Level of Evidence C).
2. It is reasonable to counsel children with stroke and their families regarding dietary improvement, the benefits of exercise, and the avoidance of tobacco products (Class IIa, Level of Evidence C).
3. It is reasonable to suggest an alternative to oral contraceptives after a stroke, particularly if there is evidence of a prothrombotic state (Class IIa, Level of Evidence C). See also earlier recommendations for SCD, CCAD, hypercoagulable state, and moyamoya disease.

### Outcome and Rehabilitation After Childhood Stroke

Between 20% and 40% of children die after a stroke.<sup>247–252</sup> The mortality is higher for hemorrhagic (about a third) than for ischemic (up to 20%, with about half related to underlying systemic illness rather than the stroke itself) stroke. Death during the acute phase is predicted by level of consciousness on admission. Recurrent stroke occurs in 6% to 15%,<sup>74,75</sup> and mortality is higher in this group.<sup>251</sup> Intractable intracranial hypertension is a major predictor of poor outcome in patients with large intracerebral or intracerebellar hemorrhage and massive hemispheric or cerebellar infarction. Recovery of language has been documented after left- and right-sided supratentorial decompression.<sup>253</sup>

Between 50% and 80% of surviving children have neurological sequelae, most commonly hemiparesis.<sup>44,250,251,254–257</sup> Neurological outcome appears to be better for those with hemorrhage,<sup>252</sup> CVST,<sup>258</sup> and posterior circulation stroke.<sup>259</sup> Other problems include neuropsychological deficits,<sup>256,260</sup> poor attention,<sup>261</sup> behavioral problems,<sup>262</sup> and poor quality of life.<sup>263,264</sup> Predictors of poor neurological, cognitive, and behavioral outcome include systemic disease,<sup>254</sup> multiple risk factors,<sup>256</sup> infarct size,<sup>265</sup> cortical involvement,<sup>264,266</sup> thromboembolism,<sup>254,267</sup> and moyamoya.<sup>268,269</sup> Early evaluation of physical and cognitive disability is the key to preventing avoidable complications and to planning rehabilitation, which should involve a multidisciplinary team.<sup>270</sup> Constraint therapy may be adapted for children and appears to be associated with improved function of the hemiparetic hand.<sup>271,272</sup> Improvement occurs over a prolonged period of time, and late deterioration is rare.<sup>265</sup>

### Recommendations for Rehabilitation After a Child's Stroke

#### Class I Recommendations

1. Age-appropriate rehabilitation and therapy programs are indicated for children after a stroke (Class I, Level of Evidence C).
2. Psychological assessment to document cognitive and language deficits is useful for planning therapy and educational programs after a child's stroke (Class I, Level of Evidence C).

## Nontraumatic Hemorrhagic Stroke

### ICH in Older Children

There are numerous published case reports and small series of children with nontraumatic ICH, along with a few large retrospective case series. Recommendations to guide the treatment of spontaneous ICH in adults were recently published.<sup>273</sup> There are several large published series of individuals with specific hemorrhage risk factors such as arteriovenous malformations (AVMs), intracranial aneurysms, or hemophilia. However, there are no controlled trials to guide the treatment of hemorrhagic stroke in children. The incidence of intraparenchymal hemorrhage is presented in Epidemiology of Childhood Stroke.

Brain hemorrhage in older children presents much like in adults, with acute headache, vomiting, and rapid deterioration of neurological function. However, the presentation may be subtler in younger children unless the hemorrhage involves the motor pathways or brainstem. In a series of 68 children with nontraumatic intraparenchymal brain hemorrhage, 40 children (58.8%) presented with headache or vomiting, and 6 others (8.8%) presented with irritability.<sup>274</sup> Focal or generalized seizures occurred in 25 individuals (36.8%), whereas hemiparesis occurred in only 11 patients (16.2%) and coma occurred in only 2 children (2.9%).<sup>274</sup>

### Hemorrhage in Infants and Term Neonates

The signs and symptoms of an ICH can be more subtle and less specific in infants and neonates than in older children, especially with smaller hemorrhages.<sup>275</sup> Consequently, it is likely that some smaller hemorrhages in neonates go unrecognized.

A term newborn with an intraparenchymal hemorrhage is less likely to have an identifiable cause for the hemorrhage than older children.<sup>33</sup> Additionally, a few clinical situations are distinct to infants and neonates. Some infants whose mothers took warfarin, phenytoin, or barbiturates during pregnancy bleed excessively owing to a reduction in vitamin K–dependent coagulation factors. These babies require a higher dose of vitamin K after birth to prevent bleeding; vitamins during the last trimester of pregnancy may also be of value. The clinical presentation of an AVM or arteriovenous fistula varies with age. Symptomatic neonates, for example, frequently present with unexplained high-output cardiac failure, and these neonates tend to fare much worse than individuals presenting later.<sup>276</sup> Older children and adolescents present much like adults, with seizures or ICH, whereas some infants develop hydrocephalus, particularly when a posterior

fossa lesion results in aneurysmal dilatation of the vein of Galen and aqueductal compression.

### Risk Factors for ICH

There are many possible causes of nontraumatic ICH, and  $\geq 1$  risk factors usually can be identified if a complete evaluation is done. A study of nontraumatic hemorrhage in children found at least 1 potential cause for the hemorrhage in 61 of 68 children (89.7%). These authors failed to identify a risk factor in only 1 of the 35 children whose evaluation included standard cerebral angiography.<sup>274</sup> The authors found an AVM or arteriovenous fistula in 23 of 68 children (32.4%). Altogether, 29 children (42.6%) had some type of vascular anomaly (arterial aneurysm, cavernous malformation, AVM, or arteriovenous fistula). Similarly, Meyer-Heim and Boltshauser<sup>275</sup> identified an AVM in 16 of the 34 children (47%) in their study with nontraumatic ICH.

Hematologic and coagulation disorders together accounted for 18 of the 68 children in the Al-Jarallah et al<sup>274</sup> series. Thrombocytopenia was present in 8 children (11.8%): 5 had thrombocytopenia resulting from cancer chemotherapy, 2 had isoimmune thrombocytopenia, and 1 had thrombocytopenia-absent radius syndrome. Three children with SCD had an ICH, clearly in 1 instance as a result of a hemorrhagic infarction.<sup>274</sup> In younger children with SCD, SAH probably stems from vascular fragility caused by the disease, but a significant number of adolescents and adults with SAH have an aneurysm or AVM and should be thoroughly evaluated for other causes.<sup>277</sup>

Ten children (14.7%) in the above series also had congenital or acquired coagulation defects.<sup>274</sup> Factor VIII deficiency occurred in 3 children, and a coagulopathy caused by hepatic failure occurred in 2 others. One child in this series had factor XIII deficiency; another 3-month-old boy had a subdural and intraparenchymal hemorrhage secondary to congenital vitamin K deficiency; and 1 child's hemorrhage was attributed to warfarin therapy. Two other children had deficiencies of protein C and protein S and may have had a hemorrhagic infarction.

The severity of the thrombocytopenia or coagulation deficiencies correlates with the risk of intraparenchymal hemorrhage. Even among patients with a given disorder, it is often the severity of the bleeding tendency rather than the specific defect that determines the risk of ICH. In the absence of trauma, the risk of ICH from thrombocytopenia is low as long as the platelet count remains above 20 000 mm<sup>3</sup>. Similarly, more severe coagulation deficiencies are more likely to cause ICH than milder deficiencies independently of the specific deficiency.<sup>278,279</sup> Of the 71 patients with a hemophilia and ICH reported by Eyster and associates,<sup>280</sup> all but 4 had severe or moderately severe ( $\leq 5\%$  of normal factor VIII activity) disease. In a prospective study of head trauma in hemophilia, 6 of 7 patients with ICH had a history of trauma.<sup>281</sup> Spontaneous hemorrhage appears more likely to occur with severe factor deficiency, whereas with milder deficiency, the bleeding must be initiated by trauma.<sup>279,282–284</sup>

Nine of 68 children (13.2%) presenting with intraparenchymal brain hemorrhage bled into the region of a brain tumor.<sup>274</sup> Although the correct diagnosis of brain tumor was

made in each case after the completion of imaging studies, the clinical presentation and initial radiographic evaluation in these children first suggested a primary brain hemorrhage. Various histological types of malignant brain tumors were found, but the tumors typically were highly malignant.

In sharp contrast to adults, systemic arterial hypertension is not a common cause of brain hemorrhage in children. Although a few of the 68 children in the Al-Jarallah et al<sup>274</sup> series had slightly elevated systemic blood pressure at presentation, none had a history of long-standing arterial hypertension or a markedly elevated blood pressure at the time of presentation. Similarly, an older autopsy series found only 1 individual with systemic hypertension among 26 patients <20 years of age with brain hemorrhage.<sup>285</sup>

Sinovenous thrombosis may be associated with intracerebral hemorrhage or SAH.<sup>6</sup> Sinovenous thrombosis is most easily excluded with MRV, although CVST can sometimes be identified with standard MRI. CVST can be suspected with CT, especially when the sagittal sinus is affected, but MRV is superior.

### Aneurysms in Children

Symptomatic intracranial aneurysms are relatively uncommon in children. One report identified 58 individuals <19 years of age among 3000 individuals (1.9%) with a ruptured intracranial aneurysm.<sup>286</sup> Presentation during childhood and adolescence is biphasic, with symptom onset most often before 2 or after 10 years of age.<sup>287</sup> However, ruptured intracranial aneurysms have been described even in newborns.<sup>288,289</sup>

Most children with an intracranial aneurysm present with SAH, although fewer children than adults present with SAH.<sup>290</sup> In 1 report of children <1 year of age, 27% of 131 children presented in some other fashion.<sup>291</sup> Some children present with ICH or IVH rather than SAH. An infectious (mycotic) aneurysm is especially likely to cause ICH.

Most aneurysms in children are saccular lesions that develop at the branch points of major intracranial arteries. Compared with adults, children are more likely to have giant aneurysms and posterior circulation involvement and less likely to have aneurysms of the anterior communicating and posterior communicating arteries.<sup>290–293</sup> About 5% of children with an intracranial aneurysm have >1 aneurysm, whereas up to 20% of adults have multiple lesions.<sup>294</sup> The likelihood of a child developing additional aneurysms in later life is unknown.

Some adult studies suggest that avoiding nicotine and maintaining a normal systemic blood pressure could reduce the likelihood of intracranial aneurysm rupture.<sup>295,296</sup> Given that tobacco use and poor dietary habits often begin during childhood and adolescence, it is reasonable to discourage young people from adopting unhealthy habits.

