

## Management of Stroke in Neonates and Children A Scientific Statement From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

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**Purpose**—Much has transpired since the last scientific statement on pediatric stroke was published 10 years ago. Although stroke has long been recognized as an adult health problem causing substantial morbidity and mortality, it is also an important cause of acquired brain injury in young patients, occurring most commonly in the neonate and throughout childhood. This scientific statement represents a synthesis of data and a consensus of the leading experts in childhood cardiovascular disease and stroke.

**Methods**—Members of the writing group were appointed by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and the American Heart Association's Manuscript Oversight Committee and were chosen to reflect the expertise of the subject matter. The writers used systematic literature reviews, references to published clinical and epidemiology studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge. This scientific statement is based on expert consensus considerations for clinical practice.

**Results**—Annualized pediatric stroke incidence rates, including both neonatal and later childhood stroke and both ischemic and hemorrhagic stroke, range from 3 to 25 per 100 000 children in developed countries. Newborns have the highest risk ratio: 1 in 4000 live births. Stroke is a clinical syndrome. Delays in diagnosis are common in both perinatal and childhood stroke but for different reasons. To develop new strategies for prevention and treatment, disease processes and risk factors that lead to pediatric stroke are discussed here to aid the clinician in rapid diagnosis and treatment. The many important differences that affect the pathophysiology and treatment of childhood stroke are discussed in each section.

**Conclusions**—Here we provide updates on perinatal and childhood stroke with a focus on the subtypes, including arterial ischemic, venous thrombotic, and hemorrhagic stroke, and updates in regard to areas of childhood stroke that have not received close attention such as sickle cell disease. Each section is highlighted with considerations for clinical practice, attendant controversies, and knowledge gaps. This statement provides the practicing provider with much-needed updated information in this field. (*Stroke*. 2019;50:e51–e96. DOI: 10.1161/STR.000000000000183.)

**Key Words:** AHA Scientific Statements ■ cerebrovascular accident ■ genetics ■ infarction  
■ perinatal care ■ thrombosis

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Much has transpired since the last scientific statement on pediatric stroke was published 10 years ago. Although stroke has long been recognized as an adult health problem causing substantial morbidity and mortality, it is also an important cause of acquired brain injury in young patients, occurring most commonly in the neonate and throughout childhood. This scientific statement represents a synthesis of data and a consensus of the leading experts in childhood cardiovascular disease and stroke.

## Overview of Childhood and Perinatal Stroke

### Introduction and Definition

The standard adult definition of stroke—an acute onset neurological sign or symptom attributable to focal brain infarction or hemorrhage—applies to children as reflected by the National Institutes of Health (NIH) Common Data Elements definition.<sup>1,2</sup> However, in the neonatal period, the acute presentation can be missed. Thus, it is important for pediatric health professionals to be able to recognize stroke at different ages and to treat stroke to preserve brain function and to promote repair and recovery.

### Classification

There are different ways of characterizing pediatric stroke. One is by age: Stroke occurring from 28 weeks' gestation to 28 postnatal days of life is broadly classified as perinatal stroke, and stroke occurring after 28 days to 18 years of age is classified as childhood stroke. Within perinatal stroke, mode of presentation distinguishes 2 varieties. Acute perinatal stroke occurs in newborn infants at or near birth and typically presents shortly after onset with focal seizures or encephalopathy. Presumed perinatal stroke refers to chronic infarcts, diagnosed in a delayed manner, that are presumed to have occurred in the perinatal period. These infants typically present with pathological early handedness or seizures, leading to brain imaging and the diagnosis of a remote infarction.<sup>3–5</sup> As in adults, pediatric stroke can also be classified according to whether the underlying cause is ischemic or hemorrhagic, as detailed in the NIH Common Data Elements.<sup>1</sup> Ischemic stroke includes arterial ischemic stroke (AIS) and venous infarction caused by cerebral sinovenous thrombosis (CSVT) or cortical vein thrombosis. In CSVT, occlusion of venous sinuses may or may not be accompanied by hemorrhage. In older infants and children, some literature uses the term *silent stroke* when asymptomatic infarcts are found on neuroimaging. However, this is a misnomer because the definition of stroke includes a clinical event; we use the term *silent infarct* in this review. However, silent infarcts are likely not truly silent; as in adults, a sufficient burden likely causes vascular cognitive impairment.

Much of adult stroke is related to the traditional risk factors for atherosclerosis, including hypertension, dyslipidemia, obesity, diabetes mellitus, and cigarette smoking. Newer risk factors, including insulin resistance and inflammation, are also important. Atherosclerosis is generally not a cause of stroke in children and adolescence, although it is now clear that the atherosclerotic process that leads to a stroke in adulthood may begin in childhood and that dyslipidemia tends to be more prevalent among children with ischemic stroke than in other children.<sup>6</sup> Children and adolescents with stroke may

be at particularly increased risk for recurrent strokes in later life related to these processes. This emphasizes the importance of promoting ideal vascular health through good diet, physical activity, and avoidance of tobacco products to protect them from recurrent strokes in adulthood.

## Epidemiology

### Perinatal Stroke

Arterial ischemic infarction accounts for ≈80% of perinatal strokes. The remainder are caused by CSVT or hemorrhage (excluding subarachnoid hemorrhage [SAH] and intraventricular hemorrhage [IVH] in premature babies). Ischemic stroke occurs in up to 1 in 3500 newborns, although some estimates are as low as 1 in 10000 newborns.<sup>7–9</sup> The ratio of ischemic stroke is dramatically higher in newborns, almost 6 times greater than in older children.<sup>8</sup>

Agarwal and colleagues<sup>9</sup> identified 60 individuals with perinatal stroke among a cohort of 208 876 live births. This represents a frequency of 29 in 100 000 live births, or 1 per 3500 live births. Their overall stroke rate for both ischemic and hemorrhagic stroke was 37 per 100 000 live births, or 1 per 2700 live births.<sup>9</sup>

Armstrong-Wells et al<sup>10</sup> identified 19 infants with hemorrhagic stroke and 1 with SAH among 323 532 live births in the Northern California Kaiser-Permanente Medical Care program, representing a population prevalence for perinatal hemorrhagic stroke of 6.2 per 100 000 live births. Cole et al<sup>11</sup> calculated the incidence of perinatal hemorrhagic stroke as 1 per 6300 live births for both hemorrhage and hemorrhagic infarction.

### Childhood Stroke

Ischemic stroke affects an estimated 1.0 to 2.0 in 100 000 children (nonneonates) annually in Western developed countries.<sup>7,12–17</sup> Incidence varies by age and sex; it is highest in infants and children <5 years of age and higher in boys than girls.<sup>12–17</sup> Black and Asian children have a higher incidence than white children.<sup>14,18</sup> Most of the increased ischemic stroke risk in black children is explained by sickle cell disease (SCD), which amplifies stroke risk >200-fold. Hemorrhagic stroke in children can be intracerebral hemorrhage (ICH), IVH, or SAH. Hemorrhagic stroke makes up about half of pediatric stroke, with an incidence of ≈1 to 1.7 in 100 000 per year.<sup>7,18</sup>

### Global Perspective

Krishnamurthi et al<sup>19</sup> used all available global data on stroke incidence, prevalence, and mortality to evaluate differences in stroke between developed and developing countries and changes from 1990 to 2013. In 2013, there were 97 792 prevalent cases of childhood ischemic stroke and 67 621 prevalent cases of childhood hemorrhagic stroke, reflecting an increase of ≈35% in the absolute numbers of prevalent childhood strokes since 1990. Although prevalence rates for childhood ischemic stroke and hemorrhagic stroke decreased significantly in developed countries, a decline was seen only in hemorrhagic stroke, with no change in prevalence rates of ischemic stroke in developing countries. Therefore, during that time, they found a significant global increase in the absolute number of prevalent strokes in children. Simultaneously,

the mortality rate significantly declined, with boys showing a trend toward higher childhood stroke death rates (95% CI, 1.5 [1.3–1.8] per 100 000) than girls (95% CI, 1.1 [0.9–1.5] per 100 000) globally in 2013.<sup>19</sup> These findings highlight an important global public health concern.

#### Recurrent Stroke

Cumulative brain injury resulting from recurrent stroke is a major concern in older infants and children and in neonates with cardiac stroke. Fullerton et al<sup>20</sup> evaluated the risk of recurrent AIS from an international perspective. They found that the cumulative rate of stroke recurrences was 6.8% (95% CI, 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year with most children on antithrombotic treatment. The strongest predictor of stroke recurrence was the presence of an arteriopathy, which resulted in a 5-fold increased recurrence risk. This risk was present despite increased use of antithrombotic agents.

### Perinatal Stroke

Perinatal stroke includes both ischemic and hemorrhagic events resulting from disruption of either arteries or veins from early gestation through the first month of life. We have chosen to use the term *perinatal* rather than *neonatal* for consistency, although both terms are found in the literature. Perinatal stroke is sometimes defined as a stroke that occurs from 28 weeks' gestation through the first 7 days of life. Other authors have expanded this interval from 20 weeks' gestation through 28 days after birth; lesions occurring even before 28 weeks have been documented.<sup>21</sup> Approximately 80% of these lesions are ischemic, and the remainder are the result of CSVT or hemorrhage.<sup>5,22</sup> Most presumed perinatal ischemic strokes are in an arterial distribution and thus are discussed under AIS in Neonates below, but some have distributions more suggestive of venous infarction.

### AIS in Neonates

#### Presentation

Newborns with AIS often present with seizures, characteristically focal motor seizures involving only 1 extremity.<sup>8,23</sup> In 1 study, seizures at the time of AIS occurred in 94% of neonates versus only 17% of older children.<sup>24</sup> Occasionally, perinatal AIS presents with encephalopathy, leading to suspicion for hypoxic-ischemic injury rather than AIS; neuroimaging distinguishes the 2 diagnoses. The left cerebral hemisphere is affected in 80% of neonates with unilateral infarctions.<sup>23</sup> Individuals with presumed perinatal stroke may seem normal after birth but later present with delayed motor milestones, epilepsy, asymmetric motor function, or early handedness.<sup>5,23,25</sup> Some of these children with presumed perinatal ischemic stroke may have had clinical or subclinical seizures that escaped detection in the neonatal period because of the challenges of distinguishing neonatal seizures from normal infant movements.<sup>23,26</sup> In a single-center cohort, the majority affected were male, and most of the lesions fell within middle cerebral artery (MCA) territories. Although arterial proximal M1 segment infarction was most common, venous periventricular infarction was next highest and accounted for 75% of subcortical injuries. Motor outcomes in this cohort were predicted by basal ganglia involvement, including leg hemiparesis,

spasticity, and need for assistive devices. Nonmotor outcomes were associated with cortical involvement, including cognitive/behavioral outcomes, visual deficits, and epilepsy.<sup>3</sup>

#### Risk Factors

Risk factors include both maternal and neonatal factors. Normal activation of coagulation factors in the mother and low levels of factors in the infant just before and after the time of delivery may contribute to the increased stroke risk in neonates.<sup>21</sup> Neonates with AIS sometimes have an inherited thrombophilia.<sup>27</sup> Other risk factors that are associated with neonatal AIS include cardiac lesions, coagulation disorders, infection, trauma, and asphyxia.<sup>21,28</sup> Porencephaly and intrauterine stroke have recently been linked to mutation of *COL4A1*.<sup>29,30</sup> *COL4A1* is a subunit of the type IV collagen and plays a role in angiogenesis.

Maternal factors that may be associated with perinatal AIS include primiparity or a history of infertility, chorioamnionitis, oligohydramnios, premature rupture of membranes, vacuum extraction, emergency cesarean section, coagulation disorders, and preeclampsia.<sup>31</sup> Individuals with presumed perinatal ischemic stroke have similar risk factors.<sup>5,25</sup> The likelihood of neonatal AIS increases dramatically with an increasing number of risk factors, but in many individuals, no single cause can be identified.<sup>31</sup>

#### Evaluation

A recent prospective case-control study on neonates with AIS has suggested that routine thrombophilia testing is not indicated.<sup>32</sup> This study demonstrated that thrombophilic conditions, including decreased levels of protein C, protein S, or antithrombin, increased levels of factor VIII, factor IX, factor XI, fibrinogen, lipoprotein(a), homocysteine, and anticardiolipin antibodies. The presence of lupus anticoagulant and genotyping of factor V Leiden (FVL), factor II (prothrombin) G20210A, and methylene tetrahydrofolate reductase C677T are rare in AIS. In fact, experts recently suggested that testing for methylene tetrahydrofolate reductase is no longer warranted.<sup>33</sup> Thrombophilia evaluation in the neonate has limited clinical utility because levels of protein C, protein S, antithrombin, and factor XI are normally decreased to 30% of adults levels, and these levels only approach adult levels at various time points during childhood.<sup>34</sup> Thrombophilia testing for the mentioned proteins in the neonatal period may be misleading and requires repeat testing for a confirmatory diagnosis.<sup>32–34</sup>

Magnetic resonance imaging (MRI) should be performed to diagnose the stroke. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) also should be performed, especially when venous thrombosis is suspected.

#### Management

Supportive care measures for AIS in neonates include the control of seizures, the optimization of oxygenation, and the correction of dehydration and anemia.<sup>35</sup> Antiplatelet therapy such as aspirin and anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is rarely indicated because of the low risk of recurrent stroke after neonatal AIS; however, it must be considered in those exceptional neonates with high risk of recurrent AIS resulting from

documented thrombophilia or complex congenital heart disease (not including patent foramen ovale [PFO]).<sup>36,37</sup>

Hyperacute stroke therapies (thrombolytics and mechanical thrombectomy) are rarely considered in neonates with AIS because there is no evidence for their use. Although endovascular procedures such as mechanical thrombectomy are sometimes used in older children with an arterial occlusion,<sup>35,38,39</sup> the small artery size of neonates precludes the use of current endovascular devices in these individuals.<sup>35</sup>

### Outcomes

The majority of neonates with AIS experience residual neurological deficits. Golomb et al<sup>40</sup> summarized 111 children with perinatal stroke, including 67 who presented as neonates and 44 whose strokes were discovered later. Seventy-six children (68%) exhibited cerebral palsy, and 55 of these individuals had at least 1 additional disability; 45 (59%) experienced cognitive or speech impairment, and 36 (47%) had epilepsy. Detailed neuropsychological testing often documents cognitive dysfunction, especially related to attention and executive function.<sup>41</sup> Such functional deficits are more likely to occur in individuals with a larger infarction, with comorbid epilepsy, or with a presumed perinatal stroke.<sup>41</sup> A study from Switzerland corroborated these findings, showing that 2 years after birth, 39% were diagnosed with cerebral palsy and 31% had delayed mental performance.<sup>23</sup>

Congenital heart disease and potentially other medical comorbidities can impair brain growth and development even in the absence of stroke; therefore, it can be difficult to ascribe neurological deficits to the stroke per se in individuals with these conditions.<sup>42</sup> Studies specific to children with presumed perinatal ischemic strokes have shown a similar array of long-term deficits, and Kirton et al<sup>3</sup> demonstrated that imaging characteristics of the brain injury can predict outcomes.

The likelihood of recurrence after a neonatal AIS is low except in those with congenital heart disease.<sup>28</sup> Fullerton et al<sup>43</sup> documented recurrent stroke in only 1 of 84 (1.2%) neonates with stroke. Lehman et al<sup>22</sup> identified only 6 individuals with a recurrent ischemic lesion among 215 neonates with AIS or CSV. However, neonates with cardiac disease may have a higher recurrence risk, similar to older infants and children with cardiac disease.<sup>28</sup>

### Rehabilitation

An early intervention program based on best available evidence of interventions that work in older children, Goals Activity Motor Enrichment, was evaluated in infants in a single randomized trial with promising results showing improved motor outcomes of participants compared with standard care.<sup>44</sup> Another study explored the effectiveness of baby constraint-induced movement therapy and baby massage in infants for improving the manual ability of infants <12 months of age with unilateral cerebral palsy. Baby constraint-induced movement therapy improved unimanual ability more than massage in these babies.<sup>45</sup>

## CSV in Neonates

### Presentation

As with AIS, the clinical manifestations of CSV in neonates are often nonspecific, with lethargy, irritability, or seizures.<sup>46–48</sup>

Symptomatic seizures are more common among neonates with CSV than in older individuals, but the occurrence of seizures at the time of presentation does not predict the occurrence of long-term epilepsy.

### Risk Factors and Causes

Conditions that are associated with CSV in neonates include gestational or delivery complications, dehydration, sepsis, meningitis, cardiac defects, and coagulation disorders.<sup>48</sup> Although these factors are commonly thought of as risk factors, no controlled studies have proved the associations.

### Management

Appropriate supportive measures include the control of epileptic seizures, the correction of dehydration and anemia, and the treatment of underlying infections.<sup>49</sup> Institutional practices for anticoagulation for perinatal CSV are highly variable in the absence of definitive studies demonstrating safety and clinical benefit. However, anticoagulation is routinely used at some institutions and appears to be generally well tolerated, even in the setting of intracranial hemorrhage.<sup>50–54</sup> Jordan et al<sup>54</sup> analyzed factors that affected the use of anticoagulation in 84 neonates with isolated CSV from 10 countries. The presence of infarction, hemorrhage, systemic illness, or dehydration did not alter the likelihood of antithrombotic administration. Babies born in the United States were significantly less likely to receive anticoagulants than babies from other parts of the world.<sup>54</sup> Moharir et al<sup>52</sup> analyzed 83 neonates with CSV from a single Canadian center. Twenty-nine of the 83 neonates (35%) received either standard heparin, LMWH, or warfarin. A major hemorrhage occurred in 3 of 21 (14%) treated with a preexisting intracranial hemorrhage and none of 17 without a preexisting hemorrhage. Follow-up imaging demonstrated CSV thrombus propagation in 10 of 35 neonates (28%) who did not receive anticoagulation and only 1 of 22 (4%) of the neonates who were treated. Thrombus propagation was associated with a new venous infarction in 10% of the neonates and a less favorable clinical outcome.<sup>52</sup> In the absence of a clinical trial, these data suggest that anticoagulation is safe for use in neonates with CSV, especially in the absence of a brain hemorrhage, and they provide preliminary evidence that such therapy is useful.<sup>52</sup> Those centers that do not routinely use anticoagulation for neonatal CSV will often consider anticoagulation for thrombus propagation on serial imaging or a deteriorating clinical status that is related to the CSV. There is no evidence for thrombolytic agents or endovascular therapy for neonatal CSV.

### Evaluation

As mentioned, thrombophilia evaluation in the neonate has limited clinical utility because levels of protein C, protein S, antithrombin, and factor XI are normally decreased to 30% of adult levels, and these levels only approach adult levels at various time points during childhood.<sup>34</sup> MRI, especially MRV, should be performed to diagnose the thrombosis.

### Outcomes

The reported frequency of long-term neurological dysfunction in neonates with CSV is variable. Individuals with a venous infarction and those with seizures at the time of diagnosis tend to experience more serious neurological sequelae.<sup>49</sup>

Individuals with large venous infarctions are more likely to experience neurodevelopmental impairment.<sup>46</sup> Fitzgerald et al<sup>48</sup> summarized 42 neonates with CSVT, and detailed follow-up data were available for 27 of the 41 survivors. Sixteen of these 27 (59%) had cognitive impairment; 18 (67%) had cerebral palsy; and 11 (41%) had epilepsy.

There is limited information about the recurrence risk of CSVT in neonates, but it appears to be low. Kenet et al<sup>55</sup> investigated the recurrence risk of CSVT in a cohort of 396 children, and none of the 22 individuals who experienced recurrent thromboses were <2 years of age at the time of their initial thrombosis.

