REVIEW ARTICLE

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Pediatric Ischemic Stroke

By Christine Fox, MD, MAS

ABSTRACT

OBJECTIVE: **Pediatric cerebrovascular disease is one of the leading causes of death and disability in children. Survivors of childhood stroke and their families are often left to cope with long-lasting sequelae, such as barriers to school reentry and long-term challenges in attaining independence as adults. Because childhood stroke is rare and providers may not be familiar with the disorder, this article reviews the risk factors, acute management, and sequelae of ischemic stroke in children.**

LATEST DEVELOPMENTS: **High-quality evidence has resulted in an organized approach to emergent treatment of ischemic stroke in adults, but most front-line providers are less prepared for emergent stroke management in children. The level of evidence for reperfusion therapies in children remains low but is growing. Thrombolysis and thrombectomy are sometimes considered for hyperacute treatment of stroke in children. Readiness for pediatric stroke at regional centers should include an organized approach to pediatric stroke triage and management based on extrapolation from adult stroke trials, expert consensus, and emerging pediatric studies.**

ESSENTIAL POINTS: **This review provides up-to-date information about ischemic stroke risk factors and management in children. Preparation for rapid stroke diagnosis and management in children may improve outcomes.**

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The institution of Dr Fox has received personal compensation in the range of $500 to $4999 for serving as a consultant for Competitive Drug Development International Ltd, research support from the American Heart Association/Bugher Foundation, and the National Institutes of Health/National Institute of Neurological Disorders and Stroke, and has received publishing royalties from a publication relating to health care.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Fox discusses the use of thrombolysis and thrombectomy for the treatment of stroke in children.

INTRODUCTION

Stroke is uncommon in children but can be a major cause of childhood mortality and morbidity when it occurs. When occurring at a young age, stroke can result in long-term neurologic sequelae and disabilities over many years. Both acute and chronic care for a child with stroke are costly. The lifetime costs for care of a child who had a stroke are generally higher than the costs of similar types of strokes in adults, and the economic burden for society is sustained over a longer period of time.[1] Adjusting to new disabilities from a stroke can be difficult for children and their families. Beyond physical health, the toll on mental and emotional health is often high for children and caregivers. For these reasons, effective stroke treatments to improve neurologic outcomes for children are essential.

By convention, a stroke that occurs in children after the first 28 days of life is considered a childhood stroke. A stroke that occurs during the first 28 days of life is considered a perinatal stroke. Perinatal arterial ischemic stroke occurs in approximately one in 3000 live full-term births,[2] which makes the weeks around birth one of the highest-risk time periods for stroke to occur. The term *presumed perinatal stroke* is used when imaging demonstrates a chronic infarct in an older

child who begins to show focal deficits during development. Childhood and perinatal strokes are categorized as distinct entities because management, workup, risk factors, and secondary stroke prevention for perinatal and childhood arterial ischemic strokes differ. This article focuses on childhood stroke except where perinatal stroke is specifically addressed.

Most children with acute ischemic stroke present with focal neurologic deficits, similar to adults with stroke.[3] In contrast to adults, children may have a stuttering rather than an abrupt symptom onset and also commonly report headache or present with an acute symptomatic seizure. About one-third of children with stroke have acute symptomatic seizures, more commonly at younger ages. In part because of these differences, stroke signs and symptoms in children are often initially attributed to a stroke mimic during the crucial first hours. Early symptoms are often mistaken for seizure, migraine, functional neurologic deficit, infection, demyelinating disease, methotrexate toxicity, or posterior reversible encephalopathy syndrome (PRES).[4,5] Accurately determining time of stroke onset and assessing neurologic deficit may be particularly challenging with young, uncooperative, or frightened children. Posterior circulation strokes are particularly challenging because presenting features such as unsteady gait and emesis are common symptoms of other health problems in childhood, and children may have a difficult time describing vertigo or dizziness. Although a myriad of chronic and acute conditions can predispose a child to stroke, many children who present with an initial stroke have no significant medical history and were previously considered to be healthy. When a previously healthy child presents with a stroke, initial disbelief that stroke can occur in children may delay diagnosis.

HYPERACUTE TREATMENT FOR PEDIATRIC STROKE

Thrombolysis and mechanical thrombectomy are generally accepted treatments for hyperacute reperfusion after stroke in appropriately selected adults.[6,7] The risk-to-benefit ratio of thrombolysis and thrombectomy in children may differ from adults, and evidence in children remains at the level of case series and meta-analyses of individual patient data.[8-12] As evidence grows, guidelines have cautiously moved from recommending against thrombolysis or thrombectomy outside of a research study toward a discussion of selecting children who may benefit from IV thrombolysis and endovascular thrombectomy in certain circumstances.[13] In 2015, American Heart Association/American Stroke Association (AHA/ASA) guidelines acknowledged that benefits of endovascular therapy were not established for children aged younger than 18 years, but may be reasonable within 6 hours of symptom onset of a large vessel occlusion.[14] A 2019 pediatric-specific stroke scientific statement from the AHA/ASA and an Australian clinical consensus practice guideline both provide considerations in which it may be reasonable or appropriate to consider hyperacute reperfusion treatment in children based on evidence extrapolated from adults.[13,15] FIGURE 9-1[15] shows the Australian clinical consensus guideline's quick reference pathway for diagnosis and acute management of childhood stroke, including an assessment for eligibility for IV thrombolysis and thrombectomy.

According to guidelines, it may be reasonable in older children to consider IV thrombolysis within the first 4.5 hours and mechanical thrombectomy within 6 hours of when the patient was last known well, with imaging confirmation of

KEY POINTS

- Perinatal arterial ischemic stroke occurs in approximately 1 in 3000 live full-term births, which makes the weeks around birth one of the highest-risk time periods for stroke to occur.
- Most children with acute ischemic stroke present with focal neurologic deficits similar to adults with stroke. Unlike adults, children may have a stuttering rather than an abrupt symptom onset and also commonly present with headache or seizure.
- Although a myriad of chronic and acute conditions can predispose a child to have a stroke, many children who present with an initial stroke have no significant medical history and were previously considered to be healthy.
- As evidence grows, guidelines have cautiously moved from recommending against IV thrombolysis or thrombectomy outside of a research study toward a discussion of selecting children who may benefit from IV thrombolysis and endovascular thrombectomy in certain circumstances.