### Disorders Associated With Intracranial Aneurysm

Various congenital and hereditary conditions increase the risk of intracranial aneurysm. The most common of these conditions are coarctation of the aorta, autosomal-dominant polycystic kidney disease, and FMD. Intracranial aneurysms also

occur with Ehlers-Danlos syndrome, primarily with type IV, and with pseudoxanthoma elasticum.

The occurrence of cerebral aneurysms in patients with coarctation of the aorta has been appreciated for many years. Fortunately, most patients with aortic coarctation do not develop an aneurysm. In 1 summary of 200 patients with aortic coarctation, only 3 patients with definite and 2 patients with probable cerebral aneurysm were identified.<sup>297</sup> The actual incidence of cerebral aneurysm in individuals with coarctation is probably higher than this because some of these patients were still young and others might have had asymptomatic lesions. Intracranial aneurysms in these patients typically do not become symptomatic until adolescence or adulthood; the average age for rupture of the aneurysm is 25 years.<sup>297</sup>

The association of autosomal-dominant polycystic kidney disease and intracranial aneurysm also is well recognized. In most instances, the aneurysm does not cause symptoms until after the second decade,<sup>298,299</sup> although unruptured aneurysms have been identified in babies with polycystic kidney disease.<sup>300</sup> In 1 series of 58 individuals with an intracranial aneurysm who were <20 years of age, only 2 had polycystic kidney disease and 7 patients had coarctation of the aorta.<sup>286</sup>

Although intracranial aneurysm occurs with increased frequency among individuals with FMD, most often the aneurysms do not become symptomatic until the patient reaches adulthood. In 1 series of 37 FMD patients, 19 (51%) had  $\geq 1$  intracranial aneurysms.<sup>301</sup> The frequency of aneurysm detection was lower in other series. There were 13 individuals (30%) with an intracranial aneurysm among 44 FMD patients in 1 report, but only 6 of the 13 had ruptured.<sup>302</sup> Another series identified 10 patients with an intracranial aneurysm among 25 FMD patients.<sup>303</sup> The precise risk of intracranial aneurysm in individuals with FMD is uncertain. Although case series like these are clearly subject to ascertainment bias, they illustrate the common occurrence of unruptured intracranial aneurysms; furthermore, most individuals with FMD are not subjected to angiography.

Most individuals with an intracranial aneurysm associated with Ehlers-Danlos syndrome have Ehlers-Danlos syndrome type IV, a dominantly inherited defect in the synthesis of type III collagen. Type III collagen constitutes the primary form of collagen in blood vessels.<sup>304</sup> Diagnosis of Ehlers-Danlos syndrome type IV depends on recognition of the typical clinical findings and demonstration of defective synthesis of type III collagen. Intracranial aneurysms also occur occasionally with Ehlers-Danlos syndrome type I<sup>305</sup> and Ehlers-Danlos syndrome type VI.<sup>306</sup> The distal portion of the ICA is the most common site for an intracranial aneurysm caused by Ehlers-Danlos syndrome.

Intracranial aneurysms occasionally occur in individuals with pseudoxanthoma elasticum. Like Ehlers-Danlos syndrome, the intracranial portion of the ICA is a common site for these aneurysms.<sup>307</sup> Likewise, aneurysms resulting from pseudoxanthoma elasticum typically present in adulthood. Marfan syndrome is often mentioned as a risk factor for aneurysm, but in fact, intracranial aneurysms are much less common than aortic aneurysms in these patients with Marfan syndrome. Several giant intracranial aneurysms have been

reported in Marfan patients,<sup>308–310</sup> and as with Ehlers-Danlos syndrome type IV and pseudoxanthoma elasticum, these lesions tend to affect the intracranial portion of the ICA.

Related individuals with an intracranial aneurysm are common.<sup>311–315</sup> Although individuals with a familial aneurysm remain asymptomatic until adulthood,<sup>316–319</sup> 2 children in 1 family developed SAH from a ruptured aneurysm.<sup>320</sup> Siblings of individuals with an intracranial aneurysm have more risk of developing an aneurysm than other family members.<sup>321</sup> One study found a 4-fold increase in the prevalence of intracranial aneurysms among first-degree relatives of aneurysm patients, but many of these individuals remained asymptomatic at the time of publication, and most of the individuals were adults, not children.<sup>322</sup> Although genetic factors increase the risk of developing an intracranial aneurysm in some families, there is no obvious mendelian inheritance pattern.<sup>323</sup> Similarly, familial aneurysms probably do not result from a single gene mutation because familial aneurysms have been linked to chromosome 19q13.3 in some families and to 7q11 in others.<sup>324,325</sup>

#### ***Follow-Up of Patients at Risk for Intracranial Aneurysm***

Rational evaluation of individuals with conditions predisposing to intracranial aneurysms can be problematic. Although only a portion of the individuals with these underlying disorders actually develop an aneurysm, the seriousness of a ruptured intracranial aneurysm underscores the need for early identification and treatment. Depending on the likely aneurysm risk associated with a given condition, it may be reasonable to screen an individual every 1 to 5 years with MRA. Although MRA is less reliable than CA for the detection of smaller aneurysms, it should be a reasonable screening tool for disorders like Ehlers-Danlos syndrome in which the ICA is often the site of aneurysm formation and the risk of CA is high. The ionizing radiation of CTA makes it a less appealing option for repeated surveillance imaging over a lifetime. In many cases, the aneurysm does not cause symptoms until adulthood, so screening would seem to gain importance as the individual matures. Although MRA is currently less reliable than CA, it is probably a better option than repeated CA in an asymptomatic individual.<sup>326</sup> Experience with CTA in children is limited, so its reliability remains uncertain. In individuals with symptoms or with questionable MRA or CTA findings, CA is appropriate.

#### ***Infective Aneurysms***

An SAH or intracerebral hemorrhage among individuals with structural heart lesions, chronic pulmonary infections, or prior intravenous drug abuse should suggest an infection-related aneurysm. Infective aneurysms in children occur most often in individuals with infective endocarditis resulting from congenital or rheumatic heart disease.<sup>327,328</sup> Fortunately, these aneurysms have become less common with the decreased incidence of rheumatic heart disease and with earlier recognition and treatment of endocarditis.<sup>329</sup> Most infective aneurysms result from bacterial infection, but fungal aneurysms may occur in immunocompromised patients and occasionally in conjunction with sinusitis.<sup>329–331</sup> A few patients have septic emboli arising from the lungs, and others have posttraumatic

meningitis.<sup>330,332</sup> One report identified 2 children with cerebral aneurysm among 250 children with human immunodeficiency virus, although neither child developed symptoms from the aneurysm.<sup>333</sup>

Because these aneurysms result from arterial damage caused by an infective embolus,<sup>328</sup> they tend to develop more distally in the cerebral vasculature than do saccular aneurysms. These aneurysms are often multiple and often cause ICH and SAH.

#### **Treatment of Intracranial Aneurysms in Children**

A complete discussion of the treatment of arterial aneurysms in children is beyond the scope of this article, but in general, the therapeutic approach used in children mirrors that used in adult aneurysm patients. Both microsurgical and endovascular techniques have been used effectively in children with intracranial aneurysms.<sup>290,292,334</sup> There is some concern that endovascular aneurysm occlusion might not provide the same long-lasting protection from rupture as a direct approach, but so far this fear has not been realized.<sup>290</sup>

For children who survive to reach medical attention, the main factors that determine survival and functional outcome are rebleeding before surgery can be done and the clinical stage at the time of presentation.<sup>293</sup> Even among younger children with an intracranial aneurysm, the outcome after treatment is equal to or better than that of adult patients.<sup>291</sup>

Aside from supportive care after an acute hemorrhage, there is little role for medical treatment. One possible exception to this rule is an infectious aneurysm, which sometimes resolves as the underlying infection is treated.

#### **Vascular Anomalies in Children**

In large series of children with spontaneous ICH, congenital vascular lesions were collectively the most common reason for bleeding, accounting for >40% of the affected children.<sup>274</sup> Congenital vascular anomalies in children include venous angiomas, capillary telangiectasias, cavernous malformations, and AVMs. Capillary telangiectasias are collections of dilated ectatic capillaries with normal intervening neural tissue and without smooth muscle or elastic fibers. These lesions are seldom associated with ICH. The risk of bleeding in individuals with venous angiomas is  $\approx 0.15\%$  per year,<sup>335</sup> but even this low number may be too high because many individuals with ICH adjacent to a venous angioma also have a nearby AVM or cavernous malformation that may have actually caused the hemorrhage. Cavernous malformations and AVMs, in contrast, carry a substantial risk of hemorrhagic stroke and are presented in more detail.

#### **Arteriovenous Malformations**

Data on the prevalence of AVM and incidence of AVM hemorrhage are scanty and are derived from studies of adults and children. In the New York Islands population-based study of all ages from 2000, the annual AVM detection rate was 1.34 per 100 000 person-years (95% CI, 1.18 to 1.49).<sup>336</sup> The incidence of first-time AVM-related hemorrhage was 0.51 per 100 000 person-years, and the estimated prevalence of AVM hemorrhage among detected cases was 0.68 per 100 000 (95% CI, 0.57 to 0.79). In a Western Australian

population-based study, the first bleed was fatal in 4.6%.<sup>337</sup> An estimated 20% of cerebral AVMs are diagnosed during infancy and childhood.<sup>338</sup>

Al-Jarallah et al<sup>274</sup> found an AVM or arteriovenous fistula in 23 of 68 (32.4%) children; altogether, 29 children (42.6%) in this series had some type of vascular anomaly (arterial aneurysm, cavernous malformation, AVM, or arteriovenous fistula). Similarly, Meyer-Heim and Boltshauser<sup>275</sup> identified an AVM in 16 of the 34 children (47%) in their report of nontraumatic ICH. More than three fourths of the AVMs that become symptomatic in children present with hemorrhage,<sup>338–340</sup> typically in the supratentorial region, where 80% of the AVMs occur.<sup>339,341</sup> In the remaining children, the AVM is discovered during an evaluation for seizures, headaches, and focal neurological deficits that are not due to an obvious hemorrhage. Occasionally, individuals present with isolated intracranial hypertension that mimics pseudotumor cerebri.<sup>342</sup> Symptomatic neonates often have unexplained high-output cardiac failure, and these neonates tend to fare much worse than individuals presenting later.<sup>276</sup> Some infants develop hydrocephalus, particularly when a posterior fossa lesion results in aneurysmal dilatation of the vein of Galen and aqueductal compression.