## Hemorrhagic Stroke in Neonates

### Presentation

As with AIS and CSVT in neonates, the presentation of brain hemorrhage in neonates tends to be nonspecific.<sup>11</sup> Of the 20 neonates described by Armstrong-Wells et al,<sup>10</sup> 65% experienced seizures and all of them exhibited encephalopathy.<sup>10</sup> Neonatal hemorrhagic stroke is more common than previously reported, occurring in at least 1 in 6300 live births. However, asymptomatic intracranial hemorrhage is found on brain MRI scans of 15% of late preterm and term newborns, so the incidence of hemorrhagic stroke, clinically symptomatic intracranial hemorrhage, is difficult to define.<sup>56</sup>

### Risk Factors and Causes

Causes of brain hemorrhage in term neonates include coagulopathy, thrombocytopenia, trauma, and, rarely, structural vascular lesions. Although no specific cause can be identified in the majority of neonates with hemorrhagic stroke, risk factors include postmaturity, emergency cesarean delivery, fetal distress, and male sex.<sup>10,57</sup> Mutations in *COL4A1* should be considered in neonates with cerebral hemorrhage, porencephaly, glaucoma, or cataracts.<sup>58,59</sup> Some hemorrhagic lesions such as periventricular hemorrhagic venous infarction may actually represent hemorrhagic conversion of an arterial or venous infarction.<sup>11</sup>

Either acquired or congenital coagulopathy may lead to intracranial hemorrhage in newborns. Hemorrhagic disease of the newborn remains problematic in areas of the world where supplemental vitamin K is not routinely administered to newborns. In the United States, intracranial hemorrhage has been documented in babies whose caregivers refused vitamin K administration after birth.<sup>60,61</sup> Breastfeeding infants may also develop vitamin K deficiency.<sup>62</sup> Babies whose mothers ingested warfarin, phenytoin, or barbiturates during pregnancy sometimes develop a vitamin K–related coagulopathy. Intracranial hemorrhage has also been documented in neonates with hemophilia A and other hereditary coagulopathies.

The role for and timing of vascular imaging to rule out a congenital structural vascular lesion (brain arteriovenous malformation [AVM] or fistula) remain unclear for all cases. Brain MRA is noninvasive but may miss smaller lesions.<sup>63</sup> Conventional angiography is considered if there is clinical evidence of a congenital arteriovenous fistula (AVF; heart failure, pulmonary hypertension, cranial bruit) or a family history suggestive of an autosomal dominant syndrome such as hereditary hemorrhagic telangiectasia (HHT).

## Management

Markedly low platelet counts and coagulation factor deficiencies should be corrected. Large doses of vitamin K may be needed to correct factor deficiencies resulting from maternal medications. Surgical evacuation of a hematoma may reduce extremely high intracranial pressure (ICP) but is rarely performed in neonates, and it is not clear whether surgery improves the eventual outcome.<sup>57</sup> Ventricular drainage and, if indicated, later shunting for progressive hydrocephalus resulting from IVH is appropriate.

## Considerations for Clinical Practice

1. Vitamin K should be routinely administered to newborns. Larger doses of vitamin K may be needed to correct factor deficiencies resulting from maternal medications.
2. Aspirin, LMWH, or UFH may be considered in neonates at risk for stroke recurrence because of severe thrombophilia or cerebral embolism resulting from cardiac disease but is generally not considered for neonates with a first ischemic infarction.
3. There is no evidence for hyperacute stroke therapies (thrombolytic agents or embolectomy) for neonates with an arterial occlusion.
4. Anticoagulation with LMWH or heparin may be considered in neonates with CSVT, particularly those with clinical deterioration or evidence of thrombus extension on serial imaging. Serial imaging at 5 to 7 days should be considered to exclude propagation when a decision is made not to anticoagulate.
5. Surgical evacuation of an intracranial hematoma in a neonate is rarely indicated but may be considered to reduce extremely high ICP.
6. Ventricular drainage and, if indicated, later shunting for progressive hydrocephalus caused by IVH is often appropriate.

## Knowledge Gaps

- An incomplete understanding of the causes of all forms of neonatal stroke limits our ability to develop preventative strategies.
- Although there is some observational evidence that anti-thrombotic agents might benefit selected neonates with AIS or CSVT, clinical trial data are lacking.

## Childhood Stroke

### Approach to a Suspected Stroke in a Child

#### Clinical Presentation

Signs and symptoms of acute stroke in children are similar to those in adults. The most common symptoms include hemiparesis and hemifacial weakness in 67% to 90%, speech or language disturbance in 20% to 50%, vision disturbance in 10% to 15%, and ataxia in 8% to 10%. Children present with nonlocalizing symptoms such as headache in 20% to 50% and altered mental status in 17% to 38%. Seizures at stroke onset are more common in children than adults, affecting 15% to 25%, especially in those <6 years of age.<sup>12–14,16,64–67</sup> Clinical presentation varies according to age, setting (inpatient versus emergency department [ED]), and stroke subtype.

Childhood AIS resulting from cardiac disease occurs in the inpatient setting more often than the outpatient setting and involves younger children, with a median age of 6 months to 3 years.<sup>68–71</sup> These children present with seizures in up to 40% and hemiparesis in 36% to 75% and are clinically covert in 14% to 40%. Braun et al<sup>72</sup> found that cardioembolic stroke may present with abrupt onset compared with a stuttering or fluctuating presentation in children with stroke caused by arteriopathy. Diagnosis of cerebral infarction is often made when imaging is obtained for other reasons (cardiac arrest, extracorporeal membrane oxygenation cannulation).

Children with moyamoya-type arteriopathies are distinguished by a high prevalence of transient ischemic attack (TIA) and a large burden of silent infarction. In a 7-year single-center cohort study of 54 children with moyamoya arteriopathy (median age at diagnosis, 7.5 years), TIAs occurred in 70% and acute AIS in 48%.<sup>73</sup> TIAs often were multiple and recurred over extended periods of time. Signs and symptoms include hemiparesis or hemisensory deficits most commonly (72%), often with chronic headache (52%) and occasionally with seizures (<10%). Imaging at the time of initial diagnosis has shown evidence of prior silent infarct in 52%. In another cohort of 60 children with moyamoya who initially presented with a TIA, 55 children (92%) had recurrent TIAs and 14 (23%) went on to ischemic infarction.<sup>74</sup> Severity of the moyamoya arteriopathy at presentation corresponded to risk of subsequent stroke.

Posterior circulation stroke represents another distinct pattern of clinical presenting features. These children present at a median age of 7 to 8 years, are predominantly male (67% to 77%), and are previously healthy children in the vast majority of cases.<sup>75,76</sup> Presenting signs and symptoms include localizing deficits referable to the posterior circulation in 70% to 100%: hemiparesis, ataxia, dysarthria, visual field deficits, and oculomotor deficits. Nonlocalizing symptoms occur in 60% to 70%, especially headache, vomiting, and altered mental status. Vertebral artery (VA) dissection is the most common underlying cause (25%–50%), especially in younger boys, and is frequently preceded by recent minor head or neck trauma. The finding of multiple posterior circulation infarcts of varying age at the time of initial presentation is especially suspicious for VA dissection.

### **Delays and Challenges of Stroke Mimics**

Multiple studies investigating time to AIS diagnosis aim to identify strategies to improve access to hyperacute therapies.<sup>72,77–81</sup> The median time from symptom onset to parent seeking medical care is highly variable, ranging from 1.7 to 21 hours, although a majority usually present within 6 hours. Median time to radiological confirmation of diagnosis is 15 to 24 hours. Children with onset of stroke during admission for other illnesses experience similar delays in radiological confirmation of ischemic stroke. The major causes of delays include delayed consideration of stroke among frontline providers and delays in accessing MRI, often related to the need for sedation or anesthesia. Delays are greater in evenings and weekends.<sup>79</sup>

Accuracy and timeliness of diagnosis by frontline providers are important challenges. ED providers correctly diagnose

a stroke in ≈60% of children, giving ≈40% of cases an incorrect initial diagnosis of a stroke mimic.<sup>82,83</sup> Studies of stroke mimics in the ED have yielded several important observations. First, the vast majority (60%–90%) of children presenting to an ED with an acute neurological syndrome, or brain attack, have some condition other than stroke. Diagnoses that commonly mimic stroke and may prompt an emergency physician to activate a “stroke alert” pathway are numerous and diverse. The most common are migraine with aura, Bell palsy, and seizure, especially with Todd paresis. Other stroke mimics include brain tumor, demyelinating disease, cerebellitis, encephalitis, epidural abscess, traumatic brain injury, syncope, intoxication, metabolic disease, and psychogenic disorders. Up to 40% of patients with stroke mimics have serious disease or time-sensitive treatment implications.<sup>80,84</sup> Clinical diagnostic strategies and tools used in adults to distinguish stroke from stroke mimics have limited utility in children, with a sensitivity of ≈60%.<sup>82,85</sup> Focal deficits are more common in children with stroke than in those with stroke mimics, but there is overlap. Nonlocalizing symptoms such as headache and altered mental status are equally common in both groups.

### **Considerations for Clinical Practice**

1. Medical education: Develop programs of education to improve knowledge and skills in diagnosis and emergency management of pediatric stroke for frontline providers, including pediatricians, emergency physicians, and emergency medical technicians. Similar education programs are needed for subspecialty providers who care for populations at high risk for stroke, including cardiologists, hematologists, cardiac intensivists, and pediatric intensivists, as well as the nursing staff caring for these children.
2. Research:
  - Develop and validate bedside clinical assessment methods for frontline providers to identify stroke in children with improved sensitivity and specificity.
  - Develop better imaging techniques for early and accurate diagnosis of stroke and cerebrovascular disease generally and for VA dissection in particular.
  - Define modifiable stroke risk factors to be incorporated into screening, early diagnosis, and preventive treatment strategies in children with heart disease.

### **AIS in Childhood**

In AIS, irreversible brain tissue ischemia occurs within minutes to hours of arterial occlusion. The time to irreversible tissue injury is shorter in the central core of the infarct and longer in the surrounding penumbra where collateral arterial supply can continue to perfuse tissue. Neuroprotective strategies to balance metabolic substrate supply with tissue metabolic demand aim to increase brain tissue survival primarily in the penumbra.

### **Hyperacute Stroke Therapies in Childhood**

Arterial recanalization therapy, including intravenous tissue-type plasminogen activator (tPA) and intra-arterial tPA or endovascular thrombectomy, has been shown to significantly benefit adults with AIS when implemented within discrete time windows.<sup>86</sup> The availability of recanalization therapy has

therefore dramatically changed the time frame for urgent diagnosis and management of stroke.<sup>87,88</sup> Whether and how to apply these therapies in childhood remain controversial.

#### *Implications of Thrombus Composition*

Thrombus composition (erythrocytes, fibrin, platelets, and leukocytes) is integral in determining susceptibility to mechanical and pharmacological disruption and recanalization. Thrombus composition directly affects physical properties, which are correlated to both effectiveness and complications of recanalization.<sup>89</sup> A recent meta-analysis reported that thrombi with a high proportion of erythrocytes and less fibrin appear as a hyperdense sign on computed tomography (CT) and are associated with increased recanalization rates.<sup>90</sup> In vitro data on the composition of thrombi created in the laboratory with the use of adult and pediatric plasma suggest that children have a more loosely woven fibrin structure in the final thrombus.<sup>91</sup> These data suggest that use of thrombolytic therapy could theoretically be more efficacious in children compared with adults. However, no pediatric thrombolytic trials have been completed.

#### *Recanalization Therapy: Thrombolytics and Endovascular Thrombectomy*

When recanalization is accomplished before tissue death, that is, within hours of stroke onset, reperfusion reduces ischemic injury. Beyond this time window, the increasing risks of recanalization, including hemorrhagic transformation of the infarct, reperfusion injury, and catheter- and device-related thrombotic and nonthrombotic complications, outweigh the benefits.

In clinical trials of adults with AIS, the optimal time window for recanalization therapy after documented stroke onset is within  $\approx 4.5$  hours for intravenous tPA treatment, 6 hours for intra-arterial tPA, 6 hours for endovascular thrombectomy, but up to 24 hours for thrombectomy in a subgroup of patients.<sup>92,93</sup> Multiple clinical trials demonstrate that among highly selected adults with AIS and large vessel occlusion, thrombectomy improves 90-day survival without disability over standard medical therapy. A 2016 pooled analysis by Goyal et al<sup>86</sup> of the 1287 adult stroke patients from the 5 endovascular thrombectomy clinical trials published by 2015 demonstrated robust clinical benefits for thrombectomy across a broad spectrum of age and initial stroke severity (moderate or severe, with few minor strokes included) and a number needed to treat of 2.6 to reduce the disability of 1 patient. Two clinical trials published in early 2018 extended the treatment window further for select patients with smaller completed infarcts yet large penumbra territories at risk for infarction. The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) showed that thrombectomy from 6 to 24 hours after onset can be beneficial in adults with NIH Stroke Scale score  $>10$  and core infarct volume  $<30$  mL (equivalent to  $<5\%$  of hemisphere volume) or NIH Stroke Scale score  $>20$  and core infarct volume  $<51$  mL (equivalent to  $10\%$  of hemisphere volume). The DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) similarly found benefit when the thrombectomy was performed in an extended time window (6–16 hours after onset) in patients

selected by perfusion imaging: an initial infarct size of  $<70$  mL and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of  $\geq 1.8$ .<sup>92</sup>

In childhood stroke, the emergence of specialized pediatric stroke expertise, institutional pathways, and increased access to rapid stroke neuroimaging make hyperacute stroke therapies for children potentially feasible.<sup>80,94</sup> A study describing the use of thrombolytics in a large, international pediatric stroke cohort<sup>95</sup> provided the impetus to design and initiate the prospective TIPS study (Thrombolysis in Pediatric Stroke).<sup>96</sup> TIPS was an NIH-funded phase 1 clinical trial to determine the safety and pharmacokinetics of intravenous tPA in children 2 to 18 years of age within 4.5 hours of AIS if vascular obstruction was diagnosed on MRI.<sup>96</sup> Although the study was closed because of low patient enrollment, the multidisciplinary TIPS investigators succeeded in establishing systems for the evaluation and care of a child with hyperacute AIS.<sup>96</sup> In the absence of clinical trial data, a consensus opinion has suggested that when intravenous tPA is considered in children, the adult dose of 0.9 mg/kg be used, which would likely be a conservative dose because developmental differences in plasminogen levels may actually make the effective dose for children higher.<sup>35</sup>

Endovascular thrombectomy has potential appeal for childhood AIS over intravenous tPA: There is a longer poststroke time window for intervention, and concerns related to the optimal pediatric tPA dose and developmental changes in plasminogen levels are moot. In a 2015 American Heart Association (AHA)/American Stroke Association (ASA) guideline on thrombectomy, the authors stated that endovascular thrombectomy may be reasonable for some acute AIS patients  $<18$  years of age, using adult parameters, while acknowledging that the benefits and risks are not established in this age group.<sup>97</sup> More than 35 cases of recanalization therapy in pediatric AIS have now been reported and pooled in the published literature, most with successful outcomes. However, the total number of children treated with thrombectomy remains unknown, and those with treatment-related complications and adverse outcomes are likely underreported in the medical literature. Hence, the true safety profile of endovascular thrombectomy in children remains unknown. Special pediatric considerations include smaller arteries (groin and cerebral), weight-based limitations for radiological contrast, radiation exposure in young children, and the arteriopathies that cause AIS in children (eg, concerns for introducing a catheter into an acutely inflamed artery, in cases of focal cerebral arteriopathy [FCA], or a chronically stenosed cerebral artery, in cases of moyamoya). Moreover, the risk-to-benefit ratios of these interventions would differ if presumptions about better stroke recovery in children versus adults are correct. Numerous studies indicate that a good outcome (no functional deficits) can be expected in one-third to one-half of children with AIS without any intervention.<sup>86,98</sup> In children, initial stroke severity measured by the Pediatric NIH Stroke Scale directly predicts outcome.<sup>99,100</sup> Hence, the risks of thrombectomy may outweigh the benefits in children with low initial stroke severity scores.

#### *Considerations for Clinical Practice*

1. In the absence of pediatric clinical trial data to guide treatment decisions, hyperacute therapies for childhood

AIS remain controversial. It would be reasonable to limit consideration of this intervention to children meeting these criteria:

- Persistent disabling neurological deficits (eg, Pediatric NIH Stroke Scale score  $\geq 6$  at the time of intervention or higher if DAWN trial criteria are being applied)
  - Radiographically confirmed cerebral large artery occlusion
  - Larger children because of concerns about introducing catheters into small groin and cerebral arteries and size-based limitations on contrast dye and radiation exposure
  - Treatment decision made in conjunction with neurologists with expertise in the treatment of children with stroke
  - Intervention performed by an endovascular surgeon with experience in both treating children and performing thrombectomy in adult stroke patients<sup>101</sup>
2. Establish systems and pathways for hyperacute pediatric stroke care. Centers that choose to offer this therapy to children should preestablish institutional pediatric hyperacute stroke pathways and consider current adult guidelines for these therapies. These pathways should include criteria for consideration of endovascular thrombectomy in children with acute AIS and large vessel occlusion.
- Establish referral networks connecting community hospitals and frontline providers to tertiary care pediatric stroke centers with specifically trained experts and technology in vascular neurology, neuroimaging, and neurocritical care. Within pediatric stroke centers, multiple systems of care need to be structured through well-designed institutional care protocols that are staffed and equipped to provide 24/7 access to care from vascular neurologists, vascular neurosurgeons, neuroradiologists, neurointerventionalists, anesthesiologists, and neurocritical care intensivists.
  - Consider the use of telestroke or telemedicine as a specific way of bringing expertise to emergency providers who may have less experience with acute focal deficits and stroke in children. Telestroke has been effective in adult stroke medicine and has been used in other settings in pediatric cardiovascular care.
  - Pediatric stroke specific guidelines should be developed at the local, regional, and national levels. To leverage regional stroke expertise, partnerships between emergency medical services, comprehensive stroke centers, and pediatric tertiary care hospitals should be encouraged.

#### Knowledge Gaps

- Safety and efficacy data for hyperacute stroke therapies in children are lacking. Children treated with such therapies should be enrolled in existing registries, for example, the Swiss NeuroPediatric Stroke Registry and the International Pediatric Stroke Study Registry.
- There is no evidence to guide how young or how small a child may safely undergo thrombectomy.
- Analyses directly comparing post-AIS neurological outcomes in children and adults, adjusted for confounders such as stroke infarct and location, would help when

considering risk-to-benefit ratios for adult stroke therapies applied to children.

#### Acute Management of Childhood AIS

Current strategies for acute management of childhood stroke rely on both pediatric and adult data that explore the treatment of hypertension, hypotension, hyperglycemia, and fever, as well as surveillance strategies to prevent complications such as cerebral swelling and seizures. Little is known about whether supportive care measures alter the effect of brain ischemia in children. However, traditional methods of neuroprotection are often used, and recent data on specific management challenges such as the role of early hemicraniectomy in large strokes are beginning to emerge.

