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REVIEW

Advances in the Diagnosis and Treatment of Pediatric Arterial Ischemic Stroke

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Abstract

Though rare, stroke in infants and children is an important cause of mortality and chronic morbidity in the pediatric population. Neuroimaging advances and implementation of pediatric stroke care protocols have led to the ability to rapidly diagnose stroke and in many cases determine the stroke etiology. Though data on efficacy of hyperacute therapies, such as intravenous thrombolysis and mechanical thrombectomy, in pediatric stroke are limited, feasibility and safety data are mounting and support careful consideration of these treatments for childhood stroke. Recent therapeutic advances allow for targeted stroke prevention efforts in high-risk conditions, such as moyamoya, sickle cell disease, cardiac disease, and genetic disorders. Despite these exciting advances, important knowledge gaps persist, including optimal dosing and type of thrombolytic agents, inclusion criteria for mechanical thrombectomy, the role of immunomodulatory therapies for focal cerebral arteriopathy, optimal long-term antithrombotic strategies, the role of patent foramen ovale closure in pediatric stroke, and optimal rehabilitation strategies after stroke of the developing brain.

Keywords Pediatric stroke · Childhood stroke · Sickle cell · Thrombectomy

Background

Cerebrovascular disorders are an important cause of mortality and chronic morbidity in children. Here, we review the most recent literature on the epidemiology, risk factors, evaluation, outcome, and treatment of pediatric arterial ischemic stroke (AIS).

Definition

The case definition for pediatric stroke has varied widely in the literature. Differences in age of onset, time at diagnosis, and cerebrovascular disorders to include have led to variability in incidence rates across studies. Perinatal stroke develops between 20 weeks gestation and 1 month of age, but it may be diagnosed months later, and it includes a diverse group of cerebrovascular disorders [1]. AIS is the most common type of cerebrovascular disorder to occur in the perinatal period. Childhood stroke develops later, between 30 days and 18 years of age, and includes AIS, hemorrhagic stroke, and sinovenous thrombosis.

Incidence

The incidence of perinatal stroke is estimated as high as one per 1100 live births [2], but lower rates have been reported [3–6]. Most estimates are based on small samples over short periods of time, with variable ascertainment methods. The rate of AIS is reported to be much higher in the perinatal period than in childhood [7]. The first population-based study of stroke in children from the 1970s found an incidence of 1 per 40,000 children for all stroke types [8]. More recent studies in Canada [9], the USA [3], the UK [10], and Sweden [11] have found similar rates. The incidence of stroke is higher in boys than girls and among Black, Asian, and Hispanic children compared to white children [10, 12]. In a community-based study of cerebrovascular disease in Texas, the incidence rate of

Invited Review: Advances in Stroke Diagnostics and Therapeutics.

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stroke was found to be higher in Mexican American children than non-Hispanic whites [13].

Clinical Presentation

The clinical presentation of AIS is related to the age of the child and location of the stroke. Infants with stroke typically present with seizures or other diffuse neurologic deficits. Some infants with stroke are not identified acutely, but are diagnosed retrospectively, when neurologic symptoms, such as emerging hemiparesis or seizures, leads to neuroimaging [5]. In contrast, children with stroke typically present with focal neurologic deficits, usually hemiplegia and/or focal seizures. Signs and symptoms of stroke in children are often misinterpreted to be other common neurologic or systemic disorders. Emergency rooms physicians are less accurate at detecting stroke in children than adults [14]. Several stroke screening tools have been shown to be highly sensitive in adults [15] but are less accurate in children [16]. Symptoms of focal weakness, seizures, ataxia, speech, or walking difficulties have been shown to discriminate stroke from migraine, a common stroke mimic in children [17]. Better screening tools to assist providers may help to alleviate delays in diagnosis that impact the study and use of acute therapies in children with stroke.