Hereditary hemorrhagic telangiectasia should be considered in patients with multiple AVMs of the nervous system.<sup>343–346</sup> Familial AVMs also have been described in families without a specific genetic condition that features vascular lesions.<sup>347</sup> AVMs also have been inconsistently described as a feature of various other genetic conditions. Multiple AVMs in the same individual are relatively common. The occurrence of an aneurysm and an AVM in the same individual is more common in children than in adults.<sup>341</sup>

Establishing the cause of the bleeding is important because the cause affects the treatment approach, the prognosis, and the stroke recurrence risk. Generally,  $\geq 1$  possible risk factors for hemorrhage can be identified if a thorough diagnostic evaluation is completed. Al-Jarallah et al,<sup>274</sup> for example, found at least 1 potential cause for the hemorrhage in 61 of 68 children (89.7%), and they failed to identify a risk factor in only 1 of the 35 children whose evaluation included CA. In about half of children presenting with hemorrhagic stroke, the underlying diagnosis may be clear on parenchymal imaging or on MRA.<sup>348</sup> Given the potential prognostic and therapeutic implications of identifying an AVM or other structural vascular lesion, CA should be considered in individuals with an unexplained ICH.

In children with known AVMs, the estimated annual hemorrhage risk is 2% to 4%; in a quarter of the patients, the hemorrhage is fatal.<sup>339,349</sup> The annual risk of hemorrhage for patients presenting in childhood is lower than for those presenting as adults,<sup>340</sup> but children with an AVM have a substantial cumulative risk given their additional years of life expectancy.<sup>350</sup> The likelihood and timing of rebleeding vary with the cause of the hemorrhage. Recurrent bleeding is uncommon in children with idiopathic hemorrhagic stroke, but there is a 13% recurrence risk for individuals with medical disorders and structural vascular lesions. Rebleeding in children with hemorrhage caused by underlying medical conditions tends to develop soon after the initial stroke,

whereas children with untreated structural vascular lesions have a risk exposure extending over many years and thus may have a greater lifetime risk of rebleeding.<sup>350</sup>

Years of cumulative risk in a child with an AVM make complete obliteration of the lesion very desirable. A thorough review of the treatment of AVMs in children is beyond the scope of this review, but in general, the treatment options in children with an AVM are similar to the methods used in adults. Endovascular embolization, microsurgical obliteration, and stereotactic radiotherapy have all been used to treat AVMs in children,<sup>351</sup> and there is some evidence that the outcome of therapy is better in children than in adults.<sup>352</sup> The treatment modalities are sometimes combined, as when embolization is performed to reduce the amount of flow through the lesion before surgery.<sup>353</sup> Recurrent hemorrhage after an apparently complete AVM obliteration occurs occasionally and may be more common in children,<sup>354</sup> suggesting the need for the patients to be followed up after treatment.<sup>355</sup>

#### *Cavernous Malformations*

Cavernous malformations are circumscribed vascular lesions with thin-walled sinusoidal spaces lined with endothelial tissue and containing intravascular or intervascular calcifications without intervening parenchymal tissue. These lesions can occur throughout the brain and even the spinal cord. Hemorrhage is the most serious complication of cavernous malformations, but many individuals remain asymptomatic, and others present with seizures, focal neurological deficit, or isolated headache. The feeding arteries and draining veins are of normal caliber, and there is no arteriovenous shunting, so bleeding tends to be less dramatic than with an AVM. More deeply situated cavernous malformations are more likely to bleed than superficial lesions.

Multiple cavernous malformations have been identified in 13% of sporadic cases and 50% of familial cases.<sup>356</sup> Genetic analysis of families with multiple cavernous malformations has identified mutations of at least 3 genes: *CCM1* (KRIT1) at 7q21-q22, *CCM2* (MGC4607) at 7p15-p13, and *CCM3* (PDCD10) at 3q25.2-q27.<sup>357–360</sup> These 3 genes account for up to 75% of the affected families, so there could be additional disease-causing genes. The exact functions of the 3 genes are not yet well understood.

Cavernous malformations often increase in size over time, probably because of repeated episodes of hemorrhage with subsequent tissue fibrosis and calcification.<sup>361</sup> Bleeding and the residual hemosiderin deposition are responsible for the characteristic “bull’s-eye” appearance of a cavernous malformation on MRI. In the absence of this pattern, these lesions may be difficult to recognize, and it is common for individuals with 1 cavernous malformation or for previously unaffected family members to develop new lesions. MRI with T2-weighted gradient-echo sequences more reliably identifies less obvious cavernous malformations than other MRI sequences or CT.<sup>362</sup> Because of the sluggish blood flow through a cavernous malformation, the lesion may not be demonstrable at all with CA.

The risk of recurrent hemorrhage from an untreated cavernous malformation is estimated to be 4.5% per year, but the risk of bleeding from deeper lesions may be higher than the

risk from superficial lesions. Intracranial cavernous malformations have been treated with both microsurgery and stereotactic radiosurgery with good results.<sup>363</sup>

#### *Diagnostic Evaluation for ICH*

Many of the conditions that promote ICH, if untreated, can lead to additional episodes of bleeding, so identification and treatment of these risk factors can reduce the likelihood of subsequent death or disability from recurrent hemorrhage. Thus, a thorough evaluation for hematologic disorders, coagulation defects, and other risk factor disorders is appropriate. The diagnostic techniques that enable us to confirm an ICH and sometimes to identify the underlying vascular abnormality that caused it are discussed in more detail in Diagnostic Evaluation of Children With Stroke.

Given the frequency of congenital vascular lesions in children with ICH, the risk of rebleeding from such lesions, and the potential benefit from treatment, it is reasonable to perform a 4-vessel CA when a child has an unexplained ICH. Some children have >1 risk factor, and the benefit of discovering a treatable vascular anomaly must be weighed against the risk of the procedure. A common approach is to complete the noninvasive portions of the evaluation first, avoiding angiography when there is an obvious and adequate explanation for a hemorrhage.

#### *Treatment of Hemorrhagic Stroke*

Management options for children with nontraumatic ICH fall into 3 categories: general efforts to stabilize the patient, measures to reduce the risk of rebleeding, and attempts to treat the hemorrhage itself. Stabilizing measures include optimizing the respiratory effort, controlling systemic hypertension, preventing epileptic seizures, and medically managing increased intracranial pressure. Additionally, individuals with SAH may benefit from control of vasospasm.

There is no compelling evidence that surgical evacuation of a supratentorial intraparenchymal hematoma is beneficial at any age.<sup>364,365</sup> Mendelow and colleagues<sup>366</sup> found no benefit from early (<24 hours) hematoma evacuation in a randomized trial of 1033 adults with nontraumatic supratentorial hemorrhage. A smaller study investigating earlier (<4 hours) surgery was halted after rebleeding occurred in 4 of 11 individuals who had early hematoma evacuation.<sup>367</sup> There is anecdotal evidence that hematoma evacuation may alleviate impending brain herniation in selected individuals. Such surgery is most likely to be beneficial for hemorrhages in the cerebellum and for individuals with large lesions in the cerebral hemisphere.<sup>368</sup>

Correction of treatable hemorrhage risk factors should reduce the likelihood of additional bleeding, although in some instances, definitive therapy may have to wait until the patient’s condition stabilizes. Surgical or endovascular obliteration of aneurysms and AVMs is effective for many individuals, but radiosurgery is being used increasingly in children with AVMs that are small or difficult to approach surgically. Several large retrospective studies have reported that radiosurgery is safe and evidently effective for the treatment of children with an AVM.<sup>369–372</sup> A full discussion of the treatment options for AVMs and aneurysms in children

is beyond the scope of this article, but most of the earlier analyses of the management of unruptured intracranial aneurysms and intracranial AVMs may apply to both children and adults.<sup>16,373</sup>

Treatment of coagulation defects and hematologic disorders should reduce the risk of subsequent hemorrhage. Brain hemorrhage is rare with platelet counts  $>20\,000\text{ mm}^3$ . Even with lower platelet counts, spontaneous ICH is uncommon in the absence of trauma. Brain hemorrhage later in the course of acquired isoimmune thrombocytopenia often coincides with a systemic viral infection, probably because the infection stimulates increased production of antiplatelet antibodies and thus a drop in the platelet count. Individuals with thrombocytopenia should avoid aspirin or other antiplatelet drugs, as well as situations that seem likely to produce head trauma. Likewise, factor VII administration can prevent or minimize intracranial traumatic hemorrhage in children with severe factor VII deficiency.

#### *Recommendations for Evaluation and Treatment of Hemorrhage in Children*

##### *Class I Recommendations*

1. Children with nontraumatic brain hemorrhage should undergo a thorough risk factor evaluation, including standard cerebral angiography when noninvasive tests have failed to establish an origin, in an effort to identify treatable risk factors before another hemorrhage occurs (Class I, Level of Evidence C).
2. Children with a severe coagulation factor deficiency should receive appropriate factor replacement therapy, and children with less severe factor deficiency should receive factor replacement after trauma (Class I, Level of Evidence A).
3. Given the risk of repeat hemorrhage from congenital vascular anomalies, these lesions should be identified and corrected whenever it is clinically feasible. Similarly, other treatable hemorrhage risk factors should be corrected (Class I, Level of Evidence C).
4. Stabilizing measures in patients with brain hemorrhage should include optimizing the respiratory effort, controlling systemic hypertension, controlling epileptic seizures, and managing increased intracranial pressure (Class I, Level of Evidence C).

##### *Class II Recommendations*

1. It is reasonable to follow up asymptomatic individuals who have a condition that predisposes them to intracranial aneurysms with a cranial MRA every 1 to 5 years, depending on the perceived level of risk posed by an underlying condition (Class IIa, Level of Evidence C). Should the individual develop symptoms that could be explained by an aneurysm, CTA or CA may be considered even if the patient's MRA fails to show evidence of an aneurysm (Class IIb, Level of Evidence C). Given the possible need for repeated studies over a period of years, CTA may be preferable to CA for screening individuals at risk for aneurysm (Class IIb, Level of Evidence C).

2. Individuals with SAH may benefit from measures to control cerebral vasospasm (Class IIb, Level of Evidence C).

##### *Class III Recommendations*

1. Surgical evacuation of a supratentorial intracerebral hematoma is not recommended for most patients (Class III, Level of Evidence C). However, information from small numbers of patients suggests that surgery may help selected individuals with developing brain herniation or extremely elevated intracranial pressure.
2. Although there is strong evidence to support the use of periodic blood transfusions in individuals with SCD who are at high risk for ischemic infarction (see Sick Cell Disease), there are no data to indicate that periodic transfusions reduce the risk of ICH caused by SCD (Class III, Level of Evidence B).