#### Blood Glucose, Temperature, Blood Pressure

Hyperglycemia is a common and well-established risk factor for adverse outcomes in adult stroke and likely a frequent and detrimental risk factor in children as well. In both populations, however, the timing and goals of treatment of hyperglycemia are poorly understood, with only a single randomized controlled trial examining the efficacy of glucose control in adult stroke.<sup>102</sup> In this study, 933 patients were randomly assigned to 2 arms: insulin infusion to maintain euglycemia and saline. The trial was stopped early because of slow enrollment but demonstrated no difference in 90-day mortality or other outcome measures. In childhood stroke, there are even fewer data. Grelli et al<sup>103</sup> performed the only study examining the influence of hyperglycemia on outcomes in childhood stroke. In this retrospective multivariate analysis of 98 children with stroke examining the association among hypertension, hypotension, hyperglycemia, fever, and Pediatric Stroke Outcome Measure, hyperglycemia was independently associated with adverse outcome. Hyperglycemia was also relatively common (18%), and hypoglycemia was rare (3%). Given the lack of data in children, it is reasonable to follow the AHA/ASA adult stroke guidelines for the management of hyperglycemia and hypoglycemia.<sup>88</sup> The ongoing SHINE trial (Stroke Hyperglycemia Insulin Network Effort) is also testing the treatment of hyperglycemia in adults.<sup>104</sup>

It is well established that pyrexia is associated with adverse outcomes in adult stroke, whereas the impact of fever in children remains uncertain. Although a single multicenter, randomized, double-blind, placebo-controlled adult trial of patients with temperatures ranging from 36°C to 39°C failed to show any difference in those treated with acetaminophen compared with those receiving placebo, post hoc analysis demonstrated a difference in expected modified Rankin Scale score at 3 months.<sup>105</sup> Although this finding suggests that treatment of fever may improve outcome, additional prospective adult evidence is lacking. In the previously mentioned retrospective analysis of childhood stroke and the impact of hyperglycemia, hypertension, and fever, Grelli et al<sup>103</sup> found no influence of fever on outcome in childhood stroke, although fever was found acutely in 38% of subjects. Given the lack of pediatric specific data, it is reasonable to follow AHA/ASA adult stroke guidelines when treating fever in children.<sup>88</sup>

In adult stroke guidelines, current AHA/ASA recommendations suggest the following:



*In patients with BP [blood pressure]  $\geq 220/120$  mm Hg who did not receive intravenous alteplase or EVT [endovascular treatment] and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.<sup>88</sup>*

Although several prospective randomized studies have examined the role of antihypertensive treatment in the acute management of adult stroke, the results of these studies have been mixed.<sup>106–109</sup> A lack of consistent results in previous studies may have been the result of differing response to treatment across stroke subtypes, an important consideration when these studies are extrapolated to childhood stroke, the pathogenesis of which is often different from that of adult stroke. Indeed, there is some evidence that acute antihypertensive treatment in adult stroke may have variable outcomes, depending on stroke presentation.<sup>107</sup>

As in adult stroke, early evidence in childhood stroke suggests that hypertension in the acute period after stroke is associated with worse outcomes. One single-center retrospective study of 53 children with ischemic stroke demonstrated an association between hypertension in the first 3 days after stroke and in-hospital mortality. These findings were confirmed by examination of a large sample of children with stroke (n=2590) from a large national database.<sup>110</sup> Grelli et al<sup>103</sup> demonstrated a high prevalence of persistent hypertension ( $\geq 2$  consecutive measurements above the 95th percentile) in childhood stroke (68%) at some point 5 days after stroke but failed to establish an association with hypertension (or hypotension) and adverse outcomes at 3 months.

Although hypertension in the first 3 to 5 days after childhood stroke may be associated with in-hospital morbidity, the causal pathway is unclear. Children with moyamoya, for example, are often hypertensive at baseline, presumably as a compensatory mechanism to improve cerebral perfusion. Up to 45% of children presenting with AIS will have an intracranial arteriopathy<sup>15</sup> such as moyamoya, and these children may be particularly sensitive to rapid decreases in blood pressure, resulting in cerebral hypoperfusion. Use of antihypertensive therapy in these children can trigger flow-related ischemia. In addition, hypotension in children with stroke should be treated aggressively, and in our experience, patients with pressure-dependent stenosis may need aggressive management and monitoring for even borderline hypotension. Treatment may include laying the head of the bed flat (although recent adult data show no benefit), intravenous fluids, and, in rare cases of a pressure-dependent lesion, salt tablets, fludrocortisone, or pressors.

#### *Seizure Management*

In acute childhood stroke, clinical seizures are common, occurring in  $>20\%$  of children with ischemic stroke.<sup>111–113</sup> In addition, subclinical seizures are found in patients with prolonged electroencephalographic monitoring, occurring acutely in 23% of all patients with clinical seizures and electroencephalographic monitoring in a single-center study.<sup>111</sup> Although detailed descriptions of protocols for seizure

monitoring in pediatric brain injury are beyond the scope of this article, clinicians who take care of children with stroke should have a high suspicion for clinical and subclinical seizures in the acute setting and should consider electroencephalographic screening or monitoring for children with altered mental status.

#### *Hemicraniectomy*

Although hemicraniectomy is rarely performed in the treatment of childhood AIS—performed in 1% of patients—it remains a potentially lifesaving option in children with large supratentorial stroke. Indeed, in the largest series of children who received hemicraniectomy after acute AIS, 95% (39 of 41) of children survived. Of the survivors, 41% had no deficit, mild deficit, or moderate deficit, and 59% had severe deficits. In a meta-analysis of the 3 largest randomized prospective trials comparing decompressive hemicraniectomy with medical management in adults, survival was improved with surgery from 29% to 78%.<sup>114</sup> Similar to the pediatric population, however, a significant number of survivors had severe deficits (45% had a modified Rankin Scale score of 4/5). A recent analysis of a large adult national inpatient sample demonstrated a strong association between later decompression and poor outcome with the use of a validated composite outcome variable.<sup>115</sup> In addition, patients with decompression performed before herniation had better outcomes than those with surgery after herniation.<sup>115</sup> This finding is particularly germane to the pediatric population, which has less brain atrophy to accommodate swelling.

In children, as in adults, hemicraniectomy in large supratentorial infarcts is decided on a case-by-case basis and in consultation between the family and treatment team. However, if hemicraniectomy is performed in the pediatric patient, earlier intervention is likely preferable. In children with large-volume infarcts (more than half of the MCA territory), treatment teams should consider either performing early prophylactic hemicraniectomy within the first 24 hours or implementing serial imaging within the first 72 hours to monitor swelling and the need for surgical intervention. In general, it is reasonable to follow adult guidelines for surgical decompression.<sup>88</sup>

Adult studies report improved outcomes and decreased mortality with decompressive craniotomy in patients with space-occupying cerebral edema secondary to large cerebellar infarctions.<sup>116,117</sup> Although limited to case series, similar findings are seen in the pediatric population.<sup>118</sup> Because poor outcomes from this intervention are rarely seen, ethical considerations are not as challenging as those seen in malignant MCA syndrome.

#### *Considerations for Clinical Practice*

1. Children with acute stroke are usually monitored in an intensive care unit setting for at least 24 hours after stroke, and general neuroprotective and neurocritical supportive care is administered.
2. Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia. Thus, hyperglycemia should be treated to achieve blood glucose levels in a range of 140 to 180 mg/dL and closely monitored

- to prevent hypoglycemia (blood glucose <60 mg/dL) in patients with acute ischemic stroke.<sup>119</sup>
3. Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke.
  4. Caution should be exercised in children with intracranial vascular stenosis such as moyamoya and in those with focal cerebral arteriopathies. In addition, hypotension in children with stroke should typically be treated aggressively.
  5. Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially life-saving. Patient/family valuations of achievable outcome states may affect decisions about surgery. Decompressive surgical evacuation of a space-occupying cerebellar infarction should be considered early in preventing and treating herniation and brainstem compression.<sup>119</sup>
  6. In children with large-volume infarcts (more than half of the MCA territory), treatment teams could consider either performing early prophylactic hemicraniectomy within the first 24 hours or implementing serial imaging and frequent clinical assessments within the first 72 hours to monitor swelling and the need for surgical intervention.

#### *Controversies in Current Practice*

- Setting for treatment: Should treatment occur only in centers with pediatric vascular neurologists?
- Hemicraniectomy management
- Blood pressure management

#### *Knowledge Gaps*

- Determining timing and appropriate candidates for hemicraniectomy
- Appropriate treatment of blood pressure because associations with worse outcome are not proven
- Appropriate treatment of hypoglycemia and hyperglycemia

#### **Risk Factors and Causes of Childhood AIS**

The causes of childhood stroke can be divided into multiple categories: cardiac, extracranial arteriopathies, intracranial arteriopathies, thrombophilia, SCD, and systemic causes such as systemic lupus erythematosus. Several approaches to stroke subtype classification have been published, which may be useful in formulating management pathways and designing clinical research.<sup>15,64,120,121</sup> In many cases, the pathogenesis is multifactorial, and thus, the determination of a cause should typically include a systematic assessment of all potential causes.

#### *Cardiac*

Cardioembolic stroke accounts for ≈30% of all childhood strokes and can occur as a result of congenital heart disease, procedure-related events, or acquired heart disease.<sup>122</sup> According to a 3-decade prospective evaluation of children with cardiac disease, 0.13% (132 per 100 000 children per year) had a stroke each year.<sup>123</sup> The increased use of assist mechanical heart devices and improved survival of patients with congenital heart disease are likely increasing this incidence annually. Children requiring therapy from a Berlin

Heart EXCOR ventricular assist device had the highest prevalence of stroke (28%–34% combined risk of ischemic and hemorrhagic stroke) among children with cardiac disease<sup>122,124,125</sup>; children treated with extracorporeal membrane oxygenation (7%–11%),<sup>126,127</sup> the Fontan procedure (1.4%–19%),<sup>128–132</sup> and cardiac catheterization (0.38%–1.3%)<sup>133,134</sup> are also at high risk for stroke. The prevalence of stroke in patients with endocarditis and cardiomyopathy is 5% to 10%,<sup>135–137</sup> whereas children with congenital heart disease have a 19-fold increased risk of stroke compared with the general population.<sup>138</sup> Data on recurrence risk of stroke after an initial event are minimal, although a recent article from the Canadian Pediatric Ischemic Stroke Registry reported a 27% recurrence risk of stroke at 10 years of age in children with congenital heart disease despite the high use of anticoagulation.<sup>28</sup>

The pathophysiology of stroke in children with cardiac disease is usually thromboembolic, although associated anomalies of the head and neck vasculature may also play a role.<sup>70</sup> In cases of congenital heart disease, ventricular assist devices, or extracorporeal membrane oxygenation, thrombus can occur from stasis or paradoxical venous embolism. The role of arrhythmia in childhood stroke and clot formation is less clearly defined, although a recent report of increased risk of arrhythmia and stroke in adults with a history of congenital atrial septal disease<sup>139</sup> raises the possibility that arrhythmia is an underrecognized cause of childhood stroke, especially in those with a history of benign congenital heart disease. Similarly, the role of PFO in childhood stroke remains uncertain. Although several small studies have suggested that PFO with right-to-left shunt is more prevalent in children with cryptogenic stroke than in normal children,<sup>140,141</sup> it is unclear when a PFO in childhood stroke is pathogenic, particularly given that the timing of normal, physiological PFO closure is variable. Identifying a PFO in childhood stroke may be important in that increasing evidence in adults suggests that adults with larger PFOs and cryptogenic stroke may benefit from PFO closure.<sup>142</sup> The Risk of Paradoxical Embolism score combines clinical predictors of recurrent stroke or TIA in adults with cryptogenic stroke and PFO: younger age, presence of cortical infarction, and absence of atherosclerotic risk factors. This score is intended to stratify the likelihood that an adult AIS was related to the PFO.<sup>143</sup> Although this score is unlikely to stratify stroke risk in children (who would have uniformly high scores because of their young age and lack of atherosclerotic risk factors), a comparable scoring system that accounts for pediatric-specific AIS risk factors and is derived from and validated in children is needed.

Children with AIS typically undergo evaluation of their heart via transthoracic echocardiogram with bubble study, as well as monitoring to assess for an arrhythmia, unless another cause is identified (Table 1). When there is a history of benign heart defect (ventricular/atrial septal disease) or stroke during exercise, Holter monitoring or cardiology consult should be considered. In cases of recurrent events, transesophageal echocardiogram with bubble, Holter monitoring, or cardiac consult should be considered (Table 2). In these cases, particular attention should be paid to the aortic arch

**Table 1. Suggested Basic Evaluation of a Child With AIS for Common Causes**

Category	Common Causes	Examination
Stroke confirmation	Ischemia Ischemia mimickers (migraine)	Brain MRI with DWI, FLAIR, GRE or SWI, T1, and T2 (optional: T1 after gadolinium, DTI, pCASL) <sup>144</sup>
Cardiac*	PFO (controversial role as a stroke cause in childhood) Congenital cardiac anomaly Acquired cardiac anomaly Arrhythmia	TTE with bubble study ECG and inpatient telemetry Consideration of 4-extremity Doppler ultrasound in cryptogenic stroke with positive bubble study
Arteriopathy	Extracranial dissection FCA-i FCA-d Moyamoya Takayasu arteritis	Brain MRA 3-D TOF and MRA of the neck with/without gadolinium (optional VWI) <sup>144</sup> or CTA of the head and neck (not preferred given exposure to radiation and intravenous contrast)
Thrombophilia*	Inherited thrombophilia Acquired thrombophilia	CBC FVL mutation Prothrombin G20210A mutation Protein C Protein S Antithrombin mutation Lupus anticoagulant Anticardiolipin antibody (IgG/IgM) Anti-β <sub>2</sub> glycoprotein antibody (IgG/IgM)
Inflammatory*	Lupus	ESR, CRP, ANA

3-D indicates 3-dimensional; AIS, arterial ischemic stroke; ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; CTA, computed tomography angiography; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; ESR, erythrocyte sedimentation rate; FCA-d, focal cerebral arteriopathy dissection type; FCA-i, focal cerebral arteriopathy inflammation type; FLAIR, fluid-attenuated inversion recovery; FVL, factor V Leiden; GRE, gradient recalled echo; Ig, immunoglobulin; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; pCASL, pseudo-continuous arterial spin labeling; PFO, patent foramen ovale; SWI, susceptibility-weighted imaging; TOF, time of flight; TTE, transthoracic echocardiogram; and VWI, vessel wall imaging.

\*May not be clinically indicated if an alternative cause is identified.

and delayed bubbles suggestive of a pulmonary level shunt, as seen in HHT. In cases of cryptogenic stroke and PFO, it is reasonable to obtain 4-extremity Doppler to assess for deep vein thrombosis as a source for a paradoxical embolus. Children should also undergo evaluation for thrombophilias when indicated.

*Extracranial Arteriopathy*

Extracranial arteriopathies are usually caused by a craniocervical arterial dissection (CCAD). Dissection is a tear in the

intimal layer of the artery that promotes platelet deposition and secondary activation of the clotting cascade. In many cases, dissection can lead to pseudoaneurysm formation, which is caused by decreased vessel wall integrity (often from dissection) and aneurysmal dilation of the affected artery. Risk factors for CCAD in children include male sex, head and neck trauma, and connective tissue disorders.<sup>75,157,159–162</sup> CCAD accounts for 7.5% of childhood stroke<sup>159</sup> and, when in the posterior circulation, is likely associated with high rates of recurrent stroke.<sup>163</sup>

Although digital subtraction angiography (DSA) remains the gold standard for detecting a CCAD, MRA and CT angiography (CTA) are increasingly being used to detect arterial abnormalities.<sup>164</sup> Currently, MRA is the first-line screening imaging used in most institutions. MRA has the advantage of indirectly visualizing the vessel wall and the lumen and sparing the patient radiation.<sup>160,164</sup> When magnetic resonance techniques are used, T1 fat-saturated neck imaging or contrast-enhanced images should typically be used to increase the sensitivity of detecting dissection.<sup>144</sup> In cases of recurrent stroke, posterior circulation stroke, or indeterminate abnormalities on initial imaging, CTA or DSA is often useful. CCAD can change over time, especially in the posterior circulation, with nearly 50% of vessel abnormalities progressing within the first year.<sup>165</sup> Therefore, serial imaging of CCAD is warranted within the first year, and potentially longer, especially to detect pseudoaneurysm formation.<sup>166</sup>

Pseudoaneurysm and dissection in the V3 segment (C1-C2 region) of the VA is a unique entity, especially in boys with posterior circulation strokes. Although the pathophysiology of this anomaly is still uncertain, and possibly the result of repetitive trauma of the artery with neck turning, it is clear that these cases have high rates of recurrent stroke.<sup>146</sup> Indeed, posterior circulation strokes in general have a 19% rate of recurrent events at 3 years.<sup>163</sup> In cases of recurrent posterior circulation stroke and dissection, patients may have evidence of arterial compression with head turning demonstrated on DSA or CTA (so-called bow hunter syndrome), and it is postulated that repetitive trauma to the artery causes recurrent injury to the vessel and a lack of vessel wall healing. In cases of V3 dissection and failure of medical management with antithrombotic therapy, surgical interventions can be considered and preferably performed in centers with expertise in children. These interventions include VA sacrifice (with single-artery involvement), C1-C2 posterior fusion (with bilateral artery involvement), and exploration of the vertebral canal for debridement of fibrous tissue (with dynamic VA compression).<sup>146</sup> Therefore, in cases with multiple infarcts of the posterior circulation, DSA should be considered to evaluate the V3 segment of the VAs, and if a pseudoaneurysm or dissection is detected, head turning during a DSA (or CTA) can be considered.