Classification and Mechanism

Identifying the cause of stroke is helpful for explaining stroke mechanism to patients, determining future stroke risk, selecting secondary prevention strategies, and stroke research. Several adult stroke classification systems have been developed and have exhibited good reliability and discriminative validity [18]. Adult classification systems have limited use in children since the causes of stroke are so different. The Childhood Arterial Ischemic Stroke Standardized Classification and Diagnostic Evaluation (CASCADE) system was developed by the International Pediatric Stroke Study (IPSS) investigators to categorize childhood strokes according to the underlying cause [19]. The CASCADE system classifies childhood AIS into seven discrete subtypes and has moderate interobserver agreement when used by experienced raters. The CASCADE subtypes include (1) small vessel arteriopathy, (2) unilateral focal cerebral arteriopathy (FCA), (3) bilateral cerebral arteriopathy, (4) aortic/cervical arteriopathy, (5) cardioembolic, (6) other, and (7) multifactorial [19]. A recent study evaluated the predictive value of the CASCADE criteria and found an association with risk of recurrent stroke and progression of arteriopathy [20].

Causes of Stroke in Children

The causes of stroke in children have varied widely among registry studies [21–23]. Most of these studies have been retrospective, without a uniform diagnostic approach or classification system, and relevant risk factors may not have been identified or recorded. The most frequently reported risk factors for AIS in children are arteriopathies, cardiac disorders, infection, hematological and metabolic disorders, and other rare causes. In many children with stroke, the cause is thought to be multifactorial [24], possibly a combination of environmental triggers and hereditary or acquired disorders that increase the risk of stroke.

Arteriopathies

The expanded use of vessel imaging has enhanced our understanding of stroke in children. Extracranial and intracranial arteriopathies are a common cause of stroke in children. Arteriopathies were identified in 53% of children in the IPSS [24]. In studies with limited use of vessel imaging, other causes are more common, which may be related to detection bias [21]. Arteriopathies lead to stroke through a variety of mechanisms including decreased blood flow and local thrombus formation.

Arterial dissections are the most common cause of extracranial arteriopathies in children. Arterial dissection is due to a tear in the intimal layer or rupture of the vasa vasorum and hemorrhage into the medial layer [25]. Intracranial dissection occurs more frequently in older children (median age 14 years) compared to extracranial dissection (median age 8 years) [26]. Arterial dissection is more common in boys, and they typically present with symptoms of hemiplegia and headache [27]. Arterial dissection has been associated with a variety of conditions, but most cases are due to trauma. Recurrent AIS occurs in up to 19% of children with arterial dissection [28].

Intracranial arteriopathies account for almost half of all childhood strokes [29] and represent a heterogenous group of disorders that can be difficult to diagnose and classify. Intracranial arteriopathies identified most often in children with AIS include inflammatory FCA, moyamoya, and arterial dissection. The vascular effects of infection in pediatric stroke (VIPS) investigators defined FCA as “unifocal and unilateral stenosis/irregularity of the large intracranial arteries of the anterior circulation” [30]. FCA can be classified into different subtypes based on the underlying etiology; these include inflammatory (FCA-i) and dissection (FCA-d) types.

Inflammatory FCA (FCA-i) is a subtype of FCA due to an inflammatory or infectious process. FCA-i has been

associated with both active and post-infectious disorders, including post-varicella arteriopathy [31]. Varicella (chicken pox) is associated with an increased risk of stroke in children [32]. Post-varicella arteriopathy can develop from a current infection or several months after infection [33]. There have been several recent reports of other infectious agents associated with FCA and stroke in children. A recent case–control study from the VIPS cohort found an increased rate of parvovirus B19 infection among cases compared to controls [34]. Dengue fever has also been reported in association with FCA and stroke [35]. An international study of children with SARS-CoV2 and AIS identified several children with vasculitis and FCA [36].