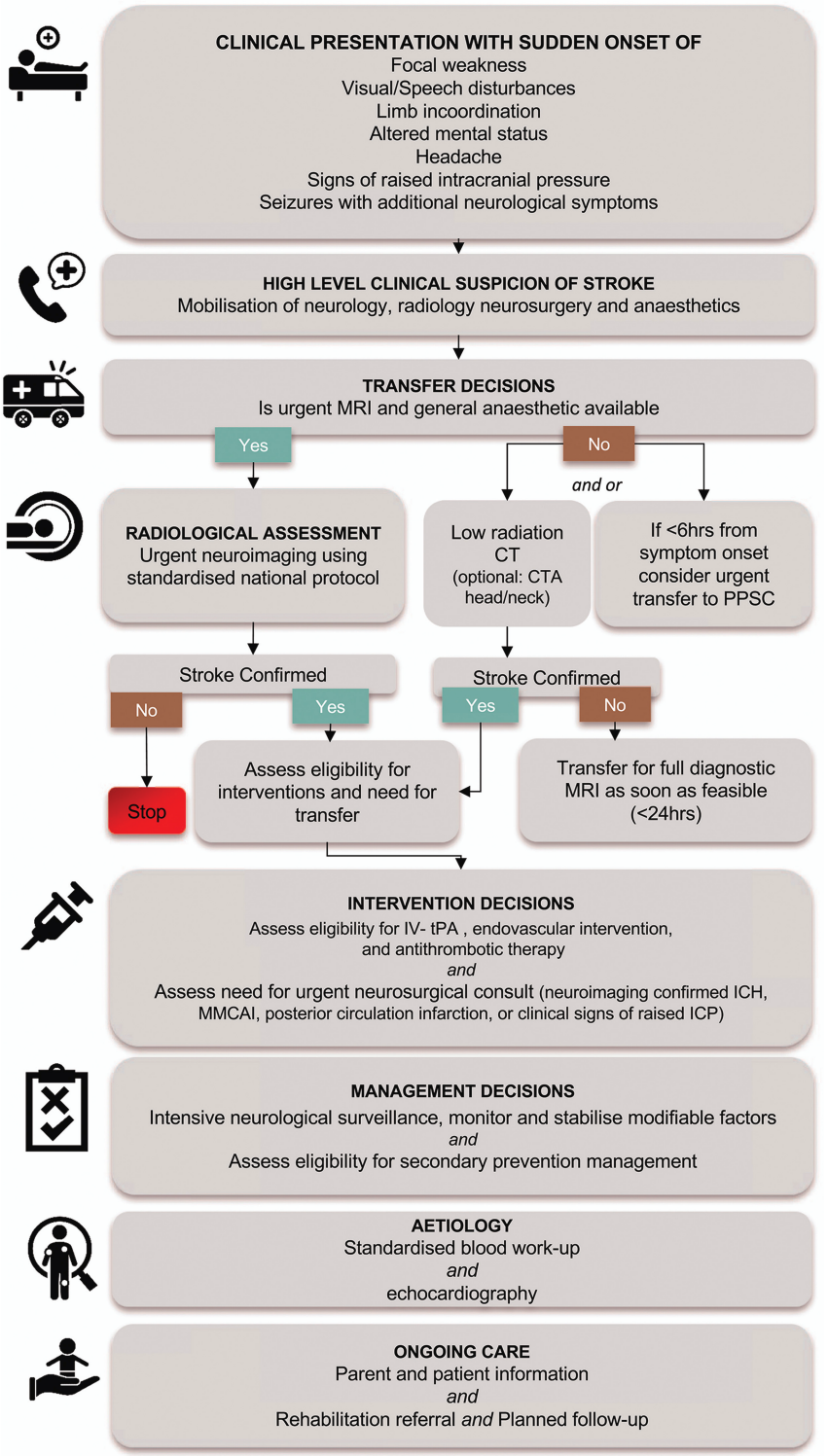

FIGURE 9-1

Australian Clinical Consensus guidelines for the diagnosis and acute management of childhood stroke.

CT = computed tomography; CTA = computed tomography angiography; ICH = intracranial hemorrhage; ICP = intracranial pressure; IV = intravenous; MMCAI = malignant middle cerebral artery infarction; MRI = magnetic resonance imaging; PPSC = primary pediatric stroke center; tPA = tissue plasminogen activator. Reprinted from Medley TL, et al, Int J Stroke.[15] © 2019 World Stroke Organization.

vessel occlusion and stroke. Although guidelines support consideration of IV thrombolysis or thrombectomy in children in specific circumstances on a case-by-case basis, these treatments are not considered a requirement. Hyperacute treatment decisions should be made in conjunction with neurologists with expertise in the treatment of children with stroke.[13] When IV thrombolysis is considered in children, it should be done in a system with established guidelines for stroke thrombolysis, using weight-based dosing similar to that in adults.[13] Using statistical modeling in a small series of children treated with appropriate weight-based recombinant tissue plasminogen activator (rtPA), the estimated risk of symptomatic intracranial hemorrhage after thrombolysis is low.[16] When mechanical thrombectomy is considered in children, it should be performed by providers with expertise in stroke thrombectomy in adults and pediatric neurointerventional treatment. Cerebral arteries do not approximate adult size until around the age of 5 years, so the size and age of a child should be considered for device selection.[17] In systems of care without availability of providers experienced in pediatric stroke treatment, the priority should instead be stabilization and transfer to the appropriate centers.