Finally, evaluation for connective tissue disorders in children with stroke and dissection is an important consideration. In adults with a history of CCAD, a family history of known connective tissue disorders or dissection is quite rare, occurring in <1% of cases.<sup>155</sup> Underlying structural anomalies that are detected via electron microscopy are quite common,<sup>157</sup>

Table 2. Targeted Evaluation of a Child With AIS for Rare Causes or Causes Requiring Additional Evaluation

Category	Rare Causes and Causes Requiring Additional Evaluation	Diagnostic Triggers	Examination
Cardiopulmonary	Cardiac cause missed by TTE	Recurrent stroke	Cardiology consult TTE with bubble study
	Arrhythmia missed by electrocardiographic screening	Clinical history of palpitations Stroke related to exercise	Cardiology consult Holter monitoring
	HHT	Frequent nosebleeds Purplish lesions and abnormal blood vessels on the hands, fingertips, face, lips, lining of the mouth, and nose	Echocardiogram with bubble study showing pulmonary-level shunt Genetic testing for <i>ACVRL1</i> , <i>ENG</i> , and <i>SMAD4</i> genes
Arteriopathy	Moyamoya	Diagnosis of moyamoya	Neurosurgery consult DSA to prepare for bypass surgery Consideration of RNF213 genetic testing; clinical screening for other entities, including <i>ACTA2 R179</i> , <i>BRCC3/MTCPI</i> , <i>GUCY1A3</i> , <i>SAMHD1</i> , Alagille syndrome, Down syndrome, microcephalic osteodysplastic primordial dwarfism, neurofibromatosis type I, PHACE syndrome, Robinow syndrome, Seckel syndrome, SCD
	FCA	FCA of uncertain origin	Consideration of CSF testing for VZV PCR, HSV PCR, and VZV IgM/IgG antibodies Consideration of VWI Consideration of DSA
	ACTA2	Straight ectatic bilateral ICAs Aortic disease Fixed dilated pupils Hypotonic bladder Malrotation of the gut Pulmonary hypertension <sup>145</sup>	<i>ACTA2</i> gene testing
	Fibromuscular dysplasia	String-of-bead appearance on angiography Hypertension Renal artery involvement Mixed hemorrhagic/ischemic stroke	Biopsy of artery (renal, temporal, or other) showing intimal or medial hyperplasia
	Dynamic VA compression/ V3 pseudoaneurysm	Male predominance Recurrent posterior circulation stroke <sup>146</sup>	Consider DSA or CTA of the neck with head turning with consideration of risks/benefits of the head-turning maneuver under anesthesia Management remains controversial
Thrombophilia		Recurrent stroke Family history of thrombophilia in first-degree relative	Hematology consult Factor VIII level Lipoprotein(a) <i>MTHFR</i> mutation and homocysteine level Hemoglobin electrophoresis
Inflammatory	cPACNS	Elevated serum inflammatory markers Personality change Headaches	Consideration of CSF testing for VZV PCR, HSV PCR, and VZV IgM/IgG Abs Consideration of VWI Consideration of conventional angiogram Consideration of brain biopsy
	DADA2 or PAN or Wegener disease	High inflammatory markers and frequent fevers Renal disease: proteinuria, hypertension Peripheral neuropathy Skin disease: livedo reticularis, hand nodules <sup>147,148</sup>	Mutations in the <i>CECR1</i> gene (DADA2) Plasma ADA2 activity Tissue biopsy (PAN)
	Other rheumatologic disease		P-ANCA, C-ANCA

(Continued)

Table 2. Continued

Category	Rare Causes and Causes Requiring Additional Evaluation	Diagnostic Triggers	Examination
Genetic/metabolic	PHACE syndrome	Congenital anomalies that include the following: Hemangioma of the head, including scalp Posterior fossa anomalies Cardiovascular anomalies, especially of the aortic arch Congenital ocular anomalies Midline defects <sup>149</sup>	Echocardiogram Ophthalmology consult Dermatology consult
	Fabry disease	Neuropathic pain in hands or feet Angiokeratomas (purple spots) between navel and knees Multisystem involvement of gastrointestinal, cardiac, and renal systems Hypohidrosis Male predominance (X-linked)	White blood cell enzymes screening for a deficiency of $\alpha$ -galactosidase A activity
	MELAS	Symmetric ischemia, especially in the deep gray structures Ischemia that does not conform to a vascular territory History of migraine headaches Family history of mitochondrial disease, unexplained hearing loss, or short stature <sup>150–152</sup>	Serum lactate MELAS mutational analysis Further mitochondrial testing if indicated
	POLG1	Status epilepticus, often severe Hepatic dysfunction Occipital infarctions <sup>153,154</sup>	<i>POLG1</i> mutation analysis
Connective tissue disorder	Nonspecific CVD	Joint hypermobility and dissection and posterior circulation stroke	Consider gene panel testing for connective tissue disorders
	Ehlers-Danlos type IV	Joint hypermobility Translucent skin (especially on chest) Triangular face Easy bruising Family history of uterine rupture, aortic rupture, or tendon rupture <sup>155–158</sup>	Consider <i>COL3A1</i> testing or gene panel testing for connective tissue disorders
	Loeys-Dietz syndrome	Joint hypermobility Characteristic facial appearance that includes widely spaced eyes Skeletal anomalies, including pectus and arachnodactyly	Consider <i>TGFBR1</i> and <i>TGFBR2</i> (encoding TGFBR1 and 2), <i>SMAD3</i> testing, or gene panel testing for connective tissue disorders

Abs indicates antibodies; AIS, arterial ischemic stroke; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; cPACNS, childhood primary angiitis of the central nervous system; CSF, cerebrospinal fluid; CTA, computed tomography angiography; CVD, cardiovascular disease; DADA2, deficiency of adenosine deaminase 2; DSA, digital subtraction angiography; FCA, focal cerebral arteriopathy; HHT, hereditary hemorrhagic telangiectasia; HSV, herpes simplex virus; ICA, internal carotid artery; Ig, immunoglobulin; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PAN, polyarteritis nodosa; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; PCR, polymerase chain reaction; PHACE, posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft, and supraumbilical raphe; RNF213, ring finger protein 213; SCD, sickle cell disease; TGFBR, transforming growth factor- $\beta$  receptor; TTE, transthoracic echocardiogram; VA, vertebral artery; VWI, vessel wall imaging; and VZV, varicella zoster virus.

however, suggesting an incomplete understanding of the genetic basis of CCAD. Although the rate of connective tissue disorders in children with CCAD is uncertain, clinical clues can assist in targeted evaluation. Children with CCAD and a family history of aortic aneurysm; uterine, ligamentous, or intestinal rupture; or arterial dissection should be considered for Ehlers-Danlos type IV testing, especially if they have characteristic features of Ehlers-Danlos type IV (thin triangular face, easy bruising, or translucent skin on the chest; Table 2). In cases with hypermobility on examination and dissection, genetic panels to evaluate for connective tissue disorders are reasonable. Identification of connective tissue disorders in these children is increasingly important in order to screen for associated vascular anomalies and to consider treatment with  $\beta$ -blocker therapy as secondary prevention for further cardiovascular events<sup>167</sup> (Table 2).

#### Intracranial Arteriopathy

Intracranial arteriopathies account for up to 45% of all childhood strokes.<sup>15</sup> The nomenclature to describe these arteriopathies has varied over the past decade, with poor agreement about classification.<sup>168</sup> The IPSS (International Pediatric Stroke Study) has recently agreed to use the term *FCA* to define “unifocal and unilateral stenosis/irregularity of the large intracranial arteries of the anterior circulation (distal internal carotid artery and/or its proximal branches).”<sup>64</sup> In addition, *FCA* dissection type (*FCA-d*) refers to “intracranial arterial dissection of the anterior circulation, typically with trauma,” whereas *FCA* inflammation type (*FCA-i*) refers to “*FCA* that is presumed inflammatory (i.e., thought to represent a focal vasculitis).”<sup>64</sup> Although the majority of these *FCAs* will not progress beyond 6 to 12 months,<sup>169</sup> *FCAs* have high 1-year recurrence rates that range from 19% to 25%, depending on the underlying pathogenesis.<sup>20</sup> Thus, families with children who have intracranial arteriopathies should be counseled about the high recurrence risk, which appears to be concentrated mostly within the first year.<sup>43</sup> Progressive disease of the distal *MCA*/proximal internal carotid artery, called moyamoya when associated with collaterals, has an even higher 1-year recurrence risk of 35%.<sup>20</sup> Moyamoya is most often bilateral but can be unilateral, especially earlier in the disease process.

In patients with *FCA-i*, evidence suggests that an infectious or parainfectious process leads to localized vessel inflammation and secondary thrombus formation and stroke. Indeed, antecedent varicella virus infection is a known cause of *FCA-i*, called postvaricella arteriopathy.<sup>170,171</sup> In addition, preceding nonspecific minor illnesses are known risk factors for *FCA-i*<sup>172,173</sup> and may lead to the development of new therapies in the future. In cases of suspected *FCA-i*, evaluation of cerebrospinal fluid (CSF) for herpes simplex virus polymerase chain reaction, varicella zoster virus (VZV) polymerase chain reaction, VZV immunoglobulin G, and VZV immunoglobulin M can assess for active herpesvirus or VZV infection that could be amenable to treatment with acyclovir, but lumbar puncture is not uniformly performed as part of an *FCA* evaluation. CSF is usually normal and is often unable to confirm either inflammation or a specific associated infection in suspected *FCA-i*. Anticoagulation is a relative contraindication for lumbar puncture. The safety and efficacy of steroid

therapy for the treatment of *FCA-i* are currently unknown in childhood stroke; therefore, planning for prospective randomized trials is currently underway. Finally, reversible cerebral vasoconstriction syndrome is an uncommon cause of intracranial arteriopathy in children; it is distinct from *FCA-i* in that it is typically bilateral and multifocal, as in adults, and often presents with thunderclap headaches.<sup>174</sup>

Recent evidence suggests that enhancement of the vessel wall on dedicated vessel wall imaging may be able to predict which patients with *FCA-i* are more likely to have progressive disease.<sup>175</sup> In addition, vessel wall imaging may help diagnose cases of *FCA-d* when intramural thrombus is identified or reversible cerebral vasoconstriction syndrome when pathognomonic features are identified (T.J. Bernard, preliminary data, 2018).<sup>176</sup> The development of strategies to differentiate between *FCA-i* and *FCA-d* is particularly important because several cases of presumed *FCA-i* have been diagnosed as *FCA-d* only at autopsy.

Moyamoya is associated with  $\approx 6\%$  to 10% of all childhood strokes and TIA in children.<sup>177,178</sup> Initial evaluation should consist of clinical assessment, including consideration of specific populations with increased risk of moyamoya; radiographic studies, MRI, and potentially DSA; and, if moyamoya is identified, discussion of screening family members with imaging and genetic testing.

The arteriopathy of moyamoya has been reported in association with a wide range of distinct populations, clinical conditions, and genetic disorders.<sup>20,177,179,180</sup> Awareness of these associations is important to the physician in order to include moyamoya as a diagnostic possibility during the initial evaluation, especially in groups who may have confounding diagnoses (such as structural cardiac disease as a potential stroke cause in children with Down syndrome) and who are at high risk of recurrent stroke if not identified in a timely manner.<sup>20,181</sup>

Although most cases of pediatric moyamoya are idiopathic, there are certain population-based patterns. Historically, Asian ancestry is an increased risk factor for moyamoya, with up to 56% of Asian American patients with moyamoya found to harbor a specific mutation of *RNF213*.<sup>182</sup> In contrast, only 3.6% to 29% of non-Asian patients with moyamoya had *RNF213* mutations.<sup>182</sup> White patients with moyamoya in the United States have a higher rate of autoimmune disorders, including type 1 diabetes mellitus (8.5% versus 0.4% in the general population) and thyroid disease (17% versus 8%).<sup>183</sup> Down syndrome (with a 26-fold increased likelihood of moyamoya), neurofibromatosis type I (with  $\approx 2\%$ –5% prevalence of moyamoya), SCD, and other associated conditions are summarized in Table 2.<sup>177,181,184–199</sup>

If moyamoya is identified on MRI, then DSA should be strongly considered because this modality has increased diagnostic sensitivity for moyamoya compared with MRI (including the ability to better differentiate vasculitis) and offers important data germane to preoperative planning. Specifically, transdural collaterals visualized on DSA are critical biomarkers of disease that can assess angiogenic potential (particularly in combination with proteomic assays), that can predict 1-year radiographic outcomes from surgery, and, when incorporated into surgical planning, have been demonstrated to reduce

perioperative stroke complications by >40% (especially in the setting of previous cranial surgery or shunting).<sup>179,200–204</sup> The risk of angiogram is generally low, with ≈1% complication rates at high-volume centers.<sup>205,206</sup> Contraindications include contrast allergies, aortic stenosis, and general medical instability precluding a sedated or anesthetized procedure.

When the diagnosis of moyamoya is made in a child, families frequently ask about the need to screen other relatives. Initial screening is commonly defined as MRI and MRA, looking for the defining radiographic characteristics of moyamoya.<sup>179,207–209</sup> Given the low rate of familial involvement (3.4%) in a large North American series, imaging of unaffected family members is generally reserved for first-degree relatives of patients who have other first- or second-degree relatives with documented moyamoya, who have clinical histories strongly suggestive of moyamoya (TIA, stroke, severe headaches, or seizures without identified cause), or who are identical twins.<sup>208</sup> Absent specific symptoms, it is reasonable to delay imaging until an age at which the child can tolerate an MRI without anesthesia. If an initial screening MRI is normal, it is unclear what, if any, interval is appropriate to recommend until a follow-up scan. However, data indicate that previously normal scans can later show clear (and clinically symptomatic) moyamoya, suggesting that follow-up may have utility.<sup>190</sup>

Genetic testing and counseling are also relevant to children and families diagnosed with moyamoya, particularly in that there is generally a high penetrance of the phenotype with most mutations and there is a potential surgical treatment if identified (unlike the less clear implications of testing for other conditions in medicine). In North America, only a small minority of pediatric moyamoya cases (<5%) appear to have clear genetic associations, unless the children have Asian heritage (in whom *RNF213* mutations are seen in 30%–50%).<sup>182,208,210,211</sup> The presence of an *RNF213* mutation with moyamoya has marked significance for familial screening because data suggest that familial penetrance is ≈23%, and if an individual carries the mutation, there is a nearly 50% likelihood of manifesting arteriopathy.<sup>211,212</sup> Other mutations are rarer but may be detected by specific clinical or radiographic phenotypes (*ACTA2* carriers with distinctive stellate arteries branching from a dilated proximal internal carotid, *GUCY* mutations with achalasia, etc).<sup>182,197,210–215</sup> Current moyamoya-associated mutations are noted in Table 2.

### Thrombophilia

In developmental hemostasis, the hemostatic system consists of platelets and proteins, which become activated and interact to form a thrombus (coagulation) followed by thrombus degradation (fibrinolysis). Both pathways have natural inhibitors modulating these processes, some of which include protein C, protein S, and antithrombin in coagulation and plasminogen activator inhibitor in fibrinolysis. In children, levels of these proteins are decreased and approach adult levels at various times during development.

Thrombophilia conditions leading to hypercoagulable states resulting from either inherited or acquired conditions have been associated with pediatric AIS. Some of these conditions have been directly associated with first incident pediatric AIS,<sup>216,217</sup> but the extent of their contribution

remains controversial because of the variability of testing in studies.<sup>218</sup> In fact, these conditions may act as triggers for AIS in the presence of other factors (eg, cardiac disease). Inherited conditions statistically associated with first incident AIS include increased levels of proteins (lipoprotein[a]), decreased levels of inhibitors of coagulation (protein C and antithrombin), or gene mutations resulting in either the inability of protein inhibition during hemostasis (prothrombin gene mutation *PTG20210* and *FVL G1691A*) or the production of an abnormal compound (increased homocysteine levels resulting from methylene tetrahydrofolate reductase C677T polymorphism).<sup>217</sup> Acquired conditions include the presence of abnormal proteins (antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, or anti- $\beta_2$  glycoprotein Ib antibodies).<sup>217</sup> Of these, elevated lipoprotein(a), FVL, *PTG20210*, protein C, and methylene tetrahydrofolate reductase polymorphisms (which result in increased homocysteine) independently increase the risk of AIS.<sup>216</sup> It is important to realize that a homozygous FVL mutation has a much higher risk for thrombosis than a population variant such as a heterozygous FVL mutation. Currently, a relationship between recurrent stroke and the following 2 abnormalities has been demonstrated in a single-center longitudinal study: protein C deficiency (relative risk, 3.5 [95% CI, 1.1–10.9]) and lipoprotein(a) (relative risk, 4.4 [95% CI, 1.9–10.5]).<sup>219</sup>

In clinical studies, testing for thrombophilic abnormalities will further characterize the pathogenesis of AIS and may determine any relationship to recurrent stroke. Without an adequately powered study to detect the impact of genetic thrombophilia on recurrence risk in pediatric AIS, definite recommendations about evaluation remain challenging.<sup>218</sup> However, laboratory testing outside of clinical studies may provide guidance for long-term management of the patient. Abnormalities in protein C, antithrombin, and, less often, FVL can result in venous thrombosis, with risk increasing with age. In postmenarchal women, use of oral contraceptives and pregnancy increase the risk of development of thrombosis in the presence of these conditions. Thromboprophylaxis may be considered after referral to an expert in this area.

Increased levels of homocysteine are associated with venous thrombosis and vascular disease in adolescence and adulthood.<sup>37</sup> Use of folic acid may decrease homocysteine levels and risk of sequelae.<sup>220</sup> Increased levels of lipoprotein(a) have been associated with vascular disease. Although there is no specific treatment, diet and lifestyle changes may decrease levels.

Children will often have positive antiphospholipid antibodies after a viral illness.<sup>221</sup> If antiphospholipid antibodies are assessed immediately after a stroke, the test should be repeated at 12 weeks after the first positive test to check validity because levels are usually higher in acute stroke. If their presence is confirmed, these children may have an increased risk for thrombosis.<sup>221</sup> In addition, non-DNA testing may need to be repeated when the child is older to ensure that adult levels of proteins have been attained. Finally, measurement of proteins or homocysteine levels in the acute phase of stroke may not be accurate and should be repeated after the acute event.

The importance of determining the presence of hemostatic protein abnormalities in children with age-appropriate ranges cannot be underestimated.

#### *Systemic Causes: Inflammatory and Genetic/Metabolic*

Systemic causes of childhood AIS are less common than other causes but are important to identify because they often alter treatment strategies. Typically, systemic causes of childhood AIS include inflammatory causes and genetic/metabolic syndromes.

Inflammatory causes of childhood stroke have some overlap with FCA-i. Childhood primary angiitis of the central nervous system (cPACNS) has an angiographic appearance similar to that of FCA-i and, when monophasic, may simply be a different term for the same disease. Progressive cPACNS may be an important separate entity that has a different presentation. Rather than presenting with AIS, children diagnosed with progressive cPACNS are more likely to have headaches and neurocognitive changes, especially mood disturbances.<sup>222</sup> Initial inflammatory serum markers may be abnormal in some of the patients with cPACNS<sup>222</sup> and predictive of recurrent events.<sup>223</sup> The presence of persistent serum inflammatory biomarkers (ie, C-reactive protein and erythrocyte sedimentation rate) beyond 1 month after stroke is suggestive of a potential progressive inflammatory disease such as cPACNS, systemic lupus erythematosus, deficiency of adenosine deaminase 2, or polyarteritis nodosa. Other clues to an inflammatory/rheumatologic disease include renal disease, proteinuria, hand nodules, frequent fevers, and livedo reticularis (Table 2). Diagnosis of these syndromes is particularly important because they may alter management, requiring long-term immunosuppressive treatment and, in the case of deficiency of adenosine deaminase 2, stopping antithrombotic therapy.

Genetic and metabolic causes of stroke are rare but have important implications for treatment and counseling of the patient family members. As previously described, specific genetic testing should be considered in moyamoya and dissection with hypermobility on examination (ie, connective tissue disorders). Other specific syndromes that should be considered in childhood AIS include ACTA2 syndrome, *COL4A1* mutations, and PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies). Mitochondrial disorders can cause stroke-like episodes that can be distinguished from AIS in that their radiographic lesions are not in an arterial distribution.

ACTA2 is an autosomal dominant syndrome that typically presents with neuroimaging findings that include subcortical white matter infarcts and straight ectatic bilateral internal carotid arteries, although aneurysms and irregularities of intracranial vessels and focal infarcts are also reported.<sup>145,197,224,225</sup> Sequelae of the mutation are largely secondary to smooth muscle dysfunction and include patent ductus arteriosus at birth, congenitally dilated and unreactive pupils, aortic arch dilation, pulmonary hypertension, hypotonic bladder, and malrotation of the gut.<sup>145,197,224,225</sup>

COL4A1 is a protein that in humans is encoded by the *COL4A1* gene on chromosome 13. It is ubiquitously

expressed in many tissues and cell types. COL4A1 plays a role in angiogenesis. Mutations in the gene have been linked to diseases of the brain, muscle, kidney, eye, and cardiovascular system.<sup>226</sup>

PHACE syndrome also presents with vascular abnormalities, but they are often less pathological. Children with PHACE present at birth with a segmental infantile hemangioma on the head/scalp, typically >5 cm, or multiple hemangiomas. Other major criteria for diagnosis include arterial abnormalities of the cervical or intracranial arteries, posterior fossa brain anomalies, aortic arch anomalies, posterior segment ocular anomalies, and midline anomalies of the chest or abdomen. The definite diagnosis of PHACE syndrome is based on the history of infantile facial hemangioma and 2 additional major criteria. Diagnosis is important because MRI of the head, MRA of the head and neck, cardiac echocardiogram, and ophthalmology consult are warranted. In addition, routine surveillance of head and neck vasculature is indicated in cases of intermediate- or high-risk vascular lesions such as complex lesions or lesions suggestive of moyamoya. Patients with PHACE syndrome are also at high risk for developing other systemic complications such as endocrinopathies.<sup>149</sup>

The characteristics of mitochondrial strokes are different from those of thrombotic events, primarily in that they do not conform to vascular territories.<sup>150–154,227–230</sup> MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) typically presents in a previously normal child with a history of migrainous headaches and vomiting.<sup>230–232</sup> Children with MELAS often have short stature and a history of seizures. Lesions are predominantly occipital and may have paradoxically increased apparent diffusion coefficient on diffusion-weighted imaging.<sup>233</sup> In addition, diffusion-weighted imaging may demonstrate hyperintensities in gyriform pattern, and T2 anomalies may expand on sequential imaging.<sup>150,233</sup> Lactic acidosis, elevated CSF protein, and ragged red fibers on muscle biopsy are typical features of the disease,<sup>233</sup> although diagnosis is confirmed through genetic sequencing. POLG1 spectrum disorders should be suspected in children with stroke and similar MRI findings in whom there is a history of encephalopathy, status epilepticus, or premorbid developmental delay.<sup>153,154</sup>

### **Evaluation of a Child With AIS**

#### *Primary Evaluation*

The basic evaluation of children with AIS is based on screening for the most common causes of stroke in children and should try to identify those causes that might lead to an immediate or delayed recurrent stroke. This includes evaluation of cardiac structure and function, radiographic screening of intracranial and extracranial cerebral vessels, thrombophilia testing, and serum analysis of inflammatory markers (Table 1). In children with stroke, MRI with diffusion-weighted imaging is the preferred method of diagnosis because there are many mimics of childhood AIS, including hemiplegic migraine, Todd paralysis, and psychogenic causes.<sup>234</sup> A recent consensus-based statement from members of the IPSS provides a description of suggested sequences for MRI and MRA in acute stroke (Table 1).<sup>144</sup> Once diagnosis is confirmed, most children should have additional evaluation with transthoracic echocardiogram, ECG, MRA of the head and neck, thrombophilia



studies, and inflammatory screening (Table 1). In some cases of known pathogenesis such as traumatic dissection or moyamoya, all of these studies may not be warranted. It is important to recognize, however, that childhood AIS is often associated with multiple risk factors<sup>235</sup> such as PFO and SCD or cardiac disease and cerebral arteriopathy.<sup>70,236</sup>

#### Secondary Evaluation

Further evaluation should be pursued in children with unexplained or recurrent stroke. In cases of arteriopathy or evidence of inflammatory disease lumbar puncture, rheumatologic screening and DSA are considerations. Patients with posterior circulation events and hyperextensibility may be candidates for neck imaging (to rule out cervical instability) or genetic screening to identify a connective tissue disorder. Undiagnosed metabolic, genetic, or rheumatologic syndromes should always be considered in children with unexplained recurrent AIS. Diagnostic clues to these syndromes are found in Table 2. Further evaluation is also dictated by the underlying pathogenesis. For instance, in moyamoya, patients usually require DSA in preparation for revascularization and consideration for an underlying genetic disorder (Table 2).