## **Sinovenous Thrombosis**

### **Cerebral Venous Sinus Thrombosis in Children**

#### *Clinical Setting of CVST*

The clinical manifestations of CVST in children are at times nonspecific and subtle.<sup>374</sup> Presentation with seizures, increased intracranial pressure,<sup>375</sup> and headache<sup>376</sup> has been well documented. Some children develop hydrocephalus,<sup>377</sup> subdural effusion or hematoma,<sup>378</sup> SAH,<sup>379</sup> or ICH or infarction.<sup>6</sup>

Various underlying conditions have been described in children with CVST (Table 8).<sup>4–6,31,54,380</sup> Many children have multiple risk factors.<sup>4–6,31,54</sup> Although the incidence of intracranial septic venous thrombosis has decreased, recent studies suggest that infection is still responsible for many CVSTs in older children.<sup>6,31,54</sup> Illnesses such as otitis media, meningitis,<sup>381</sup> and diabetic ketoacidosis<sup>382</sup> may be complicated by CVST. L-Asparaginase therapy, used primarily in children with leukemia, may result in CVST.<sup>383</sup> Of less certain significance are chronic illnesses such as inflammatory bowel disease,<sup>2,384</sup> systemic lupus erythematosus,<sup>385</sup> thyrotoxicosis,<sup>386</sup> nephrotic syndrome,<sup>387</sup> and gastroenteritis, which may increase the likelihood of CVST, especially in conjunction with dehydration.

CVST also may occur in the context of chronic hemolytic anemia,<sup>388</sup>  $\beta$ -thalassemia major,<sup>389</sup> and SCD.<sup>6,390–393</sup> Iron-deficiency anemia and microcytosis have been described in children with CVST,<sup>6,382,387,394–396</sup> sometimes in association with thrombocytosis. Anemia may be obscured by relative hemoconcentration in the acute phase, and ferritin may be an acute-phase protein, so it is reasonable to thoroughly evaluate for iron deficiency.

#### *Prothrombotic Disorders and CVST in Children*

Prothrombotic disorders are found in one third to two thirds of children with CVST.<sup>4–6,397</sup> Hereditary defects account for most prothrombotic states in children, but a few individuals have acquired deficiencies of protein C, protein S, or antithrombin (Table 3). Occasionally, infants with homozygous protein C deficiency develop severe dysfunction from widespread thromboses.<sup>398,399</sup> Elevated factor VIII levels also have

**Table 8. Disorders Reported With Cerebral Venous Sinus Thrombosis in Children**

General
Dehydration
Hypoxia (eg, poststrangulation)
Post lumbar puncture
Inflammatory bowel disease
Ulcerative colitis
Crohn disease
Systemic diseases
Systemic lupus erythematosus
Thyrotoxicosis
Behçet's disease
Anemias
Iron deficiency anemia
Sickle cell disease
Thalassemia
Autoimmune hemolytic anemia
Paroxysmal nocturnal hemoglobinuria
Malignancies and their treatment
Leukemia (asparaginase, steroids)
Lymphoma
Cardiac disease
Cyanotic congenital heart disease
Postoperative
Postcatheterization
Renal disease
Nephrotic syndrome
Chromosomal disorders
Down syndrome
Head and neck infections
Meningitis (eg, Pneumococcus), tuberculous
Mastoiditis
Ear infections
Tonsillitis
Sinusitis
Other head and neck disorders
Head injury
Brain tumor
Multiple sclerosis
Hydrocephalus (with or without shunt)
Metabolic conditions
Homocystinuria
Drugs
L-Asparaginase
Oral contraceptives
Corticosteroids
Epoetin alfa

been reported.<sup>6,400</sup> The importance of genetic polymorphisms is still debated and may be somewhat defect specific.<sup>400–403</sup> Researchers,<sup>5,404,405</sup> including Kenet et al,<sup>406</sup> noted that the presence of a *G20210A* mutation predicts recurrent thrombo-

sis in children with CVST, but the influence of other underlying prothrombotic states on the recurrent stroke risk is less clear.

Patients with homocystinuria and homozygotes for the thermolabile variant of the MTHFR gene may have some increased risk of CVST.<sup>403</sup> Hyperhomocysteinemia, shown to be a risk factor in 2 case-control series in adults,<sup>407,408</sup> and its genetic determinants may be worth excluding or treating with folic acid and/or B<sub>6</sub> and B<sub>12</sub> vitamin supplementation because this treatment has few risks. However, further studies are required to ascertain the role of these conditions, if any, among children with CVST.

### Neuroimaging in CVST

With a few exceptions, the neuroimaging findings of CVST are similar in children and adults. Neuroimaging studies are presented in more detail in Diagnostic Evaluation of Children With Stroke. It is important to study the patient early because occluded venous sinuses commonly recanalize.<sup>409</sup> Unenhanced CT scans may detect deep vein thrombosis as linear densities in the deep and cortical veins.<sup>410</sup> As the thrombus becomes less dense, contrast-enhanced CT may demonstrate the “empty delta” sign, a filling defect, in the posterior part of the sagittal sinus.<sup>4,410</sup> As Davies and Slavotinek<sup>411</sup> pointed out, however, the empty delta sign can be falsely positive in children, and CVST can be missed in up to 40% of patients.<sup>4,54,412</sup>

Diffusion and perfusion MRI detect venous congestion in CVST and help to differentiate cytotoxic and vasogenic edema.<sup>413</sup> CT venography and MRI with MRV are now the preferred methods for investigating CVST.<sup>6,412,414</sup> On MRI during the subacute phase, the thrombus generates a high signal on T1-weighted sequences. In the acute phase, the thrombus creates an isointense signal on T1-weighted imaging and a low-intensity signal on T2-weighted imaging. This pattern can be mistaken for flowing blood, but MRV will confirm an absence of flow in the thrombosed sinus. T2\* MRI appears to be more sensitive than T1- or T2-weighted or fluid-attenuated inversion recovery imaging in demonstrating CVST and associated hemorrhage.<sup>415</sup> However, MRI and MRV are techniques prone to flow artifacts, and in equivocal cases, particularly if deep venous infarction or cortical venous thrombosis is suspected, an endoluminal technique such as high-resolution CT venography or digital subtraction angiography may be required as a final arbiter.

### Treatment of CVST in Children

Treatment of CVST includes supportive or symptomatic measures such as hydration, appropriate antimicrobials, control of seizures with anticonvulsants, and control of intracranial pressure.<sup>380</sup> A randomized, placebo-controlled trial of UFH in adults was stopped early because there was clear evidence of benefit from heparin, particularly in terms of mortality.<sup>416</sup> A randomized, placebo-controlled trial of subcutaneous LMWH in adults showed a trend for better outcome in the treated group,<sup>417</sup> but the mortality was lower in this series, and there were more patients with milder presentations in the placebo arm. On the basis of these limited data, a Cochrane review concluded that anticoagulation with hep-

arin was safe and that there was some evidence of a clinically important benefit.<sup>418</sup>

Case reports and small multicenter series in children<sup>6,58,405,412</sup> suggest that anticoagulation can be safely administered to children, especially if activated partial thromboplastin time for intravenous UFH or anti-factor Xa levels for subcutaneous LMWH are monitored. A small prospective cohort study of anticoagulant therapy in 30 children with CVST reported 3 deaths among 8 untreated children compared with no deaths among the 22 treated children.<sup>58</sup> In adult series in which individuals with ICH and CVST were anticoagulated, the benefits seemed to outweigh the risk. Sixty-five percent of the 396 children with CVST described by Kenet et al<sup>406</sup> received anticoagulants, and only 6 of the 22 individuals with recurrent thrombosis in this series were receiving anticoagulation at the time of the recurrence, suggesting that the recurrence rate among untreated children is higher than in the patients who were anticoagulated.<sup>406</sup> Nevertheless, death is relatively uncommon in this age group, and many children have apparently made a full recovery without anticoagulation.

Long-term follow-up data are scant. About half of 160 children in the Canadian Registry were treated with anticoagulants, and after a mean follow-up interval of 1.6 years, 38% had neurological deficits and 8% had died. There is currently a consensus that older children without hemorrhage should be anticoagulated (International Pediatric Stroke Study consensus). There is little information to govern the length of treatment, but the most common approach is to treat with warfarin for 3 to 6 months. Few neonates with CVST have been treated with anticoagulants, and such treatment is not recommended in neonates except perhaps in selected patients with clinical deterioration or with radiological evidence of clot propagation.

There are no randomized data on thrombolysis,<sup>419–421</sup> thrombectomy,<sup>422</sup> or surgical decompression<sup>423,424</sup> in CVST, even in adults,<sup>425</sup> but each has been used with apparent success in isolated cases or small series of seriously ill patients, including children, usually in comatose individuals or those with extensive thrombosis of superficial and deep venous structures.<sup>419–421</sup> A nonrandomized study comparing urokinase thrombolysis with heparin in adults suggested a better functional outcome for the patients undergoing thrombolysis but a higher risk of hemorrhage.<sup>426</sup> These patients have a high risk of secondary complications, including status epilepticus, hydrocephalus,<sup>426</sup> and raised intracranial pressure,<sup>427,428</sup> and may benefit from intensive care and monitoring of electroencephalography and intracranial pressure, as well as neuroimaging.

Discontinuing oral contraceptives may reduce the risk of recurrent CVST, and there are several low-risk strategies such as improving the quality of the diet that can be recommended. It would be difficult to recommend a higher-risk strategy such as prolonged oral anticoagulation after a single thrombosis.

#### **Prediction of Recurrent CVST**

Kenet et al<sup>406</sup> summarized 396 consecutive children with CVST from a multicenter database. Twenty-two of these children (6%) had recurrent thrombotic episodes during an

average 36-month follow-up interval, and in 13 of these 22 children, the recurrent thrombosis involved the intracranial vessels. The predictors of recurrent thromboses cited by Kenet et al included persistent occlusion on follow-up venous imaging, heterozygosity for the *G20210A* mutation in factor II, and the lack of anticoagulant therapy. Additionally, only children whose initial thrombosis occurred after 2 years of age had a recurrent thrombosis.<sup>406</sup>

#### **Follow-Up of Children With CVST**

Because of the risk of visual loss resulting from increased intracranial pressure in individuals with CVST,<sup>258</sup> it is reasonable to promote neurological and ophthalmological follow-up, especially during the first year. Cognitive and neurological sequelae also have been reported<sup>6,44,258,429</sup> and may require rehabilitation and longer-term therapy. Occasionally, patients with cryptogenic CVST later manifest symptoms of an underlying disease, so patients should be encouraged to report back if they have concerns after discharge.