In the 6- to 24-hour window after stroke onset, adults with anterior circulation large vessel occlusion are selected by a clinical-imaging mismatch to identify those most likely to benefit from mechanical thrombectomy.[6] Children have an increased tendency to form early collaterals, so the selection criteria for children likely to benefit from mechanical thrombectomy during this extended time window are especially uncertain.[18] If durable collateral circulation is already well established, recanalization may not improve outcomes.

The National Institutes of Health Stroke Scale is a standardized neurologic examination that is used in adults to quantify neurologic deficits from stroke and determine eligibility for hyperacute treatment. The Pediatric National Institutes of Health Stroke Scale (PedNIHSS) is a modification of the adult scale with age-appropriate adaptations for performance and scoring of each item (see Useful Websites section). The PedNIHSS has been validated for use in children aged 2 years and older as a quantitative assessment of the severity of neurologic deficits that can be trended over time when considering hyperacute treatments.[19,20] **CASE 9-1** illustrates a child who was treated with mechanical thrombectomy in the extended time window, but whether the perfusion imaging techniques used in adults similarly identify core infarct and ischemic penumbra in children remains a point of controversy. As illustrated in both **CASE 9-1** and **CASE 9-2**, guidelines recommend that a stroke team including a neurologist and neurointerventional radiologist with experience in treating children and patients with stroke make hyperacute stroke treatment decisions.

Brain MRI with magnetic resonance angiography (MRA) is the optimal study for diagnosis of acute childhood arterial ischemic stroke because it readily differentiates an ischemic infarct from more common childhood stroke mimics. Head CT with CT angiography is a reasonable alternative because it is more readily available and may be easier to obtain quickly. Head CT and CT angiography may also be the preferred initial study in children with known heart disease to avoid imaging delays while assessing whether cardiac hardware is present and magnetic resonance–conditional. Whether MRI and MRA or CT and CT angiography is the initial imaging modality for a suspected childhood stroke, including vascular imaging is crucial to identify a large vessel occlusion or an arteriopathy that influences management. Consensus-based guidelines for

KEY POINTS

- Although guidelines support consideration of IV thrombolysis or thrombectomy in children in specific circumstances on a case-by-case basis, these treatments are not considered a requirement. Hyperacute treatment decisions should be made in conjunction with neurologists with expertise in the treatment of children with stroke.
- MRI and MR angiography or CT and CT angiography are both reasonable options as initial imaging modalities to evaluate for a suspected childhood stroke, taking timing, circumstances, and available resources into account. In either case, obtaining vascular imaging in addition to brain tissue imaging is crucial to identify a large vessel occlusion or an arteriopathy that influences management.

neuroimaging of acute childhood arterial ischemic strokes are available, including suggested rapid stroke MRI protocol with angiography that can usually be completed in 10 to 15 minutes to avoid sedation.[21,22] When sedation is required for neuroimaging, blood pressure should be maintained to optimize brain perfusion, particularly in the setting of arteriopathy or dependency on collateral circulation.

EARLY MANAGEMENT

The goals of acute care following childhood arterial ischemic stroke focus on limiting injury by rescuing penumbra, preventing stroke extension or early recurrence, and treating complications. Type and cross for emergent blood transfusion should be sent for children with sickle cell disease or other forms of severe anemia. Early after stroke, transiently elevated blood pressure may be a compensatory mechanism to maintain cerebral perfusion. Because of the prevalence of arteriopathies in childhood stroke with subsequent cerebrovascular narrowing or loss of normal hemodynamic compensatory mechanisms, collateral cerebral flow should be supported by initial fluid resuscitation if needed, keeping the head of bed flat, instituting bedrest, and avoiding hypotension. When treatment is needed to prevent hypertensive crisis, blood pressure should be lowered cautiously to prevent stroke extension. If vomiting is present or elevated

CASE 9-1

A right-handed 12-year-old girl was admitted for a cardiac catheterization to evaluate worsening exercise tolerance. Her history included normal development, but she had a history of complex congenital heart disease treated with several prior cardiac surgeries. The catheterization was performed in the afternoon, and she remained on a rebreather mask with some sedation overnight. The next morning her team and family were concerned that she appeared confused and had not recovered from the procedure and anesthesia as expected. A code stroke was called 12 hours after she was last known well. The intensive care unit team and neurologist found that she was aphasic with a right hemiparesis. She was rapidly taken to radiology for head CT, CT angiography, and CT perfusion study. After reviewing her imaging, which suggested that she had a large penumbra according to adult selection criteria, the neurointerventional radiologist and neurologist agreed to proceed with thrombectomy. The procedure was successful, with recanalization and complete reperfusion of all distal branches. She recovered slowly during several months of inpatient pediatric rehabilitation. One year after experiencing the stroke, her exercise was still limited by her heart disease, but she was participating in school and on her dance team.

COMMENT

This case exemplifies the challenges of postprocedural diagnosis of a cardioembolic stroke in children with congenital heart disease. Provider education about childhood stroke and a code stroke plan are critical to institutional readiness for childhood stroke thrombectomy.

intracranial pressure is a concern, the head of bed can be raised to 30 degrees. Early assessment of progressive intracranial hypertension and need for urgent decompressive hemicraniectomy may be lifesaving in children with malignant middle cerebral artery infarction or large cerebellar infarcts.[23,24] Acute symptomatic seizures and fever should be prevented or treated to minimize metabolic demands on the injured brain.[25] Electroencephalography monitoring may be needed to detect subclinical seizures.

Similar to acute stroke care in adults, a swallowing evaluation may be needed to ensure safe swallowing before advancing diet. Early assessment by physical and occupational therapists can minimize fall risks. Children with arteriopathies should advance activity cautiously and under supervision. Deep vein thromboprophylaxis (mechanical deep vein thrombosis prevention or anticoagulation) may be indicated in older children, especially in those who are obese, postpubertal, on exogenous estrogen, or who have underlying inflammatory disease. Medications that increase clotting, such as exogenous estrogens, should be discontinued if possible.