#### Considerations for Clinical Practice

1. Children with stroke typically undergo a transthoracic echocardiogram with bubble and are screened for an arrhythmia (via inpatient telemetry or electrocardiographic or Holter monitoring) unless a definitive noncardiac entity is found.
2. Imaging of the intracranial vessels is a standard component of a childhood AIS evaluation; MRA is the preferred modality because of the radiation and contrast exposure with CTA and DSA. In cases with moyamoya, DSA is typically performed to delineate anatomy before surgery.
3. Extracranial vessel imaging can be performed unless an alternative entity is found. Imaging should be of high enough quality to reasonably determine the presence/absence of a dissection or pseudoaneurysm.
4. In patients with multiple infarcts of the posterior circulation, DSA can evaluate the V3 segment. Head turning during a CTA or a DSA can reveal dynamic VA compression, but risks and benefits of such a maneuver should be carefully considered (eg, risk of thromboembolism with passive head turning under anesthesia if thrombus is present). Management of dynamic VA compression remains controversial.
5. Serial imaging of intracranial and extracranial arteriopathies (including CCAD, FCA-i, FCA-d, and moyamoya) can assist in monitoring for progression throughout the first year and possibly longer. The clinician should minimize the use of techniques that use radiation or contrast dyes when appropriate.
6. In cases of intracranial arteriopathies and posterior circulation stroke, families should be counseled about the high recurrence risk, particularly in the first year.
7. In cases of FCA, a lumbar puncture can evaluate inflammation and causative agents such as herpes simplex virus (via polymerase chain reaction) or VZV (via polymerase chain reaction and antibodies).

8. In cases of dissection and hypermobility on examination, clinicians should consider appropriate genetic screening for connective tissue disorders.
9. In cases of moyamoya, a neurosurgeon can assist in evaluating whether to revascularize; genetic counseling is helpful to discuss genetic disorders associated with moyamoya.
10. A thrombophilia evaluation is helpful in every case of childhood stroke, especially if there is no identifiable cause, medical history of thrombosis, or a first-degree relative with thrombosis history.
11. In cases without a definitive cause, screening for systemic causes such as serum testing of erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibody is helpful. Other rare causes of stroke also should be considered (Table 2), including deficiency of adenosine deaminase 2 in cases of stroke and livedo reticularis, ACAT2 in cases of straight ectatic internal carotid arteries, Fabry disease in cases with painful neuropathy, MELAS/POLGI in cases of stroke that does not conform to vascular territories, COL4A1 in cases of hemorrhage, and connective tissue disorders in cases of hyperextensibility and dissection.

#### Controversies in Current Practice

- Indication for transesophageal echocardiography in children with stroke
- Imprecise nomenclature to describe intracranial arteriopathies
- Extent of thrombophilia evaluation
- Threshold for screening patients for rare metabolic/genetic causes of childhood stroke
- Evaluation and treatment of dynamic VA compression
- PFO closure
- Treatment with antithrombotic agents if a nondominant heterozygous mutation is identified

#### Knowledge Gaps

- Role of PFO in childhood stroke pathophysiology
- Further clinical and pathophysiological understanding of posterior circulation strokes in children, especially the clinical entity consisting of V3 dissection/pseudoaneurysm, male predominance, and high recurrence risk
- Identifying which arteriopathies are inflammatory, infectious, or caused by adherent clot or dissection
- Role of steroids and acyclovir for the treatment of FCA
- Indication for genetic testing in children with dissection or moyamoya
- Utility of CSF studies in cases of FCA-i
- MRA screening of first-degree relatives of patients with moyamoya

#### Primary and Secondary Prevention of Childhood AIS

##### Primary Stroke Prevention in Children

Primary prevention has been difficult because the underlying causes of AIS are diverse and far different from the commonly occurring risk factors for adult stroke. Primary prevention has been accomplished in children with SCD, in whom long-term blood transfusion therapy decreases recurrence risk. (Stroke prevention in SCD is discussed in greater detail in the Stroke in SCD section below.) The first stroke might be prevented in some children with an intracardiac thrombus by anticoagulation or surgery. Aside from these high-risk situations, primary

stroke prevention has not been achieved in pediatric patients. Therefore, the treatment approach is, as in adults, focused on the prevention of recurrent stroke. These treatments include medical and surgical approaches, depending on the clinical scenario. Although there is little evidence to support enhancement of healthy behaviors to reduce stroke risk in children, it is important to establish healthy behaviors in childhood to reduce the risk of obesity and sedentary lifestyle, factors that lead to an increased risk later in life.

#### *Risk of Recurrent Stroke*

Although neonates have a low risk of recurrent AIS (except in the setting of complex congenital heart disease),<sup>28</sup> the risk of recurrent AIS in older children is substantial. More than 1 in 10 children will have another stroke within a year of their index stroke.<sup>20</sup> Children with arteriopathies (particularly progressive arteriopathies) have the highest recurrence risk: 1 in 3 will have another stroke within a year. Children with posterior circulation stroke have an increased recurrence rate compared with children with anterior circulation stroke.<sup>163</sup> As in adult stroke, antithrombotic agents are a mainstay of stroke prevention. During the 1990s when children with AIS did not systematically receive antithrombotic treatment, reported recurrence rates for AIS or TIA were 30% to 50%.<sup>43,237</sup> Both antiplatelet (eg, aspirin) and anticoagulant (LMWH or warfarin) medications appear to be safe in initial AIS,<sup>238,239</sup> although relative contraindications to anticoagulant therapy include very large acute infarcts or severe bleeding diathesis.

#### *Antithrombotic Therapies Used for Stroke Prevention*

The antiplatelet therapy most commonly used in children with AIS is aspirin. The anticoagulants most often used are LMWH and vitamin K antagonists. Direct oral anticoagulants (antithrombin agent: dabigatran; anti-factor Xa agents: rivaroxaban, apixaban, edoxaban) have been approved for the primary prevention of adult stroke caused by atrial fibrillation<sup>240</sup> and are currently being studied in children with venous thrombosis, including CSVT. There are no studies using these agents in childhood AIS.

The 2008 AHA scientific statement<sup>37</sup> generally supported either initial aspirin or LMWH for initial therapy in pediatric AIS. However, it remains unclear in which situations antiplatelet or anticoagulant medications are the best initial and long-term secondary prevention treatment in children. Antithrombotic treatment decisions are difficult and require individualization; children with AIS should therefore be referred to and managed in pediatric centers with on-site expertise and protocols for the management of pediatric stroke. The availability of hematology consultation with experience in stroke management is invaluable in managing children with thromboembolic stroke.

For children with uncharacterized childhood AIS, either anticoagulation or aspirin may be considered during the initial 5 to 7 days after presentation while the cause is being investigated. Once investigations for cause are complete, further refinement of the medical approach can be applied. For stroke resulting from cardiac embolism (including neonates) or in individuals with a prior thrombosis or a known prothrombotic disorder, maintenance therapy typically consists of continued anticoagulation with LMWH or warfarin for 3

to 6 months or longer. Consideration by a multidisciplinary team, including an expert in pediatric thrombosis, should be given to longer-term therapy in the presence of a severe genetic thrombophilia (eg, protein C deficiency, antithrombin deficiency, hyperhomocysteinemia). In most other children, continued maintenance therapy consists of aspirin<sup>241</sup> dosed at 3 to 5 mg·kg<sup>-1</sup>·d<sup>-1</sup>. The duration of aspirin therapy depends on the underlying condition and the ongoing risk of recurrent stroke. Most children are treated for 2 years to cover the time window when the vast majority of recurrent strokes occur.<sup>20</sup> However, the duration of antithrombotic treatment in the setting of persistent arteriopathy is unknown. No clinical trials have evaluated whether antiplatelet or anticoagulant medication is best; however, it is clear that the absence of antithrombotic therapy is associated with a 1.5- to 2-fold increased risk of recurrent stroke after index childhood AIS.<sup>8</sup>

#### *Aspirin Resistance*

Aspirin inhibits platelet cyclooxygenase-1 and prevents thromboxane B<sub>2</sub> production.<sup>242</sup> Aspirin resistance has been widely discussed in the adult literature,<sup>243</sup> including the development of major cardiovascular events secondary to lack of response to aspirin as measured in the laboratory.<sup>244</sup> However, studies do not support lack of inactivation of cyclooxygenase-1 by aspirin.<sup>245–248</sup> Enteric-coated aspirin, but not the immediate-release preparation, may result in delayed and reduced drug absorption.<sup>245,248–250</sup> Patient nonadherence and drug-drug interactions between aspirin and a nonsteroidal anti-inflammatory drug, that is, ibuprofen or naproxen, probably account for many reports of resistance.<sup>242</sup> Drug-drug interactions can be mitigated by administering aspirin 2 hours before a nonsteroidal anti-inflammatory drug.<sup>251</sup> Use of multiple daily doses of ibuprofen, however, will competitively inhibit daily low-dose aspirin platelet inhibition.<sup>251</sup> Patients with diabetes mellitus and thrombocytopenia have a faster cyclooxygenase-1 recovery; thus, aspirin should typically be given twice per day.<sup>248,252–256</sup>

#### *PFO Closure for Stroke Prevention*

As discussed, the role and treatment of PFO remain controversial in pediatric stroke. Several clinical trials of PFO closure for selected adult patients with cryptogenic stroke suggest a benefit in terms of reduction in recurrent stroke risk, although the device itself was associated with complications such as atrial fibrillation. Pediatric trials are lacking, but a large prospective observational study suggested no benefit to closure.<sup>257</sup>

#### *Considerations for Clinical Practice*

1. Children with acute stroke are typically treated initially with antithrombotic agents to prevent initial recurrent stroke, either an antiplatelet (aspirin) or an anticoagulant (LMWH or UFH), unless contraindications exist. For AIS resulting from cardiac and thrombophilia causes, anticoagulants are usually the preferred approach.
2. Long-term antithrombotic therapy may prevent later recurrent strokes; this includes either antiplatelet agents (aspirin) or anticoagulants (LMWH or warfarin), depending on the pathogenesis. Preventive medications are typically maintained for at least 2 years and, in most cases, longer term. Protection of the gastrointestinal tract should be considered with long-term aspirin use.

### Controversies in Current Practice

- For initial therapy pending confirmation of the cause, whether anticoagulant or antiplatelet therapy is best is controversial. Safety data support both approaches.
- Secondary stroke prevention strategies for many specific childhood AIS pathogeneses remain controversial, for example, steroids for FCA-i, anticoagulation for pediatric arterial dissection, and timing/type of surgery for moyamoya (see Stroke Prevention in Children With Moyamoya). The significance of PFOs (and hence the utility of PFO closure) also remains controversial in pediatric stroke.

### Knowledge Gaps

- The duration of antithrombotic therapy remains unknown, and further studies are required. However, recurrent stroke continues at lower frequencies for years after the index stroke in some children.
- Outside the setting of SCD, there have been no stroke prevention trials in children.

### Stroke Prevention in Children With Moyamoya

**Imaging Evaluation.** MRI sequences that are particularly useful in moyamoya include fluid-attenuated inversion recovery images to assess chronic infarct burden and areas of slow flow (as evidenced by the so-called ivy sign, or serpentine sulcal hyperintensity, present in  $\approx 80\%$  of cases) and MRA to visualize the circle of Willis.<sup>177,179,200,201,258–262</sup> Advances in vessel wall imaging can help to distinguish between vasculitis and moyamoya.<sup>263</sup> DSA is important for surgical planning to avoid disruption of natural collaterals from the external carotid circulation.

**Surgical Management.** Surgical revascularization is the primary treatment for moyamoya disease or syndrome.<sup>177,179,209,264,265</sup> Key points of surgical management focus on indications for surgery, timing of operation, selection of specific technique, and expectations of outcome after revascularization. Tenets of perioperative care include careful hydration (often with intravenous fluids at 1.25–1.5 times maintenance), avoidance of hyperventilation-related cerebral vasoconstriction (often caused by crying, pain, or emesis), and careful maintenance of blood pressure to avoid hypotension relative to the patient's baseline to maintain cerebral perfusion. Indications for surgical intervention include strokes, TIAs, or other clinical or radiographic evidence of compromised cerebral blood flow or cerebral perfusion reserve. Relative contraindications include very early-stage arteriopathy with normal perfusion and profound medical or neurological compromise.<sup>177,179,190,266</sup> Of note, the sparse data focused on surgical revascularization in children with ACTA2 arteriopathy suggest that this is a very high-risk population; however, indirect revascularization is still offered after appropriate risk/benefit discussions with families and with particularly strict intraoperative blood pressure control.<sup>267</sup>

Once a patient has met the criteria for revascularization, surgery should generally be done as soon as feasible, although delays of several weeks may be appropriate to coordinate skilled anesthetic and operating room staffing or to allow swelling from an acute stroke to abate.<sup>179</sup> Limited data suggest possible benefit of performing bilateral surgery (if indicated)

under a single anesthetic; however, this remains controversial, and current practices vary.<sup>268</sup>

**Surgical Approach and Outcomes.** There are 2 main categories of surgical revascularization: direct (which involves transecting a donor vessel and anastomosing it directly to a single recipient cortical vessel) and indirect (which uses some vascularized tissue such as a vessel, muscle, or pericranium to stimulate the growth of a new vascular network when placed in contact with the brain).<sup>177</sup> A 2017 systematic review of the literature and decision analysis describes the distinct risks and benefits of each approach and concludes that for children with moyamoya, the indirect approach yielded greater quality-adjusted life-years at 10 years after surgery than the direct approach.<sup>269</sup> In practice, the preferred approach continues to vary between institutions.

There is abundant evidence that surgical revascularization improves a wide range of outcome metrics in children with moyamoya. Radiographically, revascularization reverses white matter changes, improves measures of cerebral oxygenation, and increases cerebral blood flow while stabilizing stroke burden, despite progressive arteriopathy.<sup>191,265,270–274</sup> Clinically, surgery decreases ischemic symptoms, headache, and risk of hemorrhage and markedly reduces stroke rates (without surgery, stroke risk is 32% at 1 year and 66%–90% at 5 years; after surgery, stroke risk drops to  $<5\%$  for most populations at both the 1- and 5-year time points) while concomitantly improving functional and cognitive outcomes.<sup>20,190,265,269,272,273,275–277</sup>

As for many surgical procedures, an important predictor of surgical outcome is whether the child is treated at a high-volume center with a dedicated pediatric cerebrovascular team.<sup>278</sup> Recent data from a national database analysis reveal that high-volume centers (averaging  $>30$  pediatric cerebrovascular procedures annually) had shorter lengths of stay (32%), lower costs (57%), an 8-fold more likely discharge to home (versus rehabilitation), and a 15-fold lower rate of death.<sup>279</sup> These data support regionalization of care with centers of excellence for subspecialized care.

**Stroke Prevention in Children With Dynamic VA Compression** Rotation (or extension) of the neck can result in dynamic VA compression (or colloquially bow hunter syndrome, referring to the turning of the head when using a bow as an archer). In patients with single-VA physiology (resulting from hypoplasia or prior disease of the contralateral VA), dynamic compression can trigger symptoms of brainstem or cerebellar ischemia with head turning: transient vertigo, weakness, and fainting, with more severe cases leading to completed stroke.<sup>146,280,281</sup> In children, the more common presentation is recurrent posterior circulation AIS, presumably caused by artery-to-artery thromboembolism.

The pathology is typically related to dynamic compression at a specific point along the course of the VA, often at the C1–2 vertebral body level, involving the V3 segment, although compression at any level in the cervical spine can be a problem, with some reports finding C5–7 involvement in  $\approx 50\%$  of individuals.<sup>146,282</sup> The involved arterial segment can appear normal when imaged with the head at midline or can have mild irregularity, stenosis, or even frank dissection, presumably resulting from chronic mechanical injury. Compression is typically left-sided,

although bilateral cases have been reported in children.<sup>146,282</sup> Structural lesions (in children, tendon bands, congenital arcuate foramen, bony ponticles) are common causes, but ligamentous laxity with hyperrotation or congenitally narrow bony canals may also contribute, and disease may be multifactorial.<sup>146,280–282</sup>

Evaluation may begin with transcranial Doppler (TCD), which may have limited sensitivity but has very high specificity, particularly if VA velocities drop to <20% of baseline with rotation.<sup>283</sup> Neck MRI and CT may help to identify structural lesions, and neck MRA and CTA may demonstrate the presence of arterial irregularity or dissection, but the definitive diagnosis often requires a dynamic DSA looking for abrogation of flow in the VA with rotation.<sup>146,280–282</sup> Passive head turning under anesthesia must be performed with caution, particularly in patients dependent on a single VA (because of hypoplasia, aplasia, or occlusion of the other VA) or with acute thrombus in the VA that could embolize during the maneuver. The significance of dynamic VA compression remains controversial because some degree of compression may be normal. Indications of pathological compression include recurrent posterior circulation strokes and evidence of arterial irregularity or frank dissection at the level of compression, suggestive of mechanical trauma to the VA. Treatment is predicated on either decompression or fusing the abnormal motion segment of the spine.<sup>146,282</sup> In pediatric patients, follow-up is particularly important after decompression to identify delayed instability of the spine that might later require fusion.