#### **CVST in Neonates**

##### **Long-Term Sequelae**

Estimates of generalized “developmental delay” after neonatal CVST have ranged from 28%<sup>30</sup> to 58%.<sup>31</sup> A study of 19 children with neonatal CVST reported a learning disability in 1 child (5.3%).<sup>31</sup>

An estimated 6% to 28%<sup>4,30,44</sup> of the individuals with perinatal CVST are left with cerebral palsy. Children with perinatal stroke have outcomes ranging from subtle hemiplegia to severe quadriplegia. Most children with neonatal CVST learn to walk independently, usually before 2 years of age.<sup>48</sup>

Although neonates with CVST frequently present with seizures,<sup>4,30</sup> many do not have epilepsy after the neonatal period. Estimates of the incidence of epilepsy past the neonatal period range from 6% to 20% for neonatal CVST.<sup>4,49</sup> The vascular territory affected and the degree of parenchymal involvement aid in the assessment of outcome, but these factors are not strong predictors. A study of 62 children with neonatal AIS and 25 children with neonatal CVST found that the presence of bilateral infarctions predicted a lower probability of walking over time.<sup>48</sup> Neonates with CVST without infarction have better outcomes than neonates with CVST with infarction.<sup>4,48,54</sup>

##### **Acute Management of Neonatal CVST**

Although several case reports describe thrombolysis for perinatal CVST,<sup>430,431</sup> there are insufficient data to recommend this approach outside a well-designed clinical trial. In a pilot study, LMWH was used in neonates with CVST,<sup>58</sup> and no major complications were reported. One neonate who was treated with LMWH for CVST died after having an ICH.<sup>406</sup> Case reports have described the use of antithrombin concentrate<sup>59,60</sup> and protein C concentrate<sup>61</sup> to prevent CVST in neonates with congenital or iatrogenic factor deficiencies.

##### **Chronic Management of Neonatal CVST**

It is reasonable to try to prevent dehydration and anemia, 2 known precipitants of CVST.<sup>4</sup> It also is reasonable to identify and treat underlying infections.

**Recurrence Risk of CVST in Neonates**

There are few data on the recurrence risk of CVST in neonates. In the Kenet et al<sup>406</sup> cohort of 396 children with CVST, none of the 22 individuals with recurrent thrombosis were <2 years of age at the time of the initial thrombosis, implying that the risk of CVST recurrence is low among very young children. However, additional data on the recurrence risk in different age groups are needed.

**Recommendations for Treatment of Cerebral Venous Sinus Thrombosis***Class I Recommendations*

1. Supportive measures for children with CVST should include appropriate hydration, control of epileptic seizures, and treatment of elevated intracranial pressure (Class I, Level of Evidence C).
2. Children with CVST should have a complete blood count (Class I, Level of Evidence C).
3. Children with a CVST and a suspected bacterial infection should receive appropriate antibiotics (Class I, Level of Evidence C).
4. Given the potential for visual loss owing to severe or long-standing increased intracranial pressure in children with CVST, periodic assessments of the visual fields and visual acuity should be done, and appropriate measures to control elevated intracranial pressure and its complications should be instituted (Class I, Level of Evidence C).

*Class II Recommendations*

1. Children with CVST may benefit from a thorough thrombophilic screen to identify underlying coagulation defects, some of which could affect the risk of subsequent rethromboses and influence therapeutic decisions (Class IIb, Level of Evidence B).
2. Children with CVST may benefit from investigation for underlying infections with blood cultures and sinus radiographs (Class IIb, Level of Evidence B).
3. Monitoring the intracranial pressure may be considered during the acute phase of CVST (Class IIb, Level of Evidence C).
4. It is reasonable to repeat the neuroimaging studies in children with CVST to confirm vessel recanalization or recurrence of the thrombus (Class IIa, Level of Evidence C).
5. Given the frequency of epileptic seizures in children with an acute CVST, continuous electroencephalography monitoring may be considered for individuals who are unconscious and/or mechanically ventilated (Class IIb, Level of Evidence C).
6. It is reasonable to institute either intravenous UFH or subcutaneous LMWH in children with CVST, whether or not there is secondary hemorrhage, followed by warfarin therapy for 3 to 6 months (Class IIa, Level of Evidence C). For neonatal CVST treatment, refer to the "Recommendations for Perinatal Stroke, Class II Recommendations," item 5 on page 2649.
7. In selected children with CVST, the administration of a thrombolytic agent may be considered (Class IIb, Level of Evidence C).

**Diagnostic Evaluation of Children With Stroke**

A detailed discussion of neuroimaging techniques used to identify cerebrovascular lesions is beyond the scope of this review. Children who have had a stroke should undergo vascular imaging as soon as possible. MRA is a reasonable alternative to conventional arteriography in most patients.<sup>432,433</sup> Ganesan et al<sup>432</sup> and Husson et al<sup>433</sup> found a 100% positive predictive value of MRA in arteriopathy, whereas the negative predictive value was 88%. Rollins et al<sup>434</sup> concluded that conventional arteriography is a more accurate means of imaging lesions of the distal arterial branches and lesions of the internal ICA. The yield for vascular disorders is improved with fat-saturated T1 imaging of the neck and/or venous imaging. Some conditions, including extracranial arterial dissections, particularly involving the posterior circulation, and small-vessel vasculitis, are difficult to exclude on MRA. Because the risk of recurrence is high and the risk of CA is relatively low,<sup>434</sup> CA is probably justified in these circumstances. Emergency vascular imaging should include MRV in hemorrhagic and ischemic stroke because 10% of hemorrhages in the young are secondary to CVST.

Imaging modalities used in the evaluation of children with cerebrovascular disease include cranial ultrasound and Doppler ultrasound; CT, CTA, and CT perfusion; MRI, MRA, MRV, and MR perfusion; nuclear medicine, to include SPECT and perfusion techniques and PET; and CA.

Each of these modalities has relative strengths and weaknesses that influence their usefulness in a particular situation and determine whether and when they should be used. The least invasive study that will provide an adequate assessment is usually the test to perform, but whether to do a test and the order in which a study is performed will vary with the clinical situation. For example, CT is readily available and quickly completed, and many children undergo CT soon after they arrive in an emergency room. A normal CT may adequately exclude a suspected brain hemorrhage but not a recent ischemic infarction. Similarly, an MRA study may provide a reasonable view of the intracranial arteries of a child with congenital heart disease and suspected embolism, but it might be inadequate in the assessment of a child with suspected intracranial arteritis.

**Ultrasound and Doppler Sonography**

Ultrasound is a useful method of evaluating the cerebral parenchyma in neonates and infants with open fontanels. It requires no sedation or special patient preparation and can be performed portably even on unstable infants. Coronal and sagittal views of the supratentorial brain can be achieved rapidly, but imaging of the posterior fossa is more limited.

Parenchymal ischemic injury typically appears as areas of increased echogenicity and variable degrees of mass effect. However, ultrasound is less sensitive than CT and MRI in the detection of cerebral ischemic lesions.<sup>24,435</sup> Doppler sonography shows changes in cerebral blood flow velocities in infants with moderate and severe hypoxic ischemic encephalopathy.<sup>436</sup> No deleterious bioeffects have been detected or reported in the use of transcranial ultrasound in infants.<sup>437</sup>

TCD has been used to identify children at higher risk of stroke resulting from SCD (see Sick Cell Disease for more details).<sup>438–440</sup> Cerebral arterial stenosis results in elevated flow velocity in the circle of Willis that can be detected by TCD. These TCD abnormalities correlate well with the arterial abnormalities detected by MRA.<sup>439</sup> Use of TCD to assess children with other conditions has not been adequately studied.<sup>441</sup>

Direct evaluation of cervical vessels with ultrasound has been used extensively to detect atherosclerosis in adults<sup>442,443</sup> and to gauge the success of revascularization techniques such as endarterectomy, angioplasty, and stenting. The application of such techniques in children, however, has been limited.<sup>444–446</sup>

The lack of sensitivity of cranial ultrasound in the detection of cerebral ischemia limits its overall usefulness, but limited clinical trials and general consensus indicate that transcranial ultrasound is useful for identification of parenchymal hemorrhage and IVH in neonates and gross anatomic evaluation of the cerebrum alone. In certain clinical situations, this information may be sufficient to direct care such as when a critically ill neonate is too ill to tolerate being moved outside the nursery for another test.

### **Nuclear Medicine**

SPECT uses tomographic acquisition techniques for detecting the radioactive isotope to generate planar and 3-dimensional images. Because of the short half-life and low energy of the compounds used for diagnostic nuclear medicine imaging, the actual radiation dose to any individual child is quite low. Compounds and techniques used for imaging the brain typically rely on distribution of blood flow and can reflect physiological perfusion to various brain regions. Perfusion techniques can be used to quantify relative cerebral blood volume and flow.

PET scan data are generated as planar and 3-dimensional images, and fusion techniques can be used to superimpose physiological information acquired with SPECT and PET onto anatomic data acquired with CT or MR. The availability of combined PET-CT scanners allows acquisition of data in a single procedure. Use of these techniques in children has been limited thus far.

### **Computed Tomography**

Imaging on the newer CT scanners can be completed in a matter of seconds, often reducing the need for sedation. Rapid scanning capabilities also have allowed the development of CTA and CT perfusion techniques to assess vascular anatomy and relative cerebral blood flow, volume, and transit time.<sup>447,448</sup> Appropriate timing of contrast administration can allow an assessment of arterial structures before opacification of venous structures. These data can then be reconstructed in multiple planes, and volume-rendering techniques can provide 3-dimensional images of osseous and vascular structures.

CT uses ionizing radiation, a particular concern for children because recent studies have demonstrated a relative increased lifetime cancer risk even with low radiation

doses.<sup>449</sup> There is a small but finite incidence of adverse reaction to intravenous administration of contrast agents, and compromised renal function can limit the volume of contrast that can be administered safely. Contrast administered for CTA studies may limit the volume of contrast that can be safely administered in subsequent CA.

Unenhanced CT is a sensitive means of detecting ICH, and abnormal CT findings have been identified <6 hours after onset of symptoms from AIS, although CT findings also may be absent at this early stage. Although CVST is sometimes evident on CT, these lesions are more reliably identified with MRI and MRV. The sensitivity and specificity of CT findings have not been validated for children, but the general consensus of expert opinion supports the application of these findings in the pediatric population. In the neonate, the normally occurring high hematocrit can result in increased attenuation of normal cerebral vessels, and this finding can be misinterpreted as a vessel thrombosis.

CTA studies rely on the complete opacification of the vascular lumen by intravenously administered contrast material during image acquisition. Image quality depends on slice thickness, absence of motion, timing of contrast administration, and the technological specifications of the scanner itself. Although the velocity of blood flow can affect the timing of venous opacification during a CTA acquisition, it does not degrade the image quality to the degree seen with MRA. Proximity of vessels to osseous structures can hamper the demonstration of the cerebral vasculature in an angiogram-like projection. Although inherent spatial resolution of CTA studies is high, evaluation of distal cerebral arterial branches is limited relative to CA. The thin-slice profile necessary for high-quality CTA studies also results in a larger radiation dose than standard CT studies.