Moyamoya is a chronic non-inflammatory steno-occlusive intracranial arteriopathy that accounts for about 8% of AIS in children [37]. Moyamoya *disease* is characterized by an angiographic pattern of stenosis of the supraclinoid internal carotid artery with secondary development of an extensive collateral network that gives a radiographic appearance of a "puff of smoke". Moyamoya *syndrome* is a secondary complication of other medical disorders (Down syndrome, sickle cell disease, neurofibromatosis) that lead to this unique arteriopathy. The progressive steno-occlusive arteriopathy of moyamoya can lead to decreased blood flow, diminished cerebrovascular reserve, and ischemic stroke. Hemorrhage can also occur and is due to the rupture of vessels in the fragile collateral network or associated aneurysms [38]. The incidence of moyamoya disease is highest in Asia, predominantly in Japan. The disease is more common among females and peaks in children around 5–9 years of age [39]. The cause of moyamoya disease is unclear, but the high prevalence in Asian populations and familial clustering suggests a genetic disorder. Around 10–15% of cases are familial, mostly affecting siblings compared to a parent or offspring. Linkage studies have identified several genetic loci, such as *RNF213*, associated with moyamoya disease, but these have not been consistent across populations [40]. Children with moyamoya typically present with transient ischemic attacks (TIAs) or AIS but may develop other symptoms like headache or seizures. Some children with moyamoya are identified incidentally on brain imaging and have a lower risk of stroke after diagnosis than those with prior ischemic symptoms [41]. The risk of stroke in patients with moyamoya increases with disease progression. The incidence of stroke also varies according to moyamoya disease genotype and underlying cause of moyamoya syndrome [42]. Revascularization surgery is recommended to prevent the progression of the disease and risk of stroke. The primary indications for surgical intervention include clinical symptoms (stroke, TIA, or cognitive decline) or imaging evidence of progression and decreased cerebral blood flow or cerebral perfusion reserve [43]. Revascularization is associated with a decrease in symptomatic progression, headaches, and ischemic and hemorrhagic stroke [44].

Cardiac Disorders

Stroke is a well-recognized complication of cardiac disease in both children and adults. Cardiac disorders associated with stroke include congenital heart disease, intracardiac defects, cardiac procedures, cardiomyopathy, arrhythmias, infective endocarditis, and ventricular assist devices [45]. These disorders can lead to the development of thrombi within the heart, on an infected valve, or through a right to left shunt, which can embolize to the brain.

The rate of stroke among children with cardiac disease has varied widely among studies due to differences in case definitions, brain imaging, and cardiac disorders studied. A study of children with cardiac disease in the northwest US found a rate of stroke of one in 750 children [46], but higher rates have been reported among children who undergo cardiac procedures and catheterization [45]. While the incidence of stroke overall is low in children with cardiac disease, these disorders are common among registries of children with stroke. Cardiac disorders were identified in 30% of children in the IPSS [24].

Congenital heart disease (CHD) is the most common birth defect in newborns [47] and a common cause of cardioembolic stroke in children. In the IPSS, 60% of children with cardiac-related stroke had CHD. Children with CHD can be affected by a wide range of cyanotic and acyanotic heart disorders and have a 19-fold risk of stroke when compared to controls [48]. The risk of stroke is related to the underlying heart disorder, its comorbidities, and other factors including cardiac procedures and the use of mechanical support devices [49]. AIS occurs most often among children with cyanotic heart disease [45]. Children who undergo surgery for CHD have a 13-fold increased risk of stroke when compared to controls [48]. An imaging study of infants that underwent surgery for CHD identified stroke in 10% of patients, most of which were clinically silent [50]. Among infants who undergo surgery for CHD, younger postnatal age at the time of surgery and selective cerebral perfusion are associated with AIS in the post-operative period [51]. In children who undergo surgery, other risk factors for stroke may be present and likely play a role. A study of children with CHD and AIS from South Korea found that most strokes occurred during the periprocedural period, and almost half had an additional risk factor for thromboembolism [52].