CASE 9-2

A 13-year-old girl presented after experiencing a brief episode of weakness and difficulty speaking after playing lacrosse. No contact with other players or head or neck trauma occurred during the game. She recently had a mild respiratory illness. Her weakness improved after a few minutes, but the coach was worried and had her taken to the emergency department from the field. In the ambulance, she suddenly stopped speaking and became hemiparetic, with weakness affecting her right face, arm, and leg. On arrival to the emergency department, emergent imaging showed a patchy basal ganglia infarct, an irregular left middle cerebral artery without dissection, and occlusion of an M2 branch. She was rapidly transferred to a nearby children's hospital with a pediatric stroke team and was treated with IV thrombolysis at just under 4 hours after stroke onset. She was evaluated for thrombectomy, but she did not have a large vessel occlusion (the M2 branch was occluded distally). She had no complications from thrombolysis, and the next day she began to speak with some paraphasic errors. Based on typical imaging characteristics, she was diagnosed with an inflammatory focal cerebral arteriopathy. She was treated with a course of corticosteroids and a daily aspirin. After her acute stay, she completed 2 months of inpatient rehabilitation. During that time, her speech recovered, and she regained power in her right arm and leg. Two years following the stroke, she was able to run and was back to playing sports despite mild residual weakness of her right arm.

COMMENT

This case exemplifies a stuttering stroke onset common in children and a basal ganglia infarct typical of that seen in focal cerebral arteriopathy. A practiced pediatric stroke team is key to rapid childhood stroke diagnosis and thrombolysis.

Workup for Acute Childhood Stroke

Urgent laboratory testing in patients with childhood stroke includes complete blood count with differential, screening coagulation laboratory tests, and a metabolic panel with renal function. Blood draws should be minimized in small children and those with anemia. Thrombophilia screening is not urgent but may influence choice or duration of antithrombotic treatment outside of the acute period, as well as long-term counseling regarding recurrent stroke or thrombosis risk. Although elevated lipoprotein(a) is associated with childhood stroke, it is not clear that lowering lipoprotein(a) to normal levels decreases the risk of recurrence. The traditional cardiovascular risk factors of diabetes, hypertension, and hyperlipidemia are less frequently a concern in children than in adults, but screening laboratory tests could be considered in older teens or when strongly suggested by family history.

An echocardiogram should be obtained urgently to evaluate for possible cardiac thrombus or vegetation and should include a bubble study or color flow Doppler study to evaluate for a right-to-left shunt. When a right-to-left shunt is identified, venous Doppler of the extremities should then be performed to evaluate for venous thrombosis. Although arrhythmias are less common in children than in adults, a screening electrocardiogram is recommended, and more extensive cardiac monitoring may be indicated in children with known cardiac disease.[13]

PEDIATRIC STROKE RISK FACTORS

Assessment of childhood ischemic stroke risk factors can identify children at higher risk of stroke who may benefit from primary or secondary stroke prevention strategies. Many childhood arterial ischemic strokes are multifactorial rather than related to a single etiology, with overlapping genetic predisposition and acquired risk factors (FIGURE 9-2).[26] For example, a child with congenital heart disease, genetic arteriopathy, or other persistent risk may also have a prothrombotic predisposition. Acute infections such as the common cold or herpes viruses and associated inflammation can act as a stroke "trigger" in children who have other persistent underlying risk factors. Approximately 20% of children with a stroke will have a stroke recurrence, with the highest risk during the first year after the initial stroke. Previously healthy children with no stroke risk factors identified after an appropriate stroke assessment have a lower risk of recurrent stroke.[27] In contrast, stroke recurrence is common in children with complex cardiac disease,[28] persistent arteriopathy,[29] sickle cell disease,[30] or a significant thrombophilia.[31] The most prevalent childhood stroke risk factors are reviewed in the following sections.

Complex Cardiac Disease

Congenital heart disease is the most common major congenital malformation, affecting approximately 1% of live births worldwide. Children with cardiac disease often have atrial or ventricular dilation and dysfunction, right to left shunting, or alteration in blood flow patterns that increase risk for embolic disease. Disruptions in the balance of hemostasis, alteration in blood composition, or loss of endothelial integrity may result in thrombosis, bleeding, or both. About one-fourth of children with congenital heart disease have a complex form that requires surgical intervention during the first year of life to survive.[32] Many cardioembolic strokes in children are periprocedural and occur in the setting of cardiac surgery or catheterization to manage complex congenital

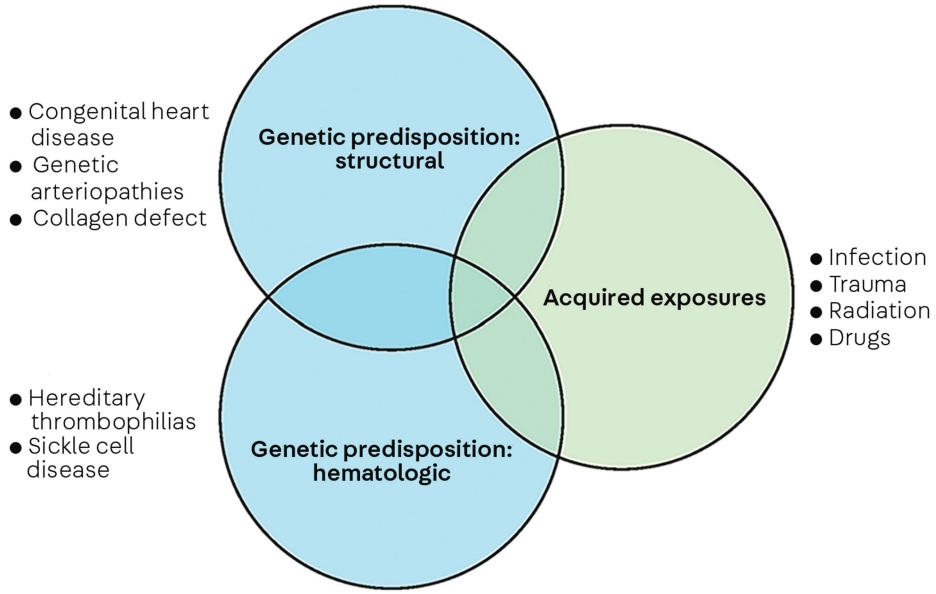

FIGURE 9-2

Children often have multifactorial risk factors for stroke with underlying predisposition and acquired exposures.