CT perfusion studies rely on rapid analysis of voxel attenuation measurements over the time period of a bolus injection of contrast material. CT also can be used to assess cerebral perfusion with inhaled stable xenon. These methods allow the calculation of relative cerebral blood flow and blood volume in the analyzed volume of tissue.<sup>447,448</sup> Because the same volume of tissue is evaluated multiple times during the analysis, the cumulative radiation dose is higher than with standard CT imaging techniques or CTA.<sup>450,451</sup> These techniques have not been studied adequately in children.

The rapid acquisition time and ease of monitoring make CT the ideal imaging technique in an unstable patient or the patient in whom acute ICH is likely. Children who have cochlear implants, cardiac pacemakers, or other contraindications to MRI are best evaluated with CT. The CT evaluation of suspected stroke in a child typically begins with a standard acquisition without contrast. Adjusted settings for children based on age and size can be determined to ensure consistency of technique.<sup>452,453</sup> CTA and CT perfusion studies can be done in individuals with a suspected vascular lesion, although it may be more feasible to perform further evaluation with MR to avoid excess radiation exposure.

### **Magnetic Resonance Imaging**

MRI is the most versatile and sensitive imaging technique for identifying ischemic brain lesions, and standard MRI se-

quences can identify such abnormalities within hours of their onset.<sup>454</sup> Contrast-enhanced MRI can demonstrate abnormal enhancement of arteries, reflecting slow flow from collateral supply, within minutes of proximal arterial occlusion.<sup>455</sup> Diffusion-weighted imaging sequences can pinpoint regions of cerebral ischemia within 45 minutes.<sup>456–458</sup> Other MR sequences are highly sensitive in the detection of parenchymal hemorrhage, IVH, and SAH.<sup>459</sup> Additionally, MR perfusion techniques can quantify relative cerebral blood flow, volume, and transit time by the use of bolus administration of gadolinium-based contrast material.<sup>460,461</sup>

MRA sequences suppress the signal from stationary tissue while accentuating the signal from blood flowing. “Saturation” pulses are applied to suppress signal from blood flowing in 1 direction, allowing confident identification of blood vessels flowing in the opposite direction. Similar techniques are used for both MRA and MRV. Turbulence of flow within a blood vessel can cause relative saturation and suppression of signal, resulting in signal loss owing to moderate to severe arterial stenosis. The generally smooth caliber and high flow rates within the cervical and cerebral vessels of children typically result in high-quality MRA examinations.

MR spectroscopy uses MR pulse sequences to generate a linear spectrum of metabolite resonances that reflect tissue physiology. The variety of specific metabolites that can be detected with MR spectroscopy is limited. However, MR spectroscopy is relatively sensitive in the detection of lactate within cerebral tissue, reflecting anaerobic metabolism as a consequence of ischemia.<sup>462</sup> Multivoxel techniques can assess a relatively larger region of tissue, identifying relative differences in various metabolite concentrations in segments of the region.

Typical MRI sequences require 3 to 5 minutes each to acquire, and assessment for cerebrovascular disease takes from 15 to 35 minutes. Patient movement during image acquisition will render most sequences useless. Consequently, successful MRI requires considerable patient cooperation, and most children require sedation. Rapid imaging techniques have been developed that allow the acquisition of images in a matter of seconds. Additional techniques using multiple rephasing pulses can reduce motion artifact to negligible levels, but the reliability of these techniques in the evaluation of brain ischemia has not been determined.

Limited clinical trials and general consensus suggest that MRI is an ideal method to evaluate neonates, infants, and children with suspected cerebral ischemia. MR studies on children with suspected stroke should include sequences to delineate anatomy and to characterize focal lesions (T1, T2, fluid-attenuated inversion recovery), sequences that would detect hemorrhage (T2\* weighting), and contrast administration to identify regions of inflammation and loss of the blood-brain barrier integrity. Diffusion-weighted imaging sequences with apparent diffusion coefficient maps help to pinpoint regions of early ischemia and infarction, although a repeat imaging study after 24 hours may help to identify lesions that were not initially apparent.

In neonates, the use of MR-compatible incubators may mitigate the adverse effects of the MR environment on small infants and neonates.<sup>463</sup> Examination length and the resources

required to sedate, monitor, and care for neonates and small infants in the MR environment may limit the ability to perform the studies on short notice.

Intracranial MRA or MRV can confirm vessel patency and define the vascular anatomy. Degradation of the MRA signal by turbulent flow may lead to overestimation of pathology; further evaluation with CTA may obviate the need for CA.<sup>464</sup> Comparison of perfusion abnormalities with regions of restricted diffusion may help to distinguish regions of infarction from ischemic penumbra. MR spectroscopy can further characterize focal lesions and may contribute to the identification of infarction versus ischemic penumbra.

### Catheter Angiography

CA is an invasive procedure, but it yields more precise detail of the vascular anatomy than other imaging modalities. Digital subtraction techniques allow subtraction of overlying bone from the images, providing an unobstructed assessment of the opacified vessels. Most children require general anesthesia to undergo CA. The risk of arterial injury is greater in an uncooperative child, and the use of general anesthesia allows a more rapid and thorough examination to be performed. When performed by experienced personnel, CA has a low complication rate.<sup>465</sup> However, relatively few CA studies are performed on children in any given medical center, so few physicians have extensive experience with CA in children. Potential complications include damage to vessels at the site of vascular access (typically the femoral artery), catheter-induced dissection or perforation of the vessels of interest, thrombosis, allergic reaction to contrast, and complications from anesthesia. Although it is still the most accurate means of evaluating the cerebral vasculature, there are finite limitations to the diagnostic accuracy of CA.<sup>464,466,467</sup>

Although CA is superior to MRA and CTA for the visualization of tertiary branches and small cerebral arteries, the likelihood of identifying a larger vessel abnormality with CA in the face of a negative MRA is relatively low.<sup>433,468</sup> Vascular lesions such as malformations and aneurysms are best evaluated with CA, and diagnostic CA may be performed in conjunction with endovascular therapy to avoid multiple angiographic procedures. Vascular lesions requiring immediate surgery can be assessed rapidly with CT and CTA, possibly eliminating the need for CA and allowing more expedient surgery.

Moyamoya vascularity (see Screening Patients With Sickle Cell Disease) can be readily identified with MRA, but CA more accurately delineates the vascular anatomy before surgery and should include visualization of both the external and internal carotid arteries to assist in presurgical planning. Perfusion techniques can document baseline parameters before intervention, with postoperative studies quantifying the effects of treatment. These perfusion studies can be performed with nuclear medicine, MR perfusion, or CT perfusion. However, the utility and reliability of these methods have not been established in the pediatric population.

During the first year of life, the risk of CA is increased because of the small size of the vascular tree, so the decision to perform angiography in these younger patients must be

**Table 9. Protocol for Systemic Heparin Administration and Adjustment in Children**

Stage	aPTT, s	Dose, units/kg	Hold, min	Rate Change, %	Repeat aPTT
I. Loading dose*		75 IV over 10 min			
II. Initial maintenance dose					
Infants <1 y		28/h			
Children >1 y		20/h			
III. Adjustment†	<50	50	0	10	4 h
	50–59	0	0	10	4 h
	60–85	0	0	0	Next day
	86–95	0	0	–10	4 h
	96–120	0	30	–10	4 h
	>120	0	60	–15	4 h
IV. Obtain blood for aPTT 4 h after heparin load and 4 h after every infusion rate change					
V. When aPTT values are in therapeutic range, perform daily CBC and aPTT measurement					

aPTT indicates activated prothrombin time; CBC, complete blood count. Adapted from Michelson et al,<sup>524</sup> with permission, and the experience of the Writing Group.

\*Some physicians omit this step.

†Heparin was adjusted to maintain aPTT at 60 to 85 seconds, assuming that this reflects an anti-factor Xa level of 0.35 to 0.70.

weighed carefully.<sup>434</sup> In many instances, MRA or CTA will suffice in these patients. Diagnostic CA may need to be done in concert with therapeutic endovascular procedures even in this very young population.

### Summary of Treatment Options for Childhood Ischemic Stroke

The treatment of stroke in infants and children is both important and understudied. The issues of treatment of ischemic stroke involve both initial treatment of the acute stroke event to preserve neurological function and long-term efforts to prevent a second stroke, which occurs in 10% to 25% of children with stroke. For children with high-risk conditions such as SCD and congenital heart disease, efforts to prevent a first stroke also are important.

Two less comprehensive sets of guidelines for the treatment of ischemic stroke have been published.<sup>270,469</sup> These 2 documents are less comprehensive than the current document and offer slightly differing recommendations and dosing guidelines.<sup>470</sup>

In some situations, the treatment decisions are relatively clear, but more often the lack of randomized controlled clinical trials makes it difficult to know the best course of action. Our limited understanding of the pathophysiology of AIS and CVST in children and the relative contributions of the platelet, coagulation, and fibrinolytic systems hampers the rational selection of treatment. Thus, the current recommendations are often by necessity pulled from less rigorous studies, based on clinical experience, or derived from relevant studies of adult patients.

Although this eclectic approach provides a rational starting point, important differences remain between children and adults, not the least of which is the dose and schedule of the drugs themselves. The sections that follow assess the rationale for using various medications in children and, when possible, make recommendations for their use in children with cerebrovascular dysfunction. In addition, Tables 9

through 11 outline possible pediatric dosing schemes for UFH, LMWH, and warfarin. These 3 tables are derived from an often-fragmented literature on pediatric stroke, from studies on adult patients, and from the authors' experience with those drugs over a period of several years.

### Supportive Treatments for AIS in Children

In addition to the use of medication to reduce the risk of recurrent stroke, there are several general measures that often are used in children with stroke. Although none of these techniques has been rigorously evaluated in children with

**Table 10. Protocol for Using LMWH in Children**

Preparation	Initial Treatment Dose	Initial Prophylactic Dose
Reviparin, body weight–dependent dose, units/kg per 12 h		
<5 kg	150	50
>5 kg	100	30
Enoxaparin, age-dependent dose, mg/kg per 12 h		
<2 mo	1.5	0.75
>2 mo	1.0	0.5
Dalteparin, all-age pediatric dose, units/kg per 24 h	129±43	92±52
Tinzaparin, age-dependent dose, units/kg		
0–2 mo		275
2–12 mo		250
1–5 y		240
5–10 y		200
10–16 y		275

Adapted from Monagle et al,<sup>459</sup> with permission, and the experience of the Writing Group.