Patent foramen ovale (PFO), especially if associated with high-risk features such as atrial septal aneurysm, is associated with an increased risk of stroke in adults [53]. Randomized clinical trials have shown a benefit of closure

in carefully selected high-risk PFO patients [54–57]. The relationship between incident and recurrent stroke and PFO in children is unclear. A large observational study found an increased rate of PFO in children with cryptogenic stroke compared to children with stroke of known etiology and children without stroke [58].

Hematologic Disorders

Blood disorders have shown stronger risk associations with stroke in children compared to adults. Blood disorders documented in children with AIS include genetic and acquired coagulation abnormalities and sickle cell disease (SCD). Prothrombotic disorders were identified in 13% of children in the IPSS but have been reported at much higher rates in other studies of children with stroke [24, 59]. Prothrombotic disorders can lead to abnormal venous and arterial thromboses.

SCD is a group of inherited disorders caused by mutations in hemoglobin and is a major risk factor for AIS in children. SCD causes abnormally shaped (sickled) red blood cells with increased fragility that interact with the vascular endothelium and cause vaso-occlusion [60]. Two major cerebrovascular manifestations of SCD are large artery intracranial occlusive disease and silent cerebral infarction (SCI). Large artery steno-occlusive disease is thought to develop from endothelial hyperplasia and intraluminal thrombosis from recurrent sickling [61]. The large vessel changes typically develop within the distal internal carotid, middle cerebral, and anterior cerebral arteries and may progress to an angiographic pattern of moyamoya. SCI is defined as chronic ischemic changes at least 3 mm in size on T2-weighted magnetic resonance imaging (MRI) without neurologic signs or symptoms related to the lesion [62]. The mechanism for SCI in SCD is unclear but thought to be related to changes in perfusion and oxygenation [63].

Children with SCD (HbSS) have a risk of AIS over 200 times that of healthy children, and 10% percent will develop symptomatic AIS before 15 years of age [60]. While symptomatic AIS is common, 32% percent of children with SCD have evidence of silent infarction [64].

Genetic prothrombotic factors likely play a greater role in individuals presenting with AIS in childhood compared to onset in later years [65]. Several genetic and acquired prothrombotic abnormalities have been evaluated in children with AIS, but the rate of these abnormalities have varied among different age groups, stroke subtypes, and international populations studied [66]. Prevalence differences are likely due to the extent and timing of investigations, small sample sizes, and population admixture and stratification [67]. Coagulation abnormalities tend to be more common in European-derived populations compared to other ethnic and racial groups. Case–control studies, utilizing hospital-based adult and population-based child controls, have shown an association between many of these abnormalities and AIS [68–71], while other studies have been negative or too small to show a difference [72–74]. The presence of a prothrombotic abnormality has also been shown to increase the risk of recurrent stroke in children [75].

Infectious Disorders

Several infectious agents have been reported in association with AIS in children. Infection can lead to cerebral ischemia through multiple mechanisms, including activation of the coagulation cascade, thrombosis from a systemic inflammatory response, septic emboli, and direct invasion of the endothelium. During serious infection, there is a rapid destruction of protein C and antithrombin III, both of which normally inhibit coagulation. Infection also produces endothelial injury and a release of inflammatory cytokines, which lead to the downregulation of thrombomodulin. Decreased levels of activated protein C and increased levels of D-dimer and C4b binding protein have also been observed in patients with AIS [76]. The timing of infection also seems to play a role in the risk of stroke and may be related to infection-related activation of the coagulation system. A population-based case–control study found that a recent infectious visit ≤ 3 days prior was associated with a 12-fold increased risk in stroke [77]. Infections were identified in 24% of children in the IPSS [24], but studies in China [22] and Turkey [78] found much higher rates in children with stroke.