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KEY POINTS

- **Because of the prevalence of arteriopathies in childhood stroke with subsequent cerebrovascular narrowing or loss of normal hemodynamic compensatory mechanisms, in the setting of acute stroke collateral cerebral flow should be supported by initial fluid resuscitation if needed, keeping the head of bed flat, instituting bedrest, and avoiding hypotension.**
- **Congenital heart disease or acquired heart disease are major risk factors for perinatal or childhood stroke, together accounting for almost one-third of arterial ischemic strokes in children.**

heart disease.[33,34] As surgical management has improved over decades, a larger group of children and young adults with complex congenital heart disease survive early childhood but remain at risk for stroke related to their underlying cardiac dysfunction. For all these reasons, congenital heart disease or acquired heart disease are major risk factors for perinatal or childhood stroke, together accounting for almost one-third of arterial ischemic strokes in children.[35] In the International Pediatric Stroke Study, which enrolled more than 3000 children with arterial ischemic stroke between 2003 and 2014, the primary etiology for stroke in 21% of participants was cardiac disease (excluding children who only had isolated patent foramen ovale [PFO]).[36] The risk of recurrent stroke in children with congenital heart disease is 27% by 10 years poststroke, with the highest risk period immediately following the initial stroke.[28] However, in part because of the large number of anatomic variations in children with congenital heart disease, no consensus exists on the optimal approach to secondary stroke prevention. Antiplatelet therapy or anticoagulation may be recommended depending on the specific cardiac anatomy and surgical cardiac repair.[37] The AHA/ASA suggests systemic anticoagulation for secondary stroke prevention in patients with congenital heart disease, with the stipulation that the nature of the specific cardiac defect, its expected management, and other factors such as the presence of thrombophilia should be considered.[13]

Stroke can occur in children without complex congenital heart disease because of paradoxical embolization across a PFO. Based on evidence extrapolated from adult patients, some children with otherwise cryptogenic stroke may benefit from PFO closure for secondary stroke prevention.[38-40] Clinical practice guidelines for PFO closure in adults[41] are a useful starting point when considering PFO closure in children, but are not directly applicable to children. The Risk of Paradoxical Embolism (RoPE) score is used to select adult patients

for PFO closure after an otherwise cryptogenic stroke[42] and calculates the score using age categories starting at 18 years or older. PFO is found in approximately one-third of the overall pediatric population and is inversely related to age, with increasingly higher prevalence in younger children.[43] In children with cryptogenic stroke, PFO prevalence is higher than in children with a known stroke etiology and higher than in healthy controls.[44] In the presence of other pediatric stroke risk factors, a paradoxical embolism through a PFO is less likely to be the causative etiology. Therefore, a thorough investigation of other risk factors has to be completed before concluding that PFO closure might be beneficial. If an alternative stroke mechanism is identified, PFO closure should not be routinely recommended. When a PFO is identified during a childhood stroke assessment, venous ultrasound of the extremities and laboratory testing for thrombophilia risk factors should be performed. Clinical features that suggest stroke is due to a paradoxical embolus include an echocardiogram demonstrating a large PFO, a PFO with aneurysm, significant right-to-left shunting, stroke onset after a Valsalva maneuver, or an identified deep venous thrombosis.

Children with underlying heart conditions are vulnerable to cardioembolic stroke resulting in a large vessel occlusion and may be candidates for mechanical thrombectomy, as illustrated by the child with an in-hospital periprocedural stroke in **CASE 9-1**. Hyperacute reperfusion treatments are a key area of ongoing pediatric stroke research. However, stroke diagnosis is frequently delayed even when the stroke occurs in the hospital after cardiac catheterization or surgery.[33,34] Barriers to early diagnosis are common, including sedating or paralytic medications in critically ill children, emergence from anesthesia after a procedure, or difficulty with neurologic examination in poorly cooperative or young children. Systematic quality measures that preemptively identify children for closer postprocedural neurologic monitoring after higher-risk cardiac procedures are key to reducing time to stroke detection and increasing opportunities for rapid treatment.

Arteriopathy

Cerebral arteriopathy is present in at least half of all children with ischemic stroke and is a risk factor for initial stroke and stroke recurrence.[45,46] The most common cause of ischemic stroke in a previously healthy child is a cervicocephalic dissection or a presumed inflammatory intracranial focal cerebral arteriopathy. The definitive etiology of inflammatory type focal cerebral arteriopathy remains unknown, although it can be related to varicella zoster virus or other herpesvirus infections. Among children with stroke related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, about one-fourth have a presumed inflammatory arteriopathy.[47] The typical appearance of an inflammatory focal cerebral arteriopathy on vascular imaging is a unilateral irregular or banded stenosis involving the distal carotid terminus, proximal middle cerebral artery, proximal anterior cerebral artery, or a combination of these (**FIGURE 9-3**[48]), in conjunction with a basal ganglia infarct from affected lenticulostriates.[48] The natural history is monophasic, with progression of the stenosis in the first days to weeks. After the acute phase, the arteriopathy stabilizes and other vascular territories do not become involved. Up to 25% of children with inflammatory focal cerebral arteriopathy have a recurrent stroke after an initial stroke from progressive lenticulostriate involvement, artery-to-artery emboli, or flow-related ischemia.[27] Although the benefit and optimal