**Table 11. Warfarin Anticoagulation Protocol for Children\***

Stage	INR	Action
Day 1	1.0–1.3	0.2 mg/kg orally
Days 2–4	1.1–1.3	Repeat day 1 loading dose
	1.4–1.9	50% of day 1 loading dose
	2.0–3.0	50% of day 1 loading dose
	3.1–3.5	25% of day 1 loading dose
	>3.5	Hold dosing until INR is <3.5, then restart according to stage III guidelines
Maintenance	1.1–1.4	Increase by 20% of dose
	1.4–1.9	Increase by 10% of dose
	2.0–3.0	No change
	3.1–3.5	Decrease by 10% of dose
	>3.5	Hold dosing until INR is <3.5, then restart at 20% less than last dose

INR indicates international normalized ratio. Adapted from Michelson et al,<sup>524</sup> with permission, and the experience of the Writing Group.

\*The protocol is designed to maintain an INR between 2 and 3 with warfarin.

stroke, supportive care of this type is generally accepted by practitioners for use in children with stroke.

Correction of hypoxemia is appropriate in all children; intuitively, it might be even more important to correct hypoxemia in individuals with an ischemic stroke because of the ischemic penumbra concept. There is no evidence that oxygen supplementation is beneficial in individuals who are not hypoxemic. Likewise, there is no established role for hyperbaric oxygen therapy except in individuals with decompression sickness or those with air embolism after cardiac surgery.

Most physicians try to stop epileptic seizures regardless of the clinical situation, and the argument is even stronger for individuals with a stroke. However, there is little evidence that the administration of antiepileptic drugs is beneficial for children with ischemic stroke in the absence of clinical or electrographic seizures. Similarly, control of serum glucose levels is recommended, along with treatment for dehydration and anemia.

There is experimental evidence that fever can worsen the effects of a brain injury<sup>471,472</sup>; even in the absence of clinical studies in children with stroke, control of fever after a stroke seems intuitively reasonable. However, although therapeutic hypothermia has been studied as a neuroprotective technique,<sup>473,474</sup> there is not enough evidence that hypothermia improves outcome to justify its use.

## Recommendations for Supportive Therapy After Stroke in Children

### Class I Recommendation

1. Supportive measures for AIS should include control of fever, maintenance of normal oxygenation, control of systemic hypertension, and normalization of serum glucose levels (Class I, Level of Evidence C).

### Class II Recommendation

1. It is reasonable to treat dehydration and anemia in children with stroke (Class IIa, Level of Evidence C).

### Class III Recommendations

1. There is no evidence that the use of supplemental oxygen is beneficial in children with stroke in the absence of hypoxemia (Class III, Level of Evidence C).
2. In the absence of clinical or electrographic seizures, prophylactic administration of antiepileptic medications in children with ischemic stroke is not necessary (Class III, Level of Evidence C).
3. In the absence of additional data confirming its safety and efficacy, hypothermia should not be used in children with stroke except in the context of a clinical trial (Class III, Level of Evidence C).

## Medications for the Secondary Prevention of Ischemic Stroke in Children

### LMWH and UFH

For acute anticoagulation, LMWHs offer several potential advantages over UFH, including reproducible pharmacokinetics and fewer monitoring tests.<sup>475</sup> On the other hand, effects of LMWHs cannot be completely reversed within minutes with protamine sulfate or fresh-frozen plasma, a potential disadvantage for LMWH compared with UFH in situations in which acute anticoagulation is needed but there is also the need for its rapid reversal. Thus, in clinical situations in which rapid reversal of the anticoagulation is anticipated, it is appropriate to use UFH. A protocol for the initiation and adjustment of LMWH in children is provided in Table 10.

Short-term anticoagulation with LMWH or UFH is sometimes initiated in children after AIS pending evaluation of the cause of the stroke. Although this strategy is no longer applied to elderly stroke patients, the likelihood of a child having an underlying condition that would benefit from anticoagulation is higher than in adults. Although children seldom develop AIS as a result of atherosclerosis, the likelihood of stroke resulting from CCAD, vasculopathy, unrecognized cardiac disease, or a coagulopathy is relatively higher than in older adults. In many medical centers, it takes a few days to adequately eliminate these conditions. For these reasons, it may be reasonable to initiate LMWH or UFH in children with AIS pending completion of the diagnostic evaluation, a different approach than would be taken in adult stroke patients.

Both LMWH and UFH are commonly used for short-term anticoagulation. For anticoagulation lasting weeks or months, the alternatives include LMWH and oral vitamin K antagonists such as warfarin. LMWH can be administered via a subcutaneous catheter that is replaced weekly, further reducing the number of needles required. Warfarin is cheaper and is sometimes better accepted because of its oral route of administration.

No studies have assessed the efficacy of LMWH in childhood ischemic stroke. Recently, data supporting the safety of LMWH in acute pediatric AIS have become available,<sup>476,477</sup> and treatment of neonates and children who have CVST with LMWH also appears to be safe.<sup>4</sup>

LMWH is given to children subcutaneously at doses of 1 mg/kg every 12 hours (or in neonates, 1.5 mg/kg every 12 hours).<sup>475</sup> Anti-factor Xa levels are used to monitor LMWH because the activated partial thromboplastin time does not reflect LMWH activity. The therapeutic range for anti-factor Xa levels is 0.5 to 1.0 U/mL in a sample drawn 4 to 6 hours after the subcutaneous dose. Once an initial therapeutic level is attained, a weekly anti-factor Xa level is usually adequate during hospitalization, with the frequency reduced to every 3 to 4 weeks in stable outpatients receiving long-term LMWH. Because LMWH is cleared renally, its use in patients with renal failure requires close monitoring.

### **Recommendations for LMWH in Children With Stroke**

#### *Class I Recommendations*

1. Anticoagulation with LMWH is useful for long-term anticoagulation of children with a substantial risk of recurrent cardiac embolism, CVST, and selected hypercoagulable states (Class I, Level of Evidence C).

#### *Class II Recommendations*

1. The protocol outlined in Table 10 is a reasonable approach to the initiation and adjustment of LMWH in children with stroke who require its use (Class IIa, Level of Evidence C).
2. The administration of LMWH or UFH may be considered in children for up to 1 week after an ischemic stroke pending further evaluation to determine the cause of the stroke (Class IIb, Level of Evidence C).

### **Warfarin**

The anticoagulant effect of warfarin typically occurs within 36 to 72 hours after daily administration is begun. Because of low levels of vitamin K in breast milk, accurate dosing of warfarin may be more difficult in breast-fed infants. Warfarin typically is selected for children requiring prolonged anticoagulation, although LMWH by subcutaneous injection is an alternative option.

Studies assessing warfarin in adults with arterial stroke have shown no net benefit over aspirin except for the prevention of cardiogenic embolism. Information on the effectiveness or optimal dosing of warfarin for the treatment of CVST or AIS in children is sparse. However, most centers aim for a target international normalized ratio of 2.0 to 3.0 on the basis of data from adult studies and studies of pediatric patients with systemic thrombosis. Several studies have provided data on the safety of warfarin use in children with cerebral and noncerebral thromboses. The risk of major hemorrhage is <3.2% per patient-year in children receiving warfarin for mechanical heart valves.<sup>469</sup> In children with arterial stroke receiving warfarin, the risk of major hemorrhagic complications has not been established. With long-term use, monitoring for bone demineralization may be worthwhile.<sup>469</sup>

The initial and maintenance dosages of warfarin to maintain the target international normalized ratio at 2.0 to 3.0 shown in Table 11 are based on both clinical experience in children and published recommendations.<sup>469</sup> There is some evidence in adults with deep vein thrombosis that long-term,

low-dose anticoagulation could be of benefit. However, studies of low-dose anticoagulation in children with various conditions have yielded inconclusive results, and studies on CVST have not been done.<sup>478,479</sup>

### **Recommendations for the Use of Warfarin in Children With Stroke**

#### *Class II Recommendations*

1. Anticoagulation with warfarin is reasonable for the long-term anticoagulation of children with a substantial risk of recurrent cardiac embolism, CCAD, CVST, or selected hypercoagulable states (Class IIa, Level of Evidence C).
2. The protocol outlined in Table 11 is a reasonable approach to the initiation and maintenance of warfarin in children with stroke who require its use (Class IIa, Level of Evidence C).

### **Aspirin and Other Antiplatelet Agents**

Aspirin (acetylsalicylic acid) is frequently used in children for the secondary prevention of recurrent stroke after TIA or stroke. In adults, aspirin reduces recurrent stroke by ≈25% and is equivalent to warfarin for longer-term stroke prevention.<sup>480–482</sup> Unfortunately, similar data are not available for children.

Safety data exist for aspirin in children, but information about its effectiveness and optimal dose in the prevention of stroke in children is sparse. In 49 children with arterial ischemic stroke treated with 2 to 5 mg/kg aspirin per day, no complications were observed during a median follow-up of 36 months.<sup>477</sup> In a nonrandomized study of recurrent stroke and TIA, children selected for aspirin treatment showed a trend for fewer recurrent events compared with children receiving no prophylaxis or anticoagulation.<sup>75</sup> In another nonrandomized study, children selected for either aspirin or anticoagulants had similar recurrence rates.<sup>477</sup> These studies cannot be interpreted to indicate that either aspirin or anticoagulants are more or less effective in children because of the inherent selection bias. However, no treatment may be associated with an increased risk of recurrence compared with any antithrombotic treatment.<sup>75,217</sup>

A commonly used aspirin dose is 3 to 5 mg/kg per day, with the dose reduced to 1 to 3 mg/kg in response to gastric distress or prolonged epistaxis. There are few age-specific data on which to base therapeutic decisions. Treatment often is recommended for a minimum of 3 to 5 years or even longer in the face of ongoing risks for recurrent stroke (eg, continued cerebral artery stenosis or presence of major congenital heart disease) or symptoms of recurrent ischemia.

Aspirin may worsen the symptoms of asthma. So far, there have been no reports of Reye's syndrome in children taking the aspirin dose above. Nevertheless, given the increased risk of Reye's syndrome after influenza and varicella, it is reasonable to give an annual influenza immunization, to verify the status of varicella vaccination, and to halt the use of aspirin during suspected influenza or varicella infections. There was no consensus about whether to discontinue the aspirin dose during other febrile illnesses. Because of concern about Reye's syndrome, some members of the group recommend that aspirin be discontinued or its dose halved during

febrile illness; others favor continuation of aspirin during most febrile illnesses, given both the lack of evidence for Reye's syndrome in this setting and the apparent increased risk of stroke during such illnesses.

In children unable to take aspirin, clopidogrel has been used occasionally for stroke at doses of  $\approx 1$  mg/kg per day; in children, it may be necessary to compound the 75 mg clopidogrel to create more flexibility in dosing. Recently, the combination of aspirin and clopidogrel has been associated with subdural hemorrhage in several children with AIS. These children had diffuse vasculopathy with cerebral atrophy.<sup>483</sup> However, adequate data on the use of ticlopidine, clopidogrel, or the combination of low-dose aspirin plus extended-release dipyridamole are lacking.