Childhood AIS has been reported as a complication of bacterial infection from meningitis, encephalitis, brain abscess, sinusitis, and sepsis. The prevalence of AIS in infants and children with bacterial meningitis has ranged from 24 to 71% [79–81]. A recent population-based study in Canada found that 37% of children with bacterial meningitis developed stroke. In this study, children with meningitis plus stroke had higher rates of morbidity and mortality than children without stroke [82]. A study of children with tuberculous meningitis in South Africa identified a stroke in 71% of children at admission. Risk factors associated with stroke at admission included young age (< 3 years), seizures, and hydrocephalus [81].

Viral infections have also been linked to childhood AIS and include varicella [32], HIV [83], parvovirus B19 [34], Zika [84], Dengue viruses [85], herpes simplex [86], Epstein Barr [87], CMV [88], and COVID-19 [36]. Studies of varicella zoster virus (VZV) have provided the most evidence supporting a link between a viral infection and AIS in children [88, 89]. A case–control study of children with AIS found a history of VZV infection within the last 9 months in 64% of cases and 9% of controls [32]. A cohort study in Canada discovered a threefold increase in the frequency of

a prior VZV infection in children with AIS compared to published controls [90]. In children with VZV, the rate of AIS has been estimated at 1/26,000 children [91].

VZV infection can produce a large vessel granulomatous angiitis with multinucleated cells that affects the distal internal carotid and proximal cerebral arteries and may lead to endothelial injury and AIS. The path in which VZV infects cerebral vessels may be related to afferent fibers from the trigeminal ganglia to the circle of Willis. During VZV infection, the virus can pass into the trigeminal ganglion and enter a latent state; upon reactivation, the virus could then travel through afferent fibers that innervate the intracranial vessels and cause a focal vasculitis and ischemic stroke [92]. A recent theory on the pathogenesis of varicella arteriopathy is that infection causes adventitial fibroblasts to transform into myofibroblasts, resulting in proliferation and migration that contributes to arterial remodeling, along with endothelial activation by VZV microparticles [93]. The recurrence rate of TIA and AIS among children with VZV-related AIS has been reported as high as 45% [90].

Several other viruses and microbial infections have been reported in association with stroke in children. The rate of parvovirus B19 and herpes simplex virus was higher in cases of children with stroke compared to controls in the VIPS (Vascular Effects of Infection in Pediatric Stroke) study [34, 94]. Recently, there have been several reports of stroke in children infected with the SARS-CoV2 virus [36, 95–97]. Multisystem inflammatory syndrome is observed in children after acute infection with severe SARS-CoV2 and has been associated with stroke. A large international registry of children with stroke and SARS-CoV2 found that inflammatory arteriopathies were the most common cause of stroke [36]. Other infections, including rickettsial infections, have also been associated with stroke in children [98, 99].

Cancer-Related Stroke

Over the last 40 years, there has been an increase in the incidence of childhood cancer in the USA [100]. Despite these changes, survival rates for children with cancer continue to improve. Children with cancer can develop neurologic complications from their disease as well as acute, chronic, and late effects from cancer therapy. Cancer is a risk factor for incident and recurrent stroke [101]. Several cancer types have been associated with stroke in children and include acute lymphoblastic leukemia, Hodgkin disease, and brain tumors. The mechanisms that typically lead to stroke in cancer patients include radiation-induced cerebrovascular disease, compression of intracranial vessels, cancer-related coagulopathy, cardioembolism, infection, and complications from chemotherapy. Cancer or tumor was present in 3% of children in the IPSS. In children who developed cancer-related AIS, 88% had a brain or hematological cancer [101]. The cause of cancer-related AIS in this cohort was most often due to arteriopathy or cardioembolism [101].