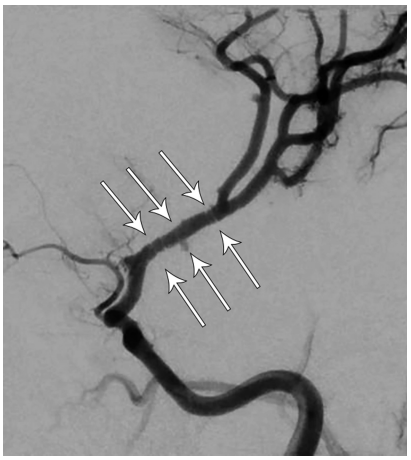

FIGURE 9-3
Typical banded appearance of inflammatory focal cerebral arteriopathy affecting the middle cerebral artery on conventional angiogram.
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dosing regimen are uncertain, children with inflammatory focal cerebral arteriopathy may be treated with corticosteroids (CASE 9-2). Based on the hypothesis that the etiology of focal cerebral arteriopathy is inflammatory, a network of European and Australian investigators designed PASTA (Paediatric Arteriopathy Steroid Aspirin Project, EudraCT 2017-002247-15), a randomized controlled trial of corticosteroids, that is ongoing in Europe.[49] The FOCAS (Focal Cerebral Arteriopathy Steroid)[50] comparative effectiveness study of early versus late corticosteroid treatment is anticipated to start in the United States in 2023.

Cervicocephalic arterial dissection accounts for approximately 10% of childhood arterial ischemic stroke[35] and half of posterior circulation childhood arterial ischemic stroke,[51] occurring spontaneously or following trauma. The radiographic appearance of an intracranial dissection may be similar to inflammatory focal cerebral arteriopathy, with some evidence for mixed arteriopathies with elements of inflammation and dissection. Children with collagenopathies or elastinopathies such as Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome, and arterial tortuosity syndrome are at increased risk for cervicocephalic arterial dissection,[52] as well as other associated comorbidities of the underlying diagnosis.

Moyamoya disease, a progressive steno-occlusive arteriopathy, may be the most prevalent risk factor for childhood stroke in Asian countries. In a Beijing study of children with ischemic stroke, moyamoya arteriopathy was reported in 69% of participants.[46] Currently, no specific medical treatments are available to successfully halt or reverse the progressive disease. Surgical revascularization is often recommended to increase collateral blood flow to hypoperfused brain and thus decrease the risk of initial and recurrent ischemic stroke. Studies have suggested that revascularization surgery is superior to medical management alone to decrease risk of ischemic injury,[53-55] although randomized studies comparing various surgical approaches or surgical versus medical management have not been done. Surgical revascularization is not without risk, with surgical morbidity of about 4% per treated hemisphere,[54,55] and the optimal selection of patients and timing for surgery has not been well defined. Experts agree that careful intraoperative anesthetic management and perioperative care to maintain cerebral perfusion minimize surgical risk, but specific practices vary across centers.[56]

Sickle Cell Disease

Without intervention, about 10% of people with sickle cell disease will sustain an ischemic stroke during childhood. In 1997, the landmark STOP (Stroke Prevention Trial in Sickle Cell Anemia)[35] clinical trial changed primary stroke

KEY POINTS

- **Systematic quality measures that preemptively identify children for closer postprocedural neurologic monitoring after higher-risk cardiac procedures are key to reducing time to stroke detection and increasing opportunities for rapid treatment.**
- **Cerebral arteriopathy is present in up to half of all children with ischemic stroke and is a risk factor for initial stroke as well as stroke recurrence.**

prevention for children with hemoglobin SS and hemoglobin Sß° thalassemia. The STOP trial showed that a protocol of screening children aged 2 to 16 years with transcranial Doppler (TCD) ultrasound can identify children with arteriopathy and then reduce stroke risk through prophylactic chronic blood transfusion. In children with elevated TCD velocity in the middle cerebral artery, regular red blood cell transfusions for at least 1 year reduced the risk of initial stroke by 92%.[57,58] The follow-up TWiTCH (TCD With Transfusions Changing to Hydroxyurea) trial found that children without severe arteriopathy whose TCDs had normalized after a period of transfusion therapy could safely transition to hydroxyurea.[59]

The acute management of a suspected stroke in children with sickle cell disease differs from other stroke etiologies and should focus on providing an emergent blood transfusion. FIGURE 9-4[60] shows the American Society of Hematology's recommended algorithm for management of acute ischemic stroke in a child with sickle cell disease.[60] Transfusion goals are to reduce the percentage of hemoglobin S to under 30% and increase the hematocrit to 30% to improve oxygen delivery to ischemic brain tissue. While awaiting transfusion, children with sickle cell disease should be treated with IV fluids and supplemental oxygen to maintain oxygen saturation greater than 93%. A transfusion should be performed for all children with sickle cell disease who present with focal neurologic symptoms, even if symptoms are resolving or have resolved.