### **Stroke in SCD**

Children with SCD, more specifically children with homozygous hemoglobin SS, referred to as sickle cell anemia, have well-documented increased rates of neurological complications, including but not limited to silent infarcts, strokes, seizures with strokes, CSVT, cerebral hemorrhages, and hyperviscosity syndrome. Other SCD phenotypes in order of decreasing frequency in the United States include the compound heterozygotes hemoglobin sickle cell and hemoglobin S $\beta^0$  thalassemia. All children with SCD phenotypes have a minimum of 50% hemoglobin S levels. In children with hemoglobin SS and S $\beta^0$  thalassemia, the hemoglobin S levels can range from  $\approx$ 85% to 95% with no hemoglobin A. The epidemiology and controlled clinical trials for primary and secondary prevention of strokes in children with SCD include only children with hemoglobin SS and hemoglobin S $\beta^0$  thalassemia. Five clinical trials have been conducted in children with these 2 phenotypes. The considerations for clinical practice for primary and secondary stroke management in children with hemoglobin SS are based on the results of these trials.

### *Acute Management of Suspected Strokes in Children With SCD*

Children with SCD presenting with focal neurological deficits or first-time seizure should prompt a neurological consult and receive a brain MRI; if an acute infarct is present, MRA or MRV should be considered, depending on the pattern of the infarct. The MRV is required in the acute setting because children with SCD have increased propensity to develop CSVT, requiring a change in management if CSVT is detected.

To avoid undertreatment of stroke in this high-risk population presenting with focal neurological deficits, prompt

intervention with simple blood transfusion therapy within several hours of presentation should occur. This is necessary to increase oxygen delivery if the hemoglobin is <10 g/dL. In general, the simple transfusion should be provided as soon as possible after focal neurological deficits and even before the MRI. With simple blood transfusion therapy, the hemoglobin should not be increased to >11 g/dL as the target. Typically, in children, for every 10 cm<sup>3</sup>/kg of packed red blood cells transfused, we expect the hemoglobin to increase  $\approx$ 2.5 to 3.0 g. To avoid hyperviscosity syndrome, the hemoglobin level should be checked within 2 hours after the transfusion. If the baseline hemoglobin is >10 g/dL, as may be the case in with children who present with hemoglobin SCD, an initial exchange blood transfusion should be performed to decrease the hemoglobin level to <10 g/dL. Regardless of the type of SCD, after a simple transfusion has been given within a 6-hour window of presentation, an exchange transfusion is recommended to lower the hemoglobin S level to  $\approx$ 15% and to increase the hemoglobin to  $\approx$ 10 g/dL. No absolute threshold is established for when an exchange transfusion should not be completed after an acute focal neurological deficit (stroke or TIA). To address the challenge of negative diffusion-weighted MRI of the brain in the setting of acute neurological event with a clinical suspicion of a stroke, repeating the MRI  $\approx$ 2 to 4 weeks after the acute presentation should be considered, especially to clarify whether the focal event was indeed a stroke.

### *Primary Stroke Prevention in Children With SCD*

Fortunately, over the past 20 years, the prevalence of stroke has decreased dramatically in children with hemoglobin SS. Adams et al<sup>284</sup> first demonstrated that an abnormal TCD measurement of the time-averaged mean maximum velocity of at least 200 cm/s in the terminal portion of the internal carotid or the proximal portion of the MCA was associated with an incidence of stroke of  $\approx$ 10 events per 100 patient-years. In this trial, Adams et al demonstrated that children with abnormal TCD measurements treated with regular blood transfusion therapy had a relative risk reduction of strokes of 92% compared with children with abnormal TCD measurements who did not receive any therapy in the trial.<sup>284</sup> The number of children who needed to be treated (7) was considered reasonable to accept when offered an opportunity to prevent strokes.<sup>284</sup>

To reduce the lifelong burden of regular blood transfusion therapy to prevent stroke, the TWITCH study (TCD With Transfusions Changing to Hydroxyurea), a multicenter, open-label, phase 3 noninferiority trial, was completed. Participants with abnormal TCD velocities were randomly allocated either to receive blood transfusion therapy or, after 12 months of monthly blood transfusion therapy, to be switched over to hydroxyurea therapy.<sup>285</sup> During the first interim analysis, noninferiority was demonstrated between the 2 treatment arms, and the study was terminated. No strokes occurred in either treatment arm, and MRI of the brain did not reveal any new silent strokes. The results of the trial have substantially changed the care for thousands of children with hemoglobin SS and hemoglobin S $\beta^0$  thalassemia with abnormal TCD velocities. A subgroup of children with abnormal TCD velocities and MRA-defined vasculopathy were excluded from the trial. For this group of children, there are mixed opinions about

switching them to hydroxyurea from regular blood transfusion therapy.

Potentially, a TCD measurement could be obtained after the child has been switched over to hydroxyurea; however, persistence of an abnormal TCD measurement after treatment with blood transfusion therapy does not confer an increased risk of stroke.<sup>286</sup> As a follow-up analysis to the STOP trial (Optimizing Primary Stroke Prevention in Sickle Cell Anemia), Kwiatkowski et al<sup>286</sup> demonstrated that TCD velocities remained abnormal in 21% of the children 2.4 years after receiving regular blood transfusion therapy, and none of these children subsequently had a stroke. Untreated SCD in children with abnormal TCD measurements of least 200 cm/s is associated with an increased rate of strokes; however, no evidence exists that after treatment with either regular blood transfusion therapy or hydroxyurea, abnormal time-averaged mean maximum velocity predicts future strokes.

#### *Secondary Stroke Prevention in Children With SCD*

A randomized controlled trial,<sup>287</sup> a single-arm controlled trial,<sup>288</sup> and a pooled analysis of several multicenter and single-center trials<sup>289</sup> have demonstrated that blood transfusion therapy is the preferred therapy for secondary stroke prevention compared with hydroxyurea therapy or observation. In 2012, Ware and colleagues<sup>287</sup> demonstrated that regular blood transfusion therapy was superior to hydroxyurea therapy for secondary stroke prevention. Adjudicated strokes occurred in 10% (7 of 67) of the group randomized to hydroxyurea therapy and none (0 of 66) of the group receiving standard therapy. The iron stores were equivalent in both groups. Thus, the study was stopped during the interim analysis on the basis of the futility of reaching the composite end point. In 2011, Hulbert and colleagues<sup>288</sup> demonstrated that regular blood transfusion therapy, even with a maximum average hemoglobin S level of <30%, was associated with a high recurrence rate of strokes and silent infarcts. Over a median duration of 5.4 years of prospective follow-up, 45% of the participants had recurrence of a cerebral infarct, either stroke or silent infarct. Worsening arteriopathy assessed with MRA was associated with an increase relative risk of infarct recurrence (stroke or silent infarct; relative risk, 12.7 [95% CI, 2.6–60.5];  $P=0.001$ ).

#### *Prevention of Strokes in Low-Resource Settings*

When studies are evaluated in a pooled analysis along with other trials, there is a clear pattern that regular blood transfusion therapy is superior to hydroxyurea and that hydroxyurea is superior to only observation for secondary stroke prevention.<sup>289</sup> The expected incidence rates of stroke recurrence while on regular blood transfusion therapy, hydroxyurea therapy, or no therapy were found to be 1.9 (95% CI, 1.0–2.9), 3.8 (95% CI, 1.9–5.7), and 29.1 (95% CI, 19.2–38.9) events per 100 patient-years, respectively. What is not known is the actual hydroxyurea dose associated with efficacious secondary stroke prevention while minimizing associated toxicity.<sup>289</sup> Traditionally, 3 options are available: 10 mg·kg<sup>-1</sup>·d<sup>-1</sup> (low dose), 20 mg·kg<sup>-1</sup>·d<sup>-1</sup> (moderate dose), and 25 to 35 mg·kg<sup>-1</sup>·d<sup>-1</sup> (maximum tolerated dose). The relative risks and benefits of each dose are unknown and may depend on local

resources for laboratory surveillance with the various doses of hydroxyurea.

#### *Alternative Strategies of Secondary Stroke Prevention*

Other less established therapies for secondary stroke prevention include surgical revascularization procedures<sup>273,274,290</sup> and hematopoietic stem cell transplantation.<sup>291,292</sup> No study to date has used a randomized controlled trial design or a rigorous before-and-after evaluation to assess neurological injury, including serial long-term assessment of neurological and neuroimaging changes with a central adjudication committee. We highly recommend that children with strokes who undergo revascularization procedures, hematopoietic stem cell transplantations, or both participate in long-term multicenter clinical trials with formal stopping rules, central adjudication of primary and secondary outcomes, and registration in [ClinicalTrials.gov](http://ClinicalTrials.gov). Even without major funding, a team-based learning collaborative effort may be feasible.<sup>290</sup>

#### *Stroke Prevention in Children With Preexisting Silent Infarcts*

The most common central nervous system complication in children with hemoglobin SS and hemoglobin Sβ<sup>0</sup> thalassemia is silent infarction, occurring in up to 33% of children with hemoglobin SS with normal TCD measurements before 15 years of age. Silent infarcts are defined as an infarct-like MRI lesion at least 3 mm in 1 dimension and visible in 2 planes on fluid-attenuated inversion recovery T2-weighted sequences and the absence of a neurological examination finding referable to the lesion.<sup>293</sup> The importance of a pediatric neurological examination is underscored by the fact that in a clinical trial setting, 7% of the children classified as having a silent infarct by hematologists were later identified as having a stroke when evaluated by a pediatric neurologist.<sup>293</sup> In a pooled analysis of 10 studies, children with hemoglobin SS with and without silent infarcts had a full-scale IQ difference of 5 points.<sup>294</sup>

The only evidence-based treatment for silent infarcts is regular blood transfusion therapy, with the goal of keeping the hemoglobin S percentage <30%. The National Institute of Neurological Disorders and Stroke–funded SIT trial (Silent Cerebral Infarct Transfusion) demonstrated that children with silent infarcts and normal TCD velocities randomly allocated to regular blood transfusion or observation had a 58% relative risk reduction of new or progressive cerebral infarcts (silent infarcts or stroke).<sup>293</sup> Thus, children with silent infarcts and normal TCD velocities not treated with regular blood transfusion therapy are at increased risk of cerebral infarcts (strokes or silent infarcts). However, for those receiving regular blood transfusion therapy, the number needed to treat was 13 to prevent 1 cerebral infarct recurrence. Other nonneurological benefits occur when regular blood transfusions are started compared with only observing silent infarcts. These benefits include statistically significant and clinically relevant decreases in incidence rates in vaso-occlusive pain events and acute chest syndrome<sup>295</sup> and improved quality of life.<sup>296</sup> The consequence of regular blood transfusions include, after a year, iron chelation to attenuate the excessive iron stores.

Four observations provide evidence to inform families and to screen for silent infarcts in school-aged children with hemoglobin SS and SB<sup>0</sup> thalassemia. Silent infarcts are associated with cognitive impairment<sup>294</sup> and poor school

performance<sup>295,297</sup>; are risk factors for future strokes and silent infarcts in children with normal TCD measurements<sup>293</sup>; can be treated with regular blood transfusion to substantially reduce the incidence rate of stroke and silent infarct recurrence<sup>293</sup>; and are common, occurring in at least 33% of school-aged children.<sup>293</sup> On the basis of this evidence, families should at least be informed of the risk of their child having a silent infarct; providers should consider screening for a silent infarct at least once with a nonsedated brain MRI. If a silent infarct is identified, then a formal cognitive assessment is useful to secure additional resources in school such as an Individual Education Plan or a 504 plan. The family should also be informed that regular blood transfusion therapy for at least 3 years is the only evidence-based strategy to prevent further neurological injury (strokes or infarcts). Given that children with silent infarcts and normal TCD velocities are at increased risk for developing strokes and silent infarcts that may go undetected, surveillance MRI of the brain every 1 to 2 years to identify progression should be considered.

Unlike in secondary prevention for strokes, for which hydroxyurea therapy has some efficacy in decreasing the rate of stroke recurrence, no similar studies have been completed in children with hemoglobin SS or S $\beta^0$  thalassemia and silent infarcts with conclusive evidence.<sup>298</sup> Although cerebral vasculopathy defined with MRA is considered a risk factor for strokes, in children with silent infarcts and normal TCD velocities, MRA-defined vasculopathy has a low prevalence (<5%) and has not been demonstrated to predict future infarct recurrence.<sup>299</sup>

#### *Avoiding Hyperviscosity Syndrome in Children With SCD*

In children and adults with SCD, a rapid rise in hemoglobin to >10 g/dL may result in hyperviscosity syndrome and devastating neurological sequelae, including but not limited to CSVT and multiple cerebral infarcts in a non-border-zone region. Given that hyperviscosity syndrome is often an iatrogenic complication of simple blood transfusion therapy,<sup>300,301</sup> limited published data describe the time course and sequelae. However, SCD providers are familiar with the sequelae, particularly the neurological sequelae, and try to avoid its occurrence. If after a simple transfusion the hemoglobin is >12 g/dL, then phlebotomy should be done promptly to decrease the hemoglobin to less than  $\approx$ 10 g/dL. When the hemoglobin is >10 g/dL, typically 10 up to 500 cm<sup>3</sup>/kg of blood can be safely removed without adverse events.

#### *Considerations for Clinical Practice*

1. Acute management of ischemic stroke in SCD should include optimal hydration, correction of hypoxemia, and correction of systemic hypotension; moyamoya-related management can be considered if such arteriopathy exists.
2. For primary stroke prevention, regular blood transfusions to reduce the percentage of hemoglobin S to a maximum of <30% or hydroxyurea therapy after 1 year of regular blood transfusion therapy should be offered to children if there is no evidence of MRA-defined moyamoya syndrome.
3. For secondary stroke prevention, children with hemoglobin SS or S $\beta^0$  thalassemia should be considered to receive regular blood transfusion therapy to reduce the

percentage of hemoglobin S to a maximum of <30% in conjunction with measures to prevent iron overload.

4. Screening for cerebral infarcts with an MRI of the brain using the SIT trial criteria for detection can be considered for children with hemoglobin SS or S $\beta^0$  thalassemia.
5. If a silent infarct is identified in a child with hemoglobin SS or S $\beta^0$  thalassemia, then cognitive assessment is warranted, and the caregivers can have the option for regular blood transfusion therapy for stroke prevention and consideration for special educational services.
6. For suspected acute cerebral infarction, prompt initial simple blood transfusion is needed to get the hemoglobin level to 10 g/dL, or if the hemoglobin is >10 g/dL, an exchange transfusion is required. The goals of the exchange transfusion are to reduce sickle hemoglobin to 15% total and the total hemoglobin to  $\approx$ 10 g/dL.
7. In children with SCD and an ICH, DSA to evaluate for a structural vascular lesion is warranted.
8. In children with hemoglobin SS or S $\beta^0$  thalassemia, it is reasonable to repeat a normal TCD annually and to repeat an abnormal study in 1 month. TCD values that are conditional can be repeated within 2 to 6 months.
9. Hydroxyurea may be considered in children and young adults with SCD and stroke who will not or cannot continue on long-term transfusion or who live in low-resource settings where regular blood transfusion therapy is not feasible.
10. Bone marrow transplantation for children with SCD and strokes should be done in a clinical trial setting that has been registered in [ClinicalTrials.gov](http://ClinicalTrials.gov).
11. Surgical revascularization procedures may be considered in a subset of carefully screened children with SCD with ischemic strokes who continue to have recurrent cerebral infarcts (strokes or silent infarcts) despite optimal blood transfusion therapy (hemoglobin S level suppressed to <30%). We highly recommend that neurosurgeons, neurologists, and hematologists who elect to perform or recommend revascularization procedures in children with strokes participate in a team-based learning collaborative or long-term multicenter clinical study.

#### **Outcomes After Childhood AIS**

##### *Mortality and Morbidity*

Although older studies suggest 20% mortality after stroke in children,<sup>235</sup> more modern studies find that mortality is quite a bit lower. A recent population-based retrospective cohort from the United States that included 123 children with ischemic stroke from a population base of 2.3 million children found that overall mortality at the time of hospital discharge was 4%.<sup>302</sup> Detailed neurological outcomes were not available from this cohort. Similarly, in the Canadian Pediatric Stroke Registry, stroke-specific mortality was 5% over a median follow-up of 2.9 years.<sup>8</sup> Outcome after hospital discharge was available in 484 of 701 children with AIS (69%). Normal neurological outcome was documented in 30%. Although 70% had neurological deficits, 36% were mild, 23% were moderate, and 10% were severe deficits. Mallick et al<sup>303</sup> found that of 94 British children with AIS, 10% died. One year after stroke, 50% of 78 survivors had a Pediatric Stroke Outcome Measure score <1. A Pediatric Stroke Outcome Measure score of 1 indicated the presence of moderate functional impairment

in 1 domain (motor, language, cognition, or behavior), so a Pediatric Stroke Outcome Measure score of <1 is excellent; mild to no impairments are present. In 95 Swiss children with AIS, longer-term outcomes were assessed at a median of 6.9 years.<sup>98</sup> Phone interview was used to obtain the modified Rankin Scale score. By this time point, 14% had died. As has been reported in other studies,<sup>303</sup> approximately half died of underlying systemic illness rather than the stroke itself. In survivors, a normal outcome was found in 27% of children, and 28% had mild impairments, that is, a modified Rankin Scale score of 1.<sup>98</sup>

#### *Cognitive Outcomes*

Cognitive outcome after AIS has been measured in small populations of children with AIS. In one of the largest studies to date, Canadian children who experience unilateral AIS after the perinatal period (n=99) had assessment of intelligence with age-appropriate Wechsler scales a mean of 3 years after stroke.<sup>304</sup> Measures of overall intelligence, verbal ability, working memory, and processing speed were significantly lower in children who had had a stroke than in the normative sample (all  $z > 2.5$ , all  $P < 0.01$ ). Children with injury to cortical and subcortical areas of the brain performed more poorly than those with damage to either the cortical or subcortical area alone. Difficulties with poor attention,<sup>305</sup> impulsivity,<sup>306</sup> and executive function are notable.

#### *Quality of Life*

Health-related quality of life is significantly lower than published norms for children of the same age after childhood AIS across all domains (physical, emotional, social, school, and cognitive functioning).<sup>307</sup> Cognitive/behavioral deficits and low verbal IQ adversely affected quality of life, especially among older children and girls; however, neurological outcome and family socioeconomic status did not.<sup>308</sup>

#### *Predictors of Outcome After Childhood Stroke*

Predictors of poor neurological outcome include infarct size,<sup>103,309</sup> combined cortical and subcortical involvement,<sup>304,310</sup> location of infarct in the basal ganglia and posterior limb of the internal capsule, basal ganglia,<sup>311</sup> multiple infarcts, and hyperglycemia<sup>103</sup> in the acute poststroke period. Brush et al<sup>312</sup> demonstrated an association between hypertension and 12-month mortality but not neurological outcome in survivors of childhood stroke. Poorer psychosocial and cognitive function was associated with both infarct size and older age at stroke onset in children.<sup>313</sup>

Several studies have found that seizures during the acute poststroke period predict poor outcome.<sup>303,314</sup> Elbers et al<sup>315</sup> found that risk factors for abnormal functional outcome included presence of arteriopathy and 1-year poststroke Pediatric Stroke Outcome Measure score of 2 ( $P < 0.05$ ). Functional status at 1 year after stroke strongly predicts long-term outcome. Self-reported anxiety or depression was present in 9 of 26 survivors of childhood AIS (35%). In adults with stroke, depression is a common complication. In children with stroke, few studies report depression, anxiety, or other emotions. Small studies confirm that inattention, reduced social competence,<sup>316,317</sup> and emotional difficulties<sup>318</sup> are present in many children, but reliable estimates are challenging in

small single-center studies. Emotional and mental health in children with a history of childhood AIS seems an important area for future study.