Rare Causes of Stroke in Children

Stroke has been reported with over 100 medical disorders in children, many of which are rare but have been reported in the literature more recently. Bow Hunter's syndrome (BHS), or rotational vertebral arteriopathy, is due to compression and or dissection of the vertebral artery with head turning [102]. The underlying cause is thought to be due to abnormal osteophytes, fibrous bands or lateral disc herniation with neck rotation or extension [103]. Children with BHS can develop vertebral dissection and stroke, but there is no consensus on treatment and prevention. Surgical treatment with C1/C2 fusion has been performed in children with BHS, but whether this treatment is more effective than medical therapy is unknown [104]. Similar to BHS, thoracic outlet syndrome (TOS) is related to compression of neurovascular structures. TOS can occur from compression of the subclavian artery from a bony structure (such as a cervical rib) and can lead to thrombus formation and stroke. Risk factors for TOS include activities that involve repetitive movement of extreme abduction and external rotation of the shoulders [105]. The mechanism through which TOS leads to stroke is unclear. One theory is that subclavian compression can lead to trauma and thrombus formation, and retrograde propagation or propulsion of the thrombus can lead to embolization in the vertebral or common carotid arteries [106]. Similar to BHS, the optimal prevention strategy is unclear, but most patients reported in the literature have undergone thoracic outlet decompression surgery as opposed to medical therapy [106].

Outcomes of Stroke in Children

The morbidity and mortality from AIS have varied among studies due to differences in functional outcome measures, stroke type, duration of follow-up, and cohort studied. Most studies have focused on motor recovery as opposed to language, vision, cognition, quality of life, or other neurologic deficits. A review of pooled data from early studies of AIS in children from 1977 to 2004 ($N = 1364$) revealed that on average 30% of children were neurologically normal, 61% developed cognitive or motor problems, and 9% died by the outcome evaluation period [107]. More recent prospective studies that used standardized functional measures found similar rates. A study of the Swiss NeuroPediatric Stroke Registry found that in children with AIS, 26% were neurologically normal, 63% developed neurologic disability, and 11% died by 6 months [108]. A study of children with AIS from the IPSS found that 74% had a neurologic deficit at

discharge and 3% died from their stroke [109]. A study from the Canadian Pediatric Stroke Registry ($N=681$) found that among infants and children with AIS, 69% died or had a neurologic deficit at a mean follow-up time of 3 years [9]. Few studies have reported long-term outcomes. An outcome study from the IPSS found that 54% of children were neurologically normal and 46% had mild, moderate, or severe disability at 2 years. The study also found that 46% of children demonstrated recovery over the 2-year follow-up period [110]. A study of children with AIS from Switzerland found that 56% of children followed for a median of 6.9 years had a favorable outcome, as defined by a modified Rankin scale score of 0–1 [111].

Several outcome predictors have been reported in children with AIS and include age at onset, clinical presentation, lesion location and volume, post-stroke seizures, and etiology of stroke [110, 112–115]. Stroke onset in childhood is associated with a poorer outcome compared to stroke in the neonatal period [110, 113, 116]. Studies of children with stroke from Canada, the USA, Israel, the UK, and the Netherlands found an association between children who present with altered levels of consciousness and/or seizures with poor outcome [9, 117–120]. Stroke volume and location have been shown to impact both motor and cognitive function [112, 121, 122]. Large lesions (defined differently in different studies), involvement of both the subcortical and cortical regions, and Wallerian degeneration within the corticospinal tract have been shown to be associated with poor motor outcome [112, 116, 123–126]. Post-stroke seizures are more common in children than adults, with a cumulative incidence of 30% at 10 years [127]. Children who develop epilepsy post-stroke have worse neurologic outcomes than children without epilepsy [119, 128]. The underlying cause of stroke has been associated with both outcome and recurrence in children. Children with arteriopathy- and cardiac-related stroke have worse outcomes than other stroke subtypes [9, 109, 129–132].