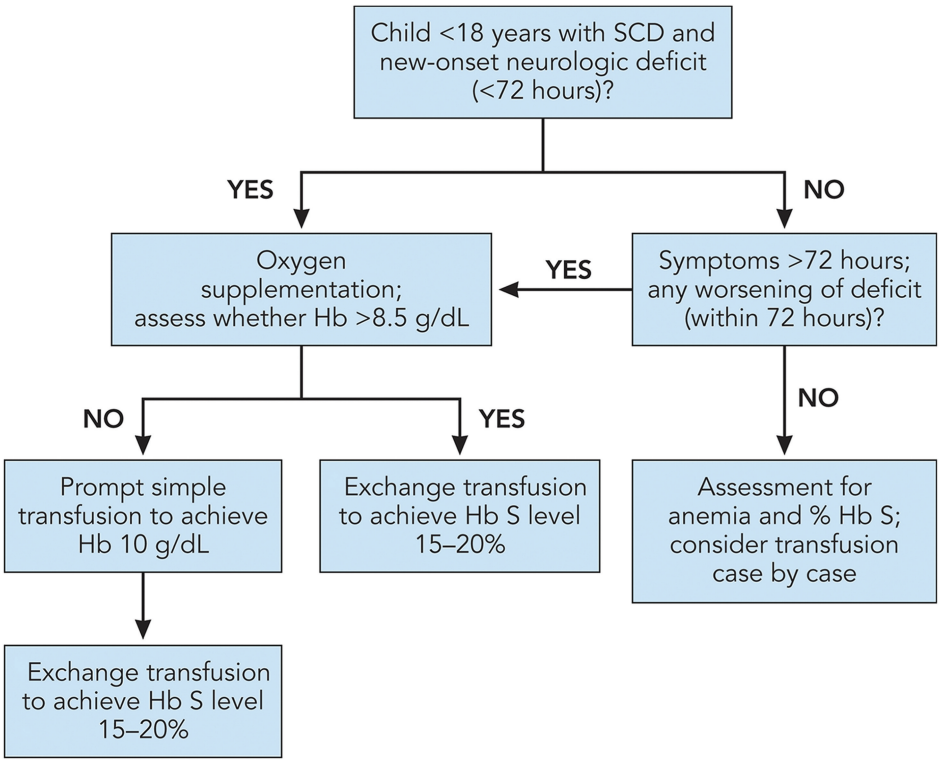

FIGURE 9-4

American Society of Hematology–recommended algorithm of management of acute ischemic stroke in children with sickle cell disease.

Hb = hemoglobin; SCD = sickle cell disease.

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Exchange transfusion is preferred when it can be done quickly, but a simple transfusion is acceptable if exchange transfusion cannot be provided quickly.

About 20% of children with sickle cell disease who have had a stroke go on to have a recurrent stroke, even if chronic red blood cell transfusion is started. Children with hemoglobin SS or hemoglobin Sß° thalassemia who have had an ischemic stroke should be managed with regular blood transfusions for secondary stroke prevention if it is safe, available, and feasible.[60] Sickle cell disease can lead to a moyamoya-like syndrome, with progressive steno-occlusive arteriopathy and collateral formation, as a further risk factor for a first or recurrent stroke.[61,62] Children with moyamoya syndrome related to sickle cell disease may benefit from surgical revascularization or stem cell transplant in addition to regular blood transfusion. The pathophysiology of progressive steno-occlusive arteriopathy related to sickle cell disease may differ from other genetic moyamoya syndromes, and the American Society of Hematology has identified treatment of sickle cell disease–related moyamoya syndrome as a priority research need.[60]

SECONDARY STROKE PREVENTION, OUTCOMES, AND RECOVERY

In children with ischemic stroke who do not have sickle cell disease or cardioembolic stroke, pediatric stroke guidelines from the American College of Chest Physicians,[63] the Royal College of Paediatrics and Child Health,[64] and the AHA/ASA[13] recommend secondary stroke prevention with aspirin (1 mg/kg/dose to 5 mg/kg/dose orally once daily) if there are no contraindications. Anticoagulation is typically recommended in children with presumed cardioembolic stroke and significant thrombophilic states such as antiphospholipid syndrome.[13,63] Although anticoagulation is often used in cervical artery dissection,[63] recent AHA/ASA guidelines note that the use of anticoagulation as opposed to antiplatelets is controversial.[13] The optimal duration of aspirin use following childhood stroke is not known, but guidelines recommend a minimum of 2 years[13,63] and it is sometimes used indefinitely.

Assessment of function by a rehabilitation specialist and consideration of inpatient rehabilitation are recommended for children following stroke. Many children benefit from inpatient rehabilitation either acutely or when medically stable. Similar to exercise recommendations for adults after stroke,[65] most survivors of childhood stroke should be encouraged to engage in fun, regular exercise and physical activity to maintain fitness, range of motion, function, and cardiovascular health over their lifetime. Although some children can continue to have improvement in function over years, others develop emerging deficits with increased academic and other cognitive demands, and ongoing evaluation is helpful.[66]

Epilepsy develops during childhood in about one-third of survivors of pediatric stroke, and prolonged or recurrent seizures in the immediate poststroke period may increase that risk.[67] Poststroke epilepsy can worsen quality of life even in the absence of other disabilities related to stroke. Often, children and families experience anxiety following stroke, and depression is common.[68] Psychosocial support is necessary both acutely as well as following discharge, including a low threshold for referring for behavioral health services.

Neuropsychological evaluation can guide early reintegration into school, with full neuropsychological testing typically performed in a delayed fashion when

KEY POINTS

- **The acute management of a suspected stroke in children with sickle cell disease differs from other stroke etiologies and should be focused on providing an emergent blood transfusion.**
- **Assessment of function by a rehabilitation specialist and consideration of inpatient rehabilitation are recommended for children following stroke.**

poststroke deficits have stabilized. Education of the family and other care settings such as the school should include stroke recognition and need for urgent evaluation for new or recurrent, even transient, neurologic deficit. Education should also include strategies to maintain vascular health throughout the patient's lifetime, including a healthy weight, normal blood pressure, and aggressive treatment of patient-specific risk factors.

PERINATAL STROKE

Risk factors for perinatal ischemic stroke include chorioamnionitis or other systemic or central nervous system infections, inherited thrombophilia, and complex congenital heart disease.[69] In infancy, focal motor seizures and encephalopathy are the most common presenting symptoms of ischemic stroke.[70,71] Some newborns may not present with any clinical signs of stroke initially, but during development they may have early handedness or fail to meet developmental milestones.

When diagnosed acutely, supportive care measures focus on seizure control, treatment of underlying conditions such as infection or dehydration, optimization of oxygenation, and cerebral perfusion with normalization of systemic blood pressure.[13] Neonatal seizures due to a stroke may require multiple loads of antiseizure medicines to end status epilepticus. Recanalization therapy with thrombolytic agents and mechanical thrombectomy for perinatal stroke lack safety and efficacy data and are not recommended. Decompressive neurosurgery is uncommon because open cranial sutures expand with increased intracranial pressure. Antiplatelet or anticoagulation treatment for secondary stroke prevention after a perinatal stroke is not typically recommended because of the low risk of stroke recurrence, except in infants with complex congenital heart disease.[28,72] If complex congenital heart disease is present, it confers a persistent risk of recurrent stroke during the newborn period and later in life.