A critical question is: During the subacute and chronic poststroke period, what interventions improve outcomes? 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>319</sup> The Canadian stroke best practice recommendations on stroke rehabilitation included a section on pediatric stroke for the first time in 2015.<sup>320</sup> The guidelines review many options. Perhaps the most important take-away message from these guidelines is that after a stroke children may “grow into their disability.” With growth, development, and additional physical and cognitive demands, deficits may emerge and new rehabilitation needs may be present.<sup>320</sup> Long-term follow-up is required for children with stroke. The strongest evidence is for constraint therapy, which received a Level of Evidence A. Constraint therapy is a form of rehabilitation therapy that improves upper extremity strength by increasing the use of the affected upper limb. Because of its long duration of treatment, the therapy has been reported to have poor compliance and concerns with patient safety. An ongoing clinical trial is evaluating its efficacy.<sup>321</sup> Constraint therapy has been associated with improved function of the hemiparetic hand.<sup>322</sup> Improvements are sustained over a prolonged period of time, and late deterioration is rare. Most of the work in constraint therapy has been done in children with perinatal stroke rather than childhood stroke. There is also preliminary evidence that bimanual therapy improves hand function.<sup>323,324</sup>

Recently, interest has developed in repetitive transcranial magnetic stimulation intervention to the contralesional hemisphere. Repetitive transcranial magnetic stimulation has been shown to be safe in children,<sup>325,326</sup> but small studies have not shown benefit. Further work with larger sample sizes and variable doses is needed. Botulinum toxin type A may be used for chemodenervation to increase the range of motion for patients with focal upper and lower limb spasticity or dystonia.<sup>327</sup> Other than constraint therapy, most rehabilitation interventions have a low level of research evidence.

#### *Considerations for Clinical Practice*

1. Age-appropriate rehabilitation and therapy programs are appropriate for children after a stroke.
2. Psychological assessment to document cognitive and language deficits is useful for planning therapy and educational programs after a child's stroke.
3. Constraint therapy should be considered in children with unilateral hand dysfunction after AIS.
4. Long-term follow-up is required for children with stroke to assess for development of new cognitive, physical, and emotional concerns that may occur over time as children grow into deficits.

#### *Knowledge Gaps*

- Emotional health and mental health in children with a history of childhood AIS are important outcomes and need further study.
- Newer rehabilitation approaches need further study.

## CSVT in Childhood

CSVT is an uncommon condition comprising a spectrum of disorders involving thrombosis of the superficial dural or deep venous system and resulting in impaired venous drainage and intracranial hypertension. If the venous pressure is sufficient to compromise incoming arterial flow, ischemia, infarction, or hemorrhage may occur. Focal brain lesions are observed in up to 50%.<sup>47,49,328,329</sup>

### Presentation

The presenting symptoms and signs of CSVT may be subtle and nonspecific and therefore pose a challenge to prompt diagnosis and treatment.<sup>330,331</sup> Unlike AIS, symptoms may develop gradually. They are often age related and may overlap with symptoms of comorbid conditions. Although neonates typically present with either encephalopathy or seizures,<sup>47,48</sup> older infants and children may manifest signs of increased ICP (headache, nausea and vomiting, lethargy, sixth nerve palsy, diplopia) or focal symptoms and signs related to venous infarction and hemorrhage.<sup>49</sup> Cavernous sinus thrombosis has a more specific presentation with unilateral proptosis and palsies of the cranial nerves (III–VI) within the cavernous sinus. CSVT may also be clinically silent, particularly when diagnosed on routine head imaging performed after head trauma or head and neck surgery.<sup>332</sup>

### Risk Factors and Causes

Both a high index of suspicion and an awareness of CSVT risk factors are needed for early diagnosis and treatment. Several large pediatric cohorts<sup>48,65,333–344</sup> have shown that CSVT often results from the convergence of multiple age-related risk factors for thrombus formation,<sup>334</sup> many of which are modifiable. These include fever,<sup>337</sup> anemia (especially iron deficiency),<sup>336,337,342,345,346</sup> dehydration,<sup>48,49,333,336</sup> and infection,<sup>334–337,343</sup> most commonly of the head and neck, such as otitis media, mastoiditis, sinusitis, orbital cellulitis, and meningoenophalitis.<sup>347</sup> Some chronic systemic and inflammatory conditions are associated with CSVT, including inflammatory bowel disease<sup>334,336,348</sup>; Behçet syndrome; systemic lupus erythematosus<sup>336,337,343,349</sup> (related to lupus anticoagulant and antiphospholipid antibodies); homocystinuria<sup>337,344</sup>; protein-losing conditions such enteropathy, nephropathy,<sup>336,339,342,350</sup> and liver failure that lead to a hypercoagulable state; congenital heart disease<sup>47,49,333</sup> (related to decreased venous return and instrumentation); and thyrotoxicosis.<sup>351,352</sup> Childhood malignancy, particularly acute lymphoblastic leukemia<sup>353,354</sup> and central nervous system tumors,<sup>332,339,342,343</sup> may be associated with CSVT as a result of a chemotherapy-related hypercoagulable state (L-asparaginase), antithrombin deficiency, or mass effect with venous compression or invasion. Prothrombotic drugs such as steroids<sup>334</sup> and estrogen-containing contraceptives have also been linked to CSVT.

### Evaluation

The neuroimaging diagnosis of CSVT can be challenging because of variations in venous anatomy and drainage and the diagnostic pitfalls of the various imaging modalities used.<sup>355–357</sup> The goal of neuroimaging is to identify thrombi in addition to secondary edema, ischemia, and hemorrhage that may influence management decisions. Modalities used include cranial ultrasound (for neonates), CT, and MRI. Each has its own

advantages and disadvantages. Noncontrast head CT is only 60% to 80% sensitive for CSVT.<sup>49,335,358</sup> Therefore, noninvasive CT venography or MRV is usually needed to diagnosis CSVT, and both techniques are highly sensitive and specific.<sup>359,360</sup> Together, CT of the brain and CT venography are very sensitive for identifying thrombi and may be more reliable for small vessels and deep venous channels, but they involve radiation exposure and are less sensitive and specific for delineating associated nonhemorrhagic brain lesions. For this reason, MRI of the brain and MRV are the diagnostic modalities of choice for pediatric CSVT.<sup>144,361,362</sup> MRV requires the use of 3-dimensional phase-contrast, 2-dimensional time-of-flight, or contrast-enhanced methods to evaluate venous anatomy. Phase contrast may be subject to motion artifact, whereas time-of-flight methods are subject to flow-related artifacts that must be interpreted with caution. Contrast-enhanced methods have fewer flow artifacts and appear to be superior to time-of-flight methods in adults. Catheter angiography is rarely used unless endovascular intervention is being considered. Parenchymal MRI is also very helpful in CSVT diagnosis and stage of injury.

Comprehensive evaluation for risk factors and acquired and genetic thrombophilia is necessary for decisions related to acute management and duration of anticoagulation therapy, as well as the prevention of recurrence. It is reasonable to consider complete blood counts, iron studies, and testing for blood, urine, respiratory, stool, and CSF pathogens as clinically indicated. Head CT scans may be needed to evaluate for mastoiditis or sinusitis. Up to 60% of children with CSVT have abnormalities detected on thrombophilia testing<sup>49,334,336,363,364</sup> compared with 15% to 25% of adults,<sup>365,366</sup> but rates have varied as a result of the heterogeneity of factors and normative ranges reported. Moreover, some abnormalities normalize on follow-up testing, suggesting that they may be transient or epiphenomena. Whether and how these abnormalities are causative are unclear from pediatric studies,<sup>55,216,344,367</sup> but data suggest that thrombophilias may increase the risk of recurrent CSVT.<sup>55</sup> Adult case-control studies suggest that certain prothrombotic factors are causative in combination with other risk factors.<sup>368–372</sup> Deficiencies of protein C, protein S, and antithrombin III are associated with increased risk of venous thrombosis. Mutations in the FVL and prothrombin 20210A genes, as well as elevated blood levels of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody), homocysteine, and lipoprotein(a), also appear to be associated with increased risk for CSVT.

### Management

There are no clinical trials of supportive care measures or anticoagulation for pediatric CSVT to guide short-term management decisions. Nevertheless, the consensus among pediatric stroke experts is that prompt recognition and treatment of risk factors and the institution of neuroprotective measures targeting normostasis are important. Antipyretics for fever, intravenous fluids for dehydration, iron supplementation or transfusions for anemia, antibiotic regimens for infection, and analgesia for headache are commonly used in children. Surgical intervention for otitis media or mastoiditis, the most frequent infections found in children with CSVT, may be needed. Some pediatric stroke experts elevate the head of the bed to 30° to balance venous drainage and to maintain cerebral



perfusion pressure, although there are no studies showing benefit with this intervention. Anticonvulsants may be required for treatment of acute symptomatic seizures, which are present in up to 60% and more common in neonates and young children.<sup>49,341</sup> Continuous video electroencephalography may be necessary to detect subclinical seizures. There are no data to support the duration of anticonvulsant use once initiated.

Surveillance and management of increased ICP are undertaken because it can impair vision and occasionally be life-threatening. Fundoscopy and visual field testing at the time of diagnosis and thereafter at regular intervals are suggested until a normal examination can be ensured. Management of a child with CSVT and increased ICP is challenging; anticoagulation for the treatment of CSVT increases the risks of either lumbar puncture or placement of an ICP monitor for direct measurements of ICP. First-line treatments for increased ICP include carbonic anhydrase inhibitors such as acetazolamide. Benefits of invasive treatment options such as lumbar puncture for large CSF volume drainage, ventriculoperitoneal shunting, and optic nerve sheath fenestration have to be balanced with the need for anticoagulation for treatment of the underlying CSVT. In cases of malignant ICP, decompressive hemicraniectomy has been used in adults but has not been reported in pediatric CSVT.

Adult CSVT clinical trials have shown a clear benefit for anticoagulation therapy.<sup>373–378</sup> Despite a lack of similar trials in children, anticoagulation is the mainstay of treatment. The one important exception is the management of septic CSVT, such as otogenic lateral sinus thrombosis, a complication of otitis media, or Lemierre syndrome (necrobacillosis). Antibiotic therapy and surgical interventions (eg, mastoidectomy) are the mainstays of therapy, whereas the role of anticoagulation remains controversial.<sup>379,380</sup> Anticoagulation may be contraindicated in the postoperative period because of the risk of postoperative hemorrhage; fortunately, recanalization rates after surgery and antibiotic therapy are high, regardless of whether anticoagulation is used.<sup>379,380</sup> However, children who are not anticoagulated should be monitored closely for clinical or imaging evidence of thrombus propagation, and anticoagulation should be strongly considered if there is evidence of progression.

Intravenous UFH, subcutaneous LMWH, and oral warfarin may be used. There are no studies on newer anticoagulants such as direct thrombin inhibitors or factor Xa inhibitors in pediatric CSVT. Available data suggest that anticoagulation is generally safe in neonates and older infants and children,<sup>50–52,381</sup> although there is some variability in practice and debate among pediatric stroke experts related to the anticoagulation of neonates with hemorrhagic lesions.<sup>54</sup> Pediatric stroke experts encourage a multidisciplinary consensus approach to anticoagulation that is tailored to the individual patient and involves neurology, hematology/thrombosis, intensive care, neurosurgery, and otolaryngology as clinically relevant. UFH may be started initially when there are concerns about existing hemorrhagic lesions or patient-specific bleeding risks and the need for quick reversal. Transition to LMWH or warfarin occurs later, usually when follow-up neuroimaging demonstrates a lack of intracranial hemorrhage or extension of existing hemorrhage. When anticoagulation is not

immediately started because of recent head trauma, surgery, or another contraindication, repeat neuroimaging may be considered in 3 to 7 days. If clot propagation or new venous infarction is observed, the need for anticoagulation can then be reconsidered. Up to one-third of children who are not initially anticoagulated may experience propagation of their thrombus in the first week after CSVT diagnosis, and up to 40% of those with clot propagation may develop additional venous infarction and worse outcome.<sup>52</sup>

Close monitoring of anticoagulation is suggested, with serial assessment of the activated partial thromboplastin time for UFH, anti-factor Xa level for LMWH, and international normalized ratio for warfarin. There is little information to govern the length of treatment, but the most common approach is to treat for 3 to 6 months and longer if there is an inherited thrombophilia or persistent risk factors for venous thrombosis that have not been mitigated. Repeat neuroimaging is often performed between 3 and 6 months to monitor for clot stability and to establish the degree of recanalization.

In rare circumstances in which there is a high risk of mortality or sudden clinical deterioration despite anticoagulation, endovascular intervention with thrombolysis or thrombectomy is sometimes considered. This may occur in the setting of extensive deep venous, multifocal, or diffuse thrombosis. Limited data support endovascular therapy in adults and children,<sup>382–386</sup> and it should be considered only when there is consensus among clinicians with expertise in pediatric stroke and neurointerventional radiologists experienced with children and the family.

### Outcomes

Large cohort studies suggest that children fare worse than adults after CSVT.<sup>308,387–392</sup> There is a wide range of reported adverse outcomes in pediatric CSVT, 25% to 74%, resulting from the heterogeneity of reported outcomes and lack of standardized outcome measurement. Studies are hampered by short follow-up durations that may not account for the full spectrum of morbidity that develops as a child ages. Reported outcomes may also be confounded by comorbid conditions that contribute to neurological deficits such as meningoencephalitis, malignancy, head trauma, neurosurgery, and congenital heart disease.<sup>391</sup> The presence of hemorrhage at CSVT diagnosis is predictive of worse outcome.<sup>52</sup> Children without cerebral edema or venous infarction are assumed to have better outcome than those who do, although this has not been shown in pediatric studies. Although the rate of recanalization (and thrombus propagation) in the acute period after CSVT diagnosis may influence prognosis, the final recanalization outcome beyond the acute period does not.<sup>52,391</sup> Reported remote symptomatic seizure and epilepsy rates range from 10% to 14%.<sup>393</sup> Mortality rates range from 0% to 23%, although the primary cause is often not reported.<sup>48,49,65,334–343</sup>

### Considerations for Clinical Practice

1. Children with suspected CSVT are diagnosed with a dedicated brain MRV or CT venography for diagnostic confirmation. Although both CT and MRI can easily identify hemorrhage and CT can identify mastoiditis or sinusitis, the presence and extent of associated venous ischemia and infarction are best delineated by MRI.

- Children with confirmed CSVT warrant a thorough evaluation for risk factors, as well as acquired and genetic thrombophilia. Modifiable risk factors, including fever, infection, anemia, and dehydration, should be treated.
- Supportive care measures include intravenous fluids, oxygenation, elevation of the head of the bed to 30°, and treatment of seizures and headache.
- Children with CSVT are routinely followed up serially for increased ICP; medical and surgical options for increased ICP and papilledema should be considered.
- Anticoagulation is the mainstay of treatment except in otogenic lateral sinus thrombosis. Choice of antithrombotic agent, dose, and route is tailored to individual patient circumstances. A multidisciplinary consensus approach to anticoagulation is recommended, particularly when CSVT is associated with hemorrhagic infarction, otitis media/mastoiditis, head trauma, or cranial surgery. Repeat MRV or CT venography is recommended to help guide length of anticoagulation.
- In rare circumstances when there is a high risk of mortality or sudden clinical deterioration, endovascular intervention with thrombolysis or thrombectomy is an option.

#### Knowledge Gaps

- Although there is evidence that antithrombotic agents can benefit adults with CSVT, controlled clinical trial data in children are lacking.
- The benefit of anticoagulation in children with CSVT diagnosed incidentally on routine neuroimaging after head or neck surgery needs further study.
- The required duration of anticoagulation therapy in any patient, especially those with genetic thrombophilias or chronic systemic or inflammatory conditions (malignancy, autoimmune conditions), is uncertain.

### Hemorrhagic Stroke in Childhood

#### Causes

Nontraumatic, spontaneous ICH, IVH, and SAH in childhood are caused by structural lesions in up to ≈75% of cases, with brain AVMs found most commonly and ≈10% of hemorrhages remaining idiopathic (Table 3).<sup>396–401</sup>

#### Acute Management of Childhood Hemorrhagic Stroke

When a hemorrhagic stroke is suspected in a child, emergency head imaging should be performed to make the diagnosis; CT scans are most often performed because of their ready availability in EDs and high sensitivity for hemorrhage. On diagnosis, initial management is predicated on stabilizing the patient, establishing a diagnosis, and preventing secondary neurological injury. If a known bleeding disorder exists while urgent imaging is being arranged, rapid correction of the defect should be carried out, including factor replacement for hemophilia, specific therapies for other hemostatic protein deficiencies, and platelet transfusion for thrombocytopenia or platelet function defect. If there is no known bleeding disorder, urgent cerebrovascular imaging becomes mandatory in addition to neurology, hematology, and neurosurgery consultation to determine the treatment plan. In addition to airway and cardiovascular management, common maneuvers include raising the head of the bed to ≈30°, isotonic fluids, normoglycemia, and normothermia. Care should be taken to avoid hypotension

**Table 3. Causes of Hemorrhagic Stroke in Children**

Structural causes of hemorrhagic stroke in children
Aneurysm
AVM
AVF
CM
Spontaneous hemorrhage into tumor
Hematologic causes of hemorrhagic stroke in children <sup>394,395</sup>
Inherited
Most common (90%)
Hemophilia A (factor VIII deficiency) or B (factor IX deficiency)
von Willebrand disease
Rare (3%–5%)
Factor VII deficiency
Factor II, factor XIII deficiency (rare)
Vitamin K–dependent clotting factor deficiency
Acquired
Idiopathic thrombocytopenic purpura

AVF indicates arteriovenous fistula; AVM, arteriovenous malformation; and CM, cavernous malformation.

because maintaining normal to high blood pressure may be important in maintaining cerebral perfusion. Seizures should be controlled, and prophylactic anticonvulsant use is controversial when no seizures have occurred. Some data in adults suggest worse outcomes with prophylactic phenytoin versus neutral outcomes with adjustment for markers of poor outcome.<sup>402,403</sup> Prophylactic levetiracetam has not been well studied after ICH in adults or children.<sup>404</sup> Despite the lack of evidence, given the high risk of seizures in children with ICH and because seizures will increase cerebral blood flow and ICP, anticonvulsants are often given for a short period of time after ICH. Similarly, the role of continuous electroencephalography after ICH in children to detect subclinical seizures has not been studied. However, to allow the detection and treatment of nonconvulsive status epilepticus, continuous electroencephalographic monitoring should be considered in children who have prolonged altered mental status or movements or vital sign changes that are suggestive of seizures that cannot be captured on a routine electroencephalography.<sup>405</sup>

Brain MRI is useful for the detection of an underlying cavernous malformation (CM) or (uncommonly) a brain tumor, although such lesions can be obscured by an acute hematoma. Vascular imaging is needed to detect brain AVMs, AVFs, or aneurysms. CTA has the advantages of high availability in EDs, the short time needed to acquire images (important in critically ill patients unable to tolerate lying flat for the longer periods of time required by MRI), and its ability to rapidly identify structural lesions with high fidelity. Disadvantages are the radiation and contrast exposure and difficulty timing the contrast bolus in small children. In addition, further definitive imaging with DSA is often required, adding to radiation and contrast exposure. For these reasons, MRA is often a better initial imaging study if it can be obtained safely. DSA

remains the gold-standard vascular imaging study but typically requires the patient's head of the bed to be flat for >1 hour, so it sometimes has to be deferred until ICPs are better controlled. Repeat brain parenchymal imaging should be considered because of the risk of rehemorrhage, reported at up to 32% of cases.<sup>406</sup>

After stabilization, workup to determine whether an undiagnosed underlying bleeding disorder exists should be done and include family history and laboratory testing.