Recurrent Stroke and Death

The reported recurrence rate of AIS in children ranges from 6 to 30% [133, 134], and most recurrences develop in the first 6 months after incident stroke [135, 136]. The recurrence rate of AIS is highest among children with TIA, cardiac disease, arteriopathies, metabolic and coagulation abnormalities, and posterior circulation strokes. A population-based study of children with stroke found a high rate of recurrent stroke among children with arteriopathy [137]. The presence of arteriopathy increased the risk of recurrent stroke fivefold in the VIPS study [28]. A study that compared the rate of recurrent AIS among children with anterior and posterior circulation stroke found much higher rates in children with posterior circulation strokes [138]. The presence of a thrombophilia or combination of coagulation abnormalities is also associated with an increased risk of recurrent stroke [134, 136].

Case fatality rates for AIS in children have ranged from 0 to 28% depending on the population studied, but recent studies have shown lower rates than in the past [8, 120, 139]. Mortality rates for AIS are highest among children less than 1 year of age. The death rate from cerebrovascular diseases in children peaks at 2.7 per 100,000 in infants, subsequently declines, and does not exceed the infant mortality rate until 35–44 years of age [140]. The mortality rate in children due to AIS is higher in males than females and in black children compared to white children [141].

Diagnostic Evaluation

Consensus guidelines have provided some guidance on the evaluation of stroke in children, but several controversies and knowledge gaps exist [43, 142–144]. The evaluation should identify the etiology and rule out other non-vascular causes that mimic stroke in children (postictal paralysis, migraine, hypoglycemia, and alternating hemiplegia). While there is limited evidence to support the use of acute therapies (intravenous [IV] tissue plasminogen activator [tPA] or mechanical thrombectomy [MT]) in children, a rapid stroke evaluation and neuroimaging seems reasonable to determine whether a favorable profile exists for hyperacute treatments. The history should include questions regarding head and neck trauma, unexplained fever or recent infection (varicella in last 12 months), drug ingestion, developmental delay, blood disorders, and associated headache. A careful family and birth history should also be taken, with special attention to neurologic disease, premature vascular disease, hematologic disease, and developmental disorders.

Acute Diagnosis of Stroke

Significant delays in the acute diagnosis of stroke in children have likely restricted access to acute therapies. Several factors have contributed to these delays including delays in arrival to medical care, diverse clinical presentations, accuracy of diagnosis among ED providers, lack of effective stroke screening tools, an absence of pediatric "code stroke" protocols, and use of imaging that is insensitive to acute ischemia [143, 145]. The American Heart Association (AHA) recommends that centers establish systems and pathways for hyperacute pediatric stroke care [43]. Standardized institutional stroke protocols have been found to improve the time to diagnosis of stroke in children [146–148]. These protocols have typically consisted of the following components: a stroke screening tool in the ED (based on time of onset and

symptoms), a code stroke activation process, a dedicated stroke responder, and a triage process for acute MRI [146, 149, 150].

Neuroimaging

MRI is the preferred imaging modality for acute stroke in children because it allows for early differentiation of stroke from mimics; this is critically important due to the high rate of stroke mimics in children. MRI is better than CT for the detection of acute ischemia and can also detect acute and chronic hemorrhage [151]. A consensus-based statement from members of the IPSS recommended the following sequences for stroke in children: DWI, FLAIR, GRE or SWI, T1 and T2 (optional sequences include T1 contrast and arterial spin labeling) [152]. Recently, several other rapid sequence MRI protocols have been recommended for stroke in children. These have included similar sequences with the addition of a time-of-flight MRA [153, 154]. Perfusion imaging is helpful in determining stroke core and penumbra and selecting patients for acute therapies. Dynamic susceptibility contrast MR perfusion is an IV contrast (gadolinium)-based perfusion technique that is commonly used in adults but seldom in children with stroke. Concerns regarding an IV bolus of contrast and gadolinium accumulation in the brain have limited its use in children. Arterial spin labeling (ASL) is a non-contrast perfusion technique that is commonly used in children with stroke. Several ASL techniques have been developed to evaluate cerebral perfusion. These techniques involve the use of radiofrequency pulses to magnetically tag arterial blood in the skull base, which is then imaged as the blood flows into the brain. A cerebral blood flow map is derived from the imaged blood as it flows into various brain regions. ASL is more useful in children than adults, since it does not require IV contrast and has better signal to noise ratio in children compared to adults [155]. Overall, the use of MRI in children with stroke has been limited due to institutional (MRI availability, anesthesia availability, lack of rapid sequence protocols) and patient-related factors [156].