BARRIERS TO RAPID CARE FOR CHILDREN WITH ACUTE ISCHEMIC STROKE

Broad public health campaigns and a robust system of prehospital triage, in-field care, and designated primary and comprehensive stroke centers for adults have decreased stroke mortality and morbidity.[73] Children benefit from early recognition of stroke and should be transferred to a hospital that can provide definitive care as soon as safely possible, but systems of care for children with stroke lag behind those for adults. Most hospitals do not have guidelines to administer IV thrombolysis for children aged younger than 18 years. In some countries, a regional hospital may have guidelines and expertise to provide thrombectomy[74] but little prehospital infrastructure or few systems of triage to identify pediatric stroke-ready hospitals and abet rapid transfer. The TIPS (Thrombolysis in Pediatric Stroke) trial was funded in 2010 as the first prospective treatment trial for acute pediatric stroke, and preparation for rapid enrollment into the multicenter study sparked the emergence of pediatric stroke centers.[4,75] Since that time, the need for greater pediatric stroke infrastructure has increasingly been recognized.[76] Individual institutions have reported that implementation of pediatric stroke guidelines and protocols have altered care by increasing the proportion of children receiving antithrombotic treatment within the first 24 hours.[77]

HEALTH DISPARITIES

Structured and organized health systems that improve the speed of triage, transport, and treatment of children in medical centers with established pediatric stroke guidelines are still lacking in many geographic areas. Globally, the burden of childhood stroke differs in countries with higher resources from lower resourced regions. While fewer population-based estimates of stroke incidence and mortality are available from low- and middle-income countries, the prevalence rates of childhood stroke appear to be significantly higher compared with countries with greater resources.[78] Estimates of death rates and disability-adjusted life years after childhood stroke are also higher in low- and middle-income countries.[78] In the VIPS (Vascular Effects of Infection in Pediatric Stroke) study, a large multinational observational cohort study of pediatric stroke, very low income (<$10,000 per year) was associated with worse neurologic outcomes compared with higher income levels.[79] The authors postulated that these health disparities may be related to racial, ethnic, or socioeconomic factors that result in fewer resources for stroke prevention and differences in stroke outcomes, and called for future research in this area.

Since the STOP trial and implementation of TCD screening in children with sickle cell disease, the excess risk of death from ischemic stroke in Black children in the United States has dropped.[80] The STOP study transformed stroke prevention for some children with sickle cell disease, but implementation of stroke prevention guidelines for many children with sickle cell disease remains challenging. Even in high-resource settings, chronic blood transfusion can be a major challenge because of red blood cell alloimmunization and the social interruption of frequent medical appointments. In low-resource settings, where global prevalence of sickle cell disease is highest, TCD ultrasound and safe blood supplies may not be available or affordable.[81] In regions where TCD screening and regular blood transfusion are not widely feasible, guidelines suggest that hydroxyurea treatment should be used rather than no treatment for preventing stroke in high-risk children with sickle cell disease.[60] The SPRING (Primary Prevention of Stroke in Children With Sickle Cell Disease in Sub-Saharan Africa II) trial in Nigeria demonstrated that children with sickle cell disease and abnormal TCD velocities treated with low-dose hydroxyurea have equivalent stroke rates compared with children treated with moderate-dose hydroxyurea. These results have changed practice in three Nigerian states to provide free low-dose hydroxyurea to children with abnormal TCD assessments.[82] More research for stroke prevention strategies that can be feasibly implemented in low-resource and high-resource settings is critically needed.

KEY POINTS

- Children benefit from early recognition of stroke and should be transferred to a hospital that can provide definitive care as soon as safely possible, but systems of care for children with stroke lag behind those for adults.
- Structured and organized health systems that improve the speed of triage, transport, and treatment of children in medical centers with established pediatric stroke guidelines are still lacking in many geographic areas.

CONCLUSION

Similar to adults, children benefit when a stroke is recognized early after onset. There is increasing recognition of the potential role of hyperacute recanalization therapies and neuroprotective care to decrease lifelong morbidity following childhood stroke. Most stroke clinical trials exclude children, so evidence for effective therapeutics that reduce disability and improve outcomes are still needed. Although pediatric acute stroke care does not benefit from the level of evidence available for adult stroke, an organized approach to care can be extrapolated from adult stroke and pediatric critical care experience, expert

consensus, and emerging pediatric stroke data. Public health measures that help people recognize stroke in children are critical.

USEFUL WEBSITES

PEDIATRIC NATIONAL INSTITUTES OF HEALTH STROKE SCALE (PedNIHSS)
Online calculator for the PedNIHSS.
mdcalc.com/calc/10270/pediatric-nih-stroke-scale-nihss

INTERNATIONAL PEDIATRIC STROKE ORGANIZATION (IPSO)
The IPSO website provides links to pediatric stroke resources for patients and families, bulletins with recent literature reviews, research opportunities, and information about training programs in pediatric stroke.
internationalpediatricstroke.org

MANAGEMENT OF STROKE IN NEONATES AND CHILDREN: A SCIENTIFIC STATEMENT FROM THE AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION[17]
aan.com/Guidelines/Home/GuidelineDetail/956

PRACTICE ADVISORY UPDATE: PATENT FORAMEN OVALE AND SECONDARY STROKE PREVENTION[21]
aan.com/Guidelines/home/GuidelineDetail/991

EXPANSION OF THE TIME WINDOW FOR TREATMENT OF ACUTE ISCHEMIC STROKE WITH INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR: A SCIENCE ADVISORY FROM THE AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION[43]
aan.com/Guidelines/Home/GuidelineDetail/369

2015 AHA/ASA FOCUSED UPDATE OF THE 2013 GUIDELINES FOR THE EARLY MANAGEMENT OF PATIENTS WITH ACUTE ISCHEMIC STROKE REGARDING ENDOVASCULAR TREATMENT[50]
aan.com/Guidelines/home/GuidelineDetail/700

PHYSICAL ACTIVITY AND EXERCISE RECOMMENDATIONS FOR STROKE SURVIVORS[70]
aan.com/Guidelines/Home/GuidelineDetail/661

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