Increased ICP is a common problem with hemorrhagic stroke and can occur as a result of direct hemorrhage mass effect or hydrocephalus that can be seen with ICH, IVH, or SAH. An external ventricular drain can be useful for the diagnosis, monitoring, and treatment of elevated ICP, although there are risks associated with placement and rehemorrhage.<sup>407</sup> Subdural bolts can also measure ICP but cannot drain CSF. Other maneuvers include raising the head of the bed, hyperventilation (to lower P<sub>CO<sub>2</sub></sub> to 25–30 mm Hg<sup>408</sup> and to induce vasoconstriction), hyperosmolar therapy (with hypertonic saline or mannitol), and sedation. Corticosteroids are generally of no use.

Ultimately, surgical decompression may be necessary. Supratentorial hematoma evacuation was of limited benefit in an adult trial but may be much more important in children, who have far less compliance and atrophy.<sup>409</sup> In particular, symptomatic hemorrhage in the posterior fossa and large or symptomatic subcortical lobar hemorrhages should be considered for evacuation to reduce mass effect and to prevent or relieve herniation syndromes.<sup>410</sup>

In some cases, decompressive hemicraniectomy, removing a portion of the skull to allow brain swelling, may be both life-saving and function sparing when there is rapid deterioration in the setting of a large AIS or ICH in adult and pediatric series.<sup>114,411–413</sup> Limited data suggest that hemicraniectomy may be most effective when performed early in the time course of the hemorrhage (24–48 hours), although there may be some utility in select cases at later times.<sup>414,415</sup> In a pediatric prospective cohort, 3 of 22 children with ICH had decompressive craniectomy; all were functionally independent.<sup>397</sup>

When a child has a brain hemorrhage while receiving anticoagulation, anticoagulation is typically held or reversed. However, there are no clear guidelines on when to restart anticoagulation. A multidisciplinary discussion is required to determine the risk-to-benefit ratio of withholding versus restarting anticoagulation, weighing factors such as the size of the bleed, the clinical status of the child, and the indication for anticoagulation, that is, high risk for thrombosis such as requiring extracorporeal membrane oxygenation, ventricular assist device, the presence of a mechanical heart valve, or a pulmonary embolism. In contrast, lower-risk situations such as a nonacute venous thromboembolism or central-line prophylaxis may allow a longer period of time without anticoagulation.

### Outcomes

Overall, outcomes can vary widely in pediatric ICH, with estimates of mortality ranging from 4% to 54%.<sup>13,397,416</sup> The most recent and largest population-based study that included 132 children with hemorrhagic stroke had the lowest mortality rate

at 4%, with 73% requiring intensive care unit admission.<sup>302</sup> Predictors of mortality include older age at presentation (11–18 years versus 1–10 years), coagulopathy, and coma.<sup>398</sup> Poorer outcomes have been associated with increased ICH volume, altered mental status within 6 hours of presentation, infratentorial location of hemorrhage, Glasgow Coma Scale score ≤7 at admission, aneurysmal cause of hemorrhage, age <3 years at the time of ICH, and underlying hematological disorders. The cause of the ICH is a critical determinant of outcome, management, and follow-up strategy.

Developing epilepsy after pediatric ICH is an important sequela. In 1 prospective cohort of 72 children and neonates with ICH, 1 year after ICH, 4% had developed epilepsy, and at 2 years after ICH, 13% had developed epilepsy.<sup>417</sup> As in AIS, the risk of epilepsy is likely to increase with increased follow-up time. ICP that required urgent intervention was a risk factor for remote symptomatic seizures and the development of epilepsy.

Cognitive outcomes have been infrequently reported after hemorrhagic stroke in children. In 1 study of pediatric hemorrhagic stroke survivors (parenchymal hemorrhage and SAH), 17 of 31 children demonstrated cognitive impairment (10 with mild impairment, 7 with moderate to severe impairment) 10 years after hemorrhage.<sup>418</sup> In another study, approximately half of school-aged children with ICH required educational services 1 year after ICH.<sup>419</sup> In a longer-term study of 82 children with hemorrhagic stroke at a median follow-up of 43 months, 40% were receiving special education.<sup>420</sup>

### Pathogenesis-Specific Evaluation, Treatment, and Follow-Up

#### Arteriovenous Malformation

**Imaging.** AVM is the most common vascular lesion to cause a spontaneous ICH in children.<sup>396–401</sup> Hemorrhage risk is estimated at up to ≈6%/y in recent studies, with a mortality rate of ≈25% per hemorrhage, providing an impetus to treat if possible.<sup>401,421–424</sup> Diagnosis is typically initially made with CTA or MRA, although DSA is ultimately needed to make treatment decisions in most cases because it offers the greatest resolution of nidus anatomy.<sup>425,426</sup>

DSA is low risk and high yield. Recent analysis of pediatric patients revealed a 0% complication rate during the procedure and a 0.4% postprocedural complication rate.<sup>205,206</sup> Up to 15% of cerebral AVMs receive some blood supply from ipsilateral or contralateral meningeal arteries, typically not visible on MRA.<sup>427</sup> DSA can offer important predictive data on the risk of hemorrhage, including outflow stenosis, smaller size, and deep venous drainage.<sup>428</sup> DSA may need to be delayed several weeks after hemorrhage (or repeated) because pressure from the clot may obscure AVM anatomy, which can become evident as the clot resorbs.<sup>429</sup>

#### Genetic Screening

Although most AVMs are thought to be isolated developmental lesions, there are known genetic conditions predisposing individuals to multiple AVMs. Mutations in *RASA-1* are associated with problems in vessel development, including familial high-flow arteriovenous lesions and cutaneous capillary malformations with or without skeletal overgrowth in an

affected limb in a small number of families.<sup>430</sup> HHT is a genetic condition that predisposes affected individuals to AVMs throughout the body. Up to 35% of multiple intracranial AVMs associated with HHT were in children, although the mean age at presentation for HHT is 35 years.<sup>431</sup> HHT guidelines recommend AVM screening with MRI of the brain in the first 6 months of life or at the time of diagnosis.<sup>432</sup> For individuals >2 years of age, contrasted MRI is recommended. It may be reasonable to wait >5 years after initial screening imaging studies to rescreen, given the low reported rate of de novo lesion development.<sup>433</sup> In children with a known brain AVM, the presence of frequent nosebleeds, small telangiectasias visible on skin examination, or family history of AVMs should prompt consideration of HHT.<sup>434</sup>

**Treatment.** The treatment approach is typically based on both AVM location and anatomy and is predicated on obliteration of the lesion, which can be achieved by surgery, radiation, embolization, or a combination of therapies. In some cases, the risk of treatment may outweigh the risk of observation, particularly for large lesions or those located in eloquent parts of the brain. Multimodality therapy of AVMs has been advocated by several investigators.<sup>435–438</sup>

In children, surgical resection (with or without embolization) is used as a first-line therapy in the majority of low- to moderate-risk AVMs (even without hemorrhage) with >95% cure rates, contrary to the more controversial data in adult patients from the ARUBA trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformations).<sup>423,439,440</sup> However, ARUBA was a randomized trial, and the data provided for AVMs in children reflect surgical series. These are not directly comparable, and the issue has not been addressed in a randomized design among children. Radiation therapy (typically single dose or staged radiosurgery) is also highly effective, and there is an overlap between a cohort of AVMs that can likely be treated with similar outcomes by either radiation or surgery. Pediatric data suggest that embolization alone may increase the rate of posttreatment hemorrhage relative to the natural history, leading to the recommendation to avoid embolization as a stand-alone therapy for pediatric AVMs.<sup>423,440,441</sup>

**Outcomes and Follow-Up.** AVM obliteration rates are dependent on the size and location of the lesion. Recent studies of AVMs treated with surgery report a >95% obliteration rate, with complications present in ≈15% of cases, most commonly loss of some visual fields.<sup>423,439</sup> For AVMs with similar anatomy, radiation therapy is reported to provide 63% to 85% cure rates.<sup>442,443</sup> Management of deep lesions, including thalamic and brainstem AVMs, is higher risk but can still provide reasonable outcomes in selected cases (54% radiographic cure).<sup>439,441,442,444,445</sup> Higher-grade lesions have lower rates of successful treatment (≈35%) with radiosurgery.<sup>446</sup> In all cases, long-term follow-up, including posttreatment DSA, is critical because recurrence rates are as high as 11%.<sup>447,448</sup> Typically, a perioperative and 1-year postoperative DSA may be considered, followed by MRI/MRA annually for up to 5 years.<sup>439,441,448</sup>

#### Arteriovenous Fistula

**Imaging.** MRI and MRA are useful in the evaluation of AVFs but have limitations. Cross-sectional imaging may be

nondiagnostic or may show only sinus thrombosis or dilated vessels. MRI is important for visualizing secondary effects of venous hypertension, including cerebral edema, hydrocephalus, and ischemic atrophy or infarction.<sup>449–451</sup> DSA is the gold standard for the evaluation of AVFs.<sup>450,452,453</sup> For AVFs, one must see evidence of arteriovenous shunting directly into a dural sinus from meningeal branches of the external and internal carotid artery and VA or a direct connection into a pial vein.<sup>454</sup>

**Genetic Screening.** In patients with documented AVFs, recent data suggest that ≈9% will harbor known mutations.<sup>455–457</sup> *RASA-1*- and HHT-related mutations (*ENG* and *ACVRL1*) were most common, with clinical findings including multiple cranial lesions, spinal AVF/AVM, hypercoagulable states, and capillary hemangioma (in *RASA-1*).<sup>430,455,456,457</sup>

**Treatment.** Any symptomatic, high-flow identified lesion should be considered for treatment.<sup>458–462</sup> AVF treatment involves endovascular or microsurgical techniques to close the fistulous connection (with rare reports of radiation therapy).<sup>454,463</sup> Recent data from pediatric AVF series suggest that dural AVFs have a higher likelihood of successful treatment with solely endovascular techniques (85%), whereas pial AVFs have a greater probability of combined endovascular–open surgical approaches (71%).<sup>456,457</sup>

**Outcomes and Follow-Up.** Age is a critical determinant of outcome for children with AVFs. For those >2 years of age, 72% had a good clinical outcome, whereas children <2 years of age had higher complication rates and more frequently needed multiple procedures.<sup>464,465</sup> Current reports of AVF treatment suggest high rates of lesional obliteration (86%), with age-appropriate outcome scores at an average of 16 months of follow-up.<sup>456,457</sup> Reported procedural complication rates are high (≈60%), and major complications (including death) are in the range of 10% to 12%.<sup>464–466</sup> These risks correlate directly with age; children <1 year of age have the highest complication rates (up to 85%), and children >2 years of age have much lower rates (closer to 33%).<sup>464,465</sup>

After treatment of AVFs, patients should be monitored for the development of hydrocephalus, which may be a result of venous thrombosis, altered venous outflow, or deranged CSF dynamics.

#### Aneurysms

**Imaging.** CTA is useful for the detection of aneurysm in the setting of SAH in children.<sup>37</sup> Patterns of hemorrhage in pediatric aneurysm CT studies include SAH (60%), IVH (10%–15%), ICH (10%–15%), and subdural hemorrhage (1%–3%).<sup>467–470</sup> MRI, including MRA,<sup>471</sup> is also useful.<sup>472</sup> Overall, MRI or MRA was able to identify the source of SAH correctly in 66% of cases.<sup>473</sup> DSA is the gold standard of imaging in aneurysms and detects lesional pathology in 97% of patients (versus 80% of the time without DSA).<sup>399</sup>

**Genetic Screening.** Familial aneurysms are very rare, accounting for 5% to 20% of all reported cases in children and young adults but <5% of prepubertal cases.<sup>474,475</sup> In general, screening with MRI or MRA of family members is limited to patients with multiple affected first-degree relatives or multiple aneurysms without an infectious source.

**Treatment.** The decision to treat or observe a given aneurysm can be complex and is best made by a multidisciplinary team including neurosurgeons, endovascular specialists, and neurologists.<sup>476</sup> If treatment is planned, success is predicated on removing the lesion from circulation while preserving normal blood flow to the brain. This can be achieved by open surgery, endovascular techniques, or a combination of approaches.

In general, aneurysms that have ruptured, that demonstrate enlargement over time, or that have symptomatic lesions should be considered for treatment. Depending on location and patient status, it may be reasonable to have a lower threshold for treating unruptured aneurysms detected in children compared with those in adults given their longer remaining life span. Mycotic aneurysms sometimes will regress with effective antibiotic therapy, obviating the need for other interventions. In addition, flow-related aneurysms located proximal to a lesion such as an AVM may regress after definitive treatment of the primary lesion (such as resection of the AVM), demonstrating another scenario in which direct aneurysm treatment might not be required.<sup>477,478</sup>

Although debatable, lesions  $\leq 2$  mm in size and those located outside the subarachnoid space are sometimes followed up. Much controversy surrounds the large study of unruptured aneurysms published in 1998, but it is important to recognize that these were predominantly adult patients with questionable relation to the pediatric population, given the differences in life span, aneurysm origin, and risk factors.<sup>479,480</sup>

**Outcomes and Follow-Up.** Overall, treatment morbidity and mortality vary widely, depending on age, aneurysm type, and presentation. Recent series describe average mortality rates of 1% to 3% and morbidity rates of 8% to 14%.<sup>481–483</sup> Posttreatment and post-hemorrhage issues include stroke, hydrocephalus, vasospasm, and electrolyte derangements. Some patients may benefit from triple-H therapy—hypertension, hypervolemia, and hemodilution—to reduce the risk of vasospasm (after aneurysm treatment).<sup>484,485</sup> The value of using calcium channel blocking agents (eg, nimodipine) in children is unknown.

Outcomes vary widely, ranging from 13% to 95% for good results and from 3% to 100% for mortality.<sup>486</sup> Ventriculoperitoneal shunts are required in 14% of patients.<sup>467</sup> Of patients who survive treatment, 91% go on to independent living.<sup>487</sup> Follow-up is critical;  $\approx 40\%$  of patients can develop recurrent or de novo aneurysms.<sup>488</sup> In addition to the periprocedural angiogram to confirm obliteration of the aneurysm, an annual MRI or MRA is recommended for 5 years, with some centers suggesting lifetime imaging every 3 to 5 years thereafter.<sup>489</sup>

#### *Cavernous Malformations*

**Imaging.** Evaluation of CMs usually begins with CT or MRI because they are not visualized with angiography. An acute clot may obscure the lesion, requiring reimaging in several weeks, once swelling and blood products are diminished. MRI studies are often pathognomonic, typically a multilobulated appearance with blooming on susceptibility imaging resulting from hemosiderin deposition.<sup>490–492</sup> If multiple CMs are seen on imaging, a familial or postradiation pathogenesis should

be considered.<sup>493</sup> Developmental venous anomalies are commonly seen in association with CMs.<sup>494,495</sup>

**Genetic Screening.** Screening of first-degree relatives with genetic counseling should be considered in patients who have multiple CMs on imaging or if there is a known family history of CMs because a germline mutation is likely, with *CCM1*, *CCM2*, or *CCM3* found in  $>90\%$  of familial cases.<sup>496</sup> If multiple intracranial lesions are seen on imaging, the likelihood of a familial form of the disease approaches 85%, whereas single lesions have only an  $\approx 16\%$  likelihood of harboring a germline mutation.<sup>496</sup>

**Treatment.** Treatment of CM is either surgical resection or observation, with data supporting excision of symptomatic lesions (seizure, focal headache, neurological deficits), lesions with recurrent hemorrhage, or lesions with high risk of neurological deficit (eg, large lesions or those located in the posterior fossa).<sup>497–499</sup> Brainstem CMs are far more challenging; surgical resection generally carries greater risks than observation (resection has been associated with 6% mortality, 33% perioperative morbidity, and 21% persistent iatrogenic deficits).<sup>500,501</sup> There has been debate about the utility of extirpation of asymptomatic lesions. For patients with multiple CMs, resection should be limited to symptomatic lesions or lesions with documented expansion over time.<sup>502,503</sup> Radiation therapy is controversial and generally reserved for surgically inaccessible lesions with a demonstrated malignant natural history.<sup>504</sup>

**Outcomes and Follow-Up.** Surgical outcomes are excellent, with most pediatric series reporting a nearly 0% mortality rate and a 4% to 5% rate of new permanent deficits.<sup>505,506</sup> Surgical resection of the most common type of CM in children, supratentorial lobar lesions, provides high rates of symptomatic improvement, with 98% resection rates and abrogation of seizures in 96% of patients, with a 5% complication rate.<sup>498</sup> Radiographic follow-up is indicated because CMs can recur and generation of new lesions has been documented, particularly in the setting of radiation-induced lesions and in familial cases.<sup>493,507</sup> Many institutions perform annual MRI studies for the first 3 to 5 years after surgery and at greater intervals thereafter.<sup>498,503</sup>

#### *Considerations for Clinical Practice*

1. Acute hemorrhagic stroke management includes airway and cardiovascular management, seizure control (when present), raising the head of the bed to  $\approx 30^\circ$  (to reduce swelling), isotonic fluids, normoglycemia, and normothermia.
2. If a bleeding disorder is known, rapid correction should be instituted.
3. If there is no known bleeding disorder, MRA can be performed when the patient is stable. Unless an alternative cause is identified (eg, hemophilia, trauma), all pediatric patients with hemorrhagic stroke should ultimately have DSA before a hemorrhage is deemed idiopathic.
4. Symptomatic hematomas can be assessed for evacuation.
5. AVMs, AVFs, and aneurysms should receive multidisciplinary consultation and consideration of catheter angiography.
6. Treatment of unruptured AVMs in children is usually surgery as a first-line choice in low-grade lesions,

followed by radiation or surgery for higher-grade lesions. Observation may be appropriate in some cases, for example, larger lesions and those in eloquent areas of cortex.

7. AVFs are treated in children, with embolization as first-line therapy in most cases, followed by surgery in select cases. Observation may be appropriate in some cases.
8. Symptomatic or enlarging supratentorial or cerebellar CMs can be assessed for treatment with surgical resection.
9. Careful skin examinations for vascular birthmarks that indicate an underlying genetic syndrome are helpful in childhood hemorrhagic stroke.

**Controversies in Current Practice for Evaluation of Childhood Stroke**

- Brainstem CMs in children should generally be observed.
- Asymptomatic, incidentally discovered AVMs should be considered for treatment in most children.
- Genetic screening should be considered in children with pial AVF, AVM, or CM if there is a suggestive family history, multiple or unusually complex malformations, or vascular birthmarks on examination.

- Screening for the presence of a thrombus should be performed for dural AVFs not related to trauma.
- Management of asymptomatic small aneurysms.

**Knowledge Gaps**

- The utility of prophylactic anticonvulsants after ICH in children
- Long-term outcome of conservatively treated AVMs in children
- Role of biomarkers in the diagnosis of cerebrovascular disease
- Ideal timing of surgery for hemorrhagic stroke
- Appropriate management of SAH vasospasm in children

**Conclusions**

We have provided updates on perinatal and childhood stroke, especially in regard to areas of childhood stroke that have not received close attention such as SCD. Each section provides considerations for clinical practice, attendant controversies, and knowledge gaps. This statement should provide the practicing provider who evaluates neonates and children with stroke with much-needed updated information.

**Disclosures**

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Heather J. Fullerton	University of California, San Francisco	AHA (grant on salary support)†; Marc & Lynne Benioff (gift to UCSF Foundation for pediatric stroke research)†; NIH (grants on childhood stroke)†	None	None	None	None	None	None
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\*Modest.  
†Significant.

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Mitchell S. Elkind	Columbia University	NINDS (NOMAS grant on stroke incidence and risk factors)†	BMS-Pfizer Alliance for Eliquis (they provide support in kind for stroke trial)†; Roche (they provide support in kind for a trial of stroke)†	None	Merck/ Organon†	None	Boehringer-Ingelheim, Inc*; BioTelemetry/ Cardionet*; Abbott*; Medtronic*	Biogen (PI of clinical trial)*; AHA/ASA (board member and chair of ASA)*; UpToDate (royalties for chapters on stroke)*

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\*Modest.

†Significant.

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