Etiologic Investigations

A comprehensive evaluation of children with stroke should include cardiac, hematologic, metabolic, inflammatory, and brain and vessel imaging studies, as evidence suggests that children with stroke may have multiple risk factors [43]. Advanced studies should be considered for children with cryptogenic or recurrent stroke. The primary goal is to utilize an iterative approach to identify the cause of stroke for secondary prevention and to determine prognosis. The AHA guidelines for the management of stroke in neonates and children recommend a baseline evaluation for all children with stroke (Table 1) [43]. Depending on the clinical context, advanced diagnostic studies can be considered when the stroke remains cryptogenic and/or recurs (Table 2).

Table 1 Standard basic evaluation of childhood stroke

Standard diagnostic studies	Stroke etiology
MRI head	Rule out stroke mimics
TTE with bubble study, EKG	PFO, cardiac arrhythmias, identification of intracardiac thrombus
MRA brain and neck or CTA head and neck	Dissection, arteriopathies
Coagulation studies	Inherited or acquired thrombophilias
ESR, CRP, ANA	Inflammatory disorders

TTE transthoracic echocardiogram, *EKG* electrocardiogram, *MRA* magnetic resonance angiography, *CTA* computed tomography angiography, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibody

The approach to diagnostic evaluation of perinatal stroke differs from childhood stroke, as most perinatal strokes occur due to a convergence of multiple risk factors specific to the perinatal period [157]. Transthoracic echocardiography and neurovascular imaging can be performed to rule out intracardiac thrombus, abnormal cardiac anatomy, and cerebrovascular abnormalities. Several recent studies have shown that thrombophilia testing is low yield and does not typically predict recurrence risk or change management [74, 158], so these extensive laboratory studies can be reserved for children with concerning family histories or recurrent thromboembolic events.

Evidence Gaps and Diagnostic Testing

There are limited studies regarding the indications, utility, and cost-effectiveness of diagnostic studies for stroke in children. For example, a study examining the diagnostic yield of various studies in young adults (18–45 years old) with stroke showed that Holter monitoring, vasculitis panels, and toxicology screening were low yield studies [159]. The diagnostic yield of these and other studies in childhood stroke is unknown.

The role of PFO in the pathogenesis of stroke in children is unclear, as discussed below. The need for additional studies beyond standard transthoracic echocardiography with agitated saline, such as transesophageal echocardiography or transcranial Doppler (TCD) ultrasound with agitated saline, to identify and characterize PFO is also uncertain.

Several genetic and acquired prothrombotic abnormalities have been evaluated in children with AIS, and the rates of these abnormalities have varied widely among studies. Many of these abnormalities, including antithrombin deficiency, protein C deficiency, elevated lipoprotein(a), and antiphospholipid antibodies, have been associated with

Table 2 Advanced diagnostic evaluation of childhood stroke

Advanced diagnostic studies	Stroke etiology
Holter monitoring	Arrhythmia
Cerebral angiography	Moyamoya, FCA, covert dissection
Lumbar puncture	Infectious/inflammatory FCA, meningitis/encephalitis, primary angiitis of the central nervous system
Artery biopsy	Fibromuscular dysplasia
Genetic/metabolic studies	HHT, Moyamoya, arteriopathies, thrombophilia, inflammatory disorders, Fabry's, MELAS, POLG1, connective tissue disorders, DADA2
Brain biopsy	Angiography-negative childhood primary angiitis of the central nervous system
Dynamic