### Recommendations for Aspirin Use in Children With Stroke

#### Class II Recommendations

1. Aspirin is a reasonable option for the secondary prevention of AIS in children whose infarction is not due to SCD and in children who are not known to have a high risk of recurrent embolism or a severe hypercoagulable disorder (Class IIa, Level of Evidence C).
2. A dose of 3 to 5 mg/kg per day is a reasonable initial aspirin dose for stroke prevention in children (Class IIa, Level of Evidence C). If dose-related side effects occur with this aspirin dose, a dose reduction to 1 to 3 mg/kg may be considered (Class IIb, Level of Evidence C).
3. In children taking aspirin for stroke prevention, it is reasonable to vaccinate for varicella and to administer an annual influenza vaccine in an effort to reduce the risk of Reye's syndrome (Class IIa, Level of Evidence C). It is reasonable to withhold aspirin during influenza and varicella infections (Class IIa, Level of Evidence C).

### Thrombolytic Therapy

Although there have been a few reports of the use of tissue plasminogen activator (tPA) in children with ischemic stroke,<sup>484–487</sup> safety and efficacy data for either intravenous or intraarterial thrombolysis in children with acute arterial occlusion are lacking. Thrombolytic therapy for venous occlusion typically requires a higher drug dose and a longer duration of therapy than would be used for an arterial occlusion.<sup>488</sup>

In children with systemic thromboses, tPA often dissolves the clot but has a high complication rate. In 1 report, for example, all but 15% of the 80 children treated with tPA had complete or partial clot dissolution, but 40% of these children had major complications, and another 30% had minor complications.<sup>489</sup> Janjua et al<sup>490</sup> analyzed 46 patients <18 years of age who received tPA for AIS between 2000 and 2003 and concluded that the safety and efficacy of thrombolytic therapy for these individuals could not be determined. Similarly, the use of tPA and other thrombolytic agents cannot be endorsed by this committee except in the context of a clinical trial.

As in adults receiving tPA, it is likely that its delayed administration will lead to an unacceptable rate of intracerebral hemorrhage in children. If tPA is considered, it is imperative to adhere to the accepted time limits used in adults: administration of intravenous tPA within 3 hours of stroke onset and intraarterial tPA within 6 hours of stroke

onset for anterior circulation strokes.<sup>491,492</sup> This is a serious limitation in children with stroke because they often seek attention much later than older individuals with stroke.<sup>493</sup> There is some evidence that a lower-dose tPA regimen might be effective in children.<sup>494</sup> If this observation is valid, it might provide the basis for additional trials designed to improve the safety profile of tPA in children.

### Recommendations for Thrombolytic Therapy for Childhood Stroke

#### Class II Recommendation

1. Thrombolytic therapy with tPA may be considered in selected children with CVST (Class IIb, Level of Evidence C).

#### Class III Recommendation

1. Until there are additional published safety and efficacy data, tPA generally is not recommended for children with AIS outside a clinical trial (Class III, Level of Evidence C). However, there was no consensus about the use of tPA in older adolescents who otherwise meet standard adult tPA eligibility criteria.

### Screening Relatives of Children With Stroke

Many thrombophilias are familial. When a child with stroke is found to have a thrombophilic condition, other family members may harbor the same condition and be at risk for early pathological thrombosis. Children with perinatal stroke who do not have a thrombophilic condition may still have affected mothers; perinatal stroke in the neonate has been associated with prothrombotic conditions in both the fetus and mother.<sup>495,496</sup>

### Risk for Carriers of Inherited Thrombophilias

There is evidence that carriers of inherited thrombophilias are at increased risk of thrombosis. The Italian Research Group on Inherited Thrombophilia looked at relatives of patients with pathological thrombosis and known thrombophilia and found that the incidence of venous thromboembolism (per 100 patient-years) was 1.07 for carriers of antithrombin deficiency, 0.54 for protein C deficiency, 0.50 for protein S deficiency, and 0.30 for patients with activated protein C resistance.<sup>497</sup> Makris et al<sup>498</sup> examined 109 first-degree relatives of 28 patients with known protein S deficiency caused by the *PROS1* gene defect and found that relatives who carried that defect had a 5-fold-higher risk of thrombosis than relatives who did not carry the defect. Lensen et al<sup>499</sup> examined 182 first- and second-degree family members of patients with the factor V Leiden mutation in the Netherlands and found that carriers of the mutation had a venous thrombosis rate of 0.56% per year,  $\approx 6$  times higher than the rate in the general Dutch population. Martinelli et al<sup>500</sup> examined 1076 relatives of probands in Italy with the factor V Leiden mutation, prothrombin 20210GA mutation, or both and found an annual incidence of venous thrombosis of 0.19% for carriers of the factor V Leiden mutation and 0.13% for carriers of the prothrombin 20210GA mutation. The importance of MTHFR mutations is controversial. Several studies

suggest that these mutations increase the risk of pathological thrombosis,<sup>501–503</sup> whereas several other studies suggest that the risk is not increased.<sup>504,505</sup>

Carriers of multiple mutations are probably at even higher risk. Bucciarelli et al<sup>497</sup> found that the incidence per 100 patient-years of venous thromboembolism in carriers of double defects (deficiency of 2 of the following: protein C, protein S, antithrombin, or activated protein C resistance screen) was 0.67. Martinelli et al<sup>500</sup> found that the annual incidence of thrombosis in carriers of both the factor V Leiden mutation and the prothrombin 20210 gene defect was 0.42% compared with <0.20% in carriers of only 1 of those 2 mutations. Meinardi et al<sup>506</sup> found that carriage of additional thrombophilic risk factors together with the factor V Leiden mutation dramatically raised the incidence and prevalence of thrombosis. The incidence of pathological thrombosis was 0.39 in heterozygotes carrying only the factor V Leiden mutation (prevalence, 10.8%), 0.57 in double heterozygotes with factor V Leiden and prothrombin 20210GA (prevalence, 16%), 1.41 for homozygotes for factor V Leiden (prevalence, 36.8%), and 4.76% for double heterozygotes for factor V Leiden together with inherited protein C or S deficiency (prevalence 40%). Keijzer et al<sup>501</sup> found that the relative risk of recurrent venous thrombosis in carriers of both the MTHFR 677TT mutation and the factor V Leiden mutation was 18.7.

High-risk periods such as surgery, immobilization, pregnancy and the puerperium, and oral contraceptive use also raise the risk of pathological thrombosis in carriers of these mutations; many episodes of pathological thrombosis occur during these periods.<sup>497</sup> Carriers of multiple thrombotic mutations appear to be at particularly high risk during these periods.<sup>497,507</sup> It is controversial how significant prothrombotic risk factors are in causing pregnancy complications that might be due to thrombosis such as multiple miscarriages.<sup>508–511</sup> However, the MTHFR C677T mutation in mothers has been linked to an increased risk of neural tube defects in their children.<sup>512</sup>

### Risk of Screening

There may be unanticipated risks and psychosocial effects from screening for thrombophilias. Some asymptomatic individuals could face job-related issues or be denied healthcare coverage if it became known that they carry one of these mutations.<sup>513</sup> The health risks of being without insurance are well known.<sup>514–516</sup>

### Previous Guidelines

Several medical groups have issued guidelines on screening. The College of American Pathologists states that asymptomatic family members should give informed consent before evaluation is started and that testing for factors such as the factor V Leiden mutation may be appropriate in asymptomatic family members who have a strong family history of early thrombosis or

asymptomatic female family members who are pregnant or considering oral contraceptive use.<sup>517,518</sup> Guidelines developed by the American College of Obstetricians and Gynecologists suggest screening pregnant women with a family history of thrombosis for both genetic and nongenetic prothrombotic risk factors.<sup>519</sup> Carriers of the factor V Leiden mutation may be at higher risk for thrombosis when they use oral contraceptives; for this reason, both the College of American Pathologists and the American College of Medical Genetics suggest that asymptomatic female relatives of factor V Leiden carriers receive screening for factor V Leiden.<sup>518,520</sup> However, as described above, other prothrombotic risk factors may interact with oral contraceptives or other prothrombotic states to raise the risk of thrombosis. The Royal College of Obstetricians and Gynaecologists in London (United Kingdom) suggests offering thrombophilia screening to women with a positive family history before starting oral contraception<sup>521</sup> or hormone replacement therapy.<sup>522</sup> This is a constantly changing field, and updated recommendations from these groups can be found on their Web sites: [www.cap.org](http://www.cap.org), [www.acmg.net](http://www.acmg.net), and [www.guideline.gov](http://www.guideline.gov) (American College of Obstetricians and Gynecologists and Royal College of Obstetricians and Gynaecologists guidelines).

## Recommendations for Screening Family Members for Stroke Risk Factors

### Class II Recommendations

1. Thrombophilia screening may be offered to family members of children with ischemic stroke or CVST and known thrombophilic defects. It is reasonable to counsel family members about the risks and benefits of this screening (Class IIa, Level of Evidence C).
2. Thrombophilia screening may be offered to the mothers of children with ischemic stroke that occurred before, during, or immediately after birth even if thrombophilia screening in the neonate is negative. It is reasonable to counsel the individual about the risks and benefits of this screening (Class IIa, Level of Evidence C).

### Future Considerations

Cerebrovascular disorders occur relatively often among children and adolescents, and stroke in children is now a common topic in the literature. Nevertheless, the incidence of stroke among children is low enough that it is difficult to plan clinical trials designed to improve therapy. There are enough age-specific differences in the cause, manifestations, and treatment responses in individuals with stroke that we must be cautious when attempting to apply our knowledge of stroke in adults to children with stroke. Although large-scale clinical trials will be difficult to mount in children with stroke, continued research and additional experience are imperative if we are to better understand this important group of conditions.<sup>523,524</sup>

Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12 month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
James Bale	University of Utah Health Sciences	None	None	None	None	None	None	None
Louis Caplan	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Vijeya Ganesan	Great Ormond Street Hospital for Children NHS Trust and UCL Institute of Child Health	None	None	None	None	None	None	None
Steven Pavlakis	Maimonides Medical Center	National Institutes of Health*	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period or 5% or more of the person's gross income or (2) the person owns 5% or more of the voting stock or share of the entity or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

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# Correction

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33. On page 2649, Table 2, 4 conditions were removed because they are not known to be genetic. They were “Neurocutaneous syndromes,” “Encephalotrigeminal angiomas,” “Klippel-Trenaunay-Weber syndrome,” Snedden syndrome,“ and ”Susac syndrome.“ The entry ”Neurofibromatosis type 1“ should not be indented, because it is no longer a subheading of Neurocutaneous syndromes. The authors provided this updated information after publication in the journal.

The corrected version can now be viewed online at <http://stroke.ahajournals.org>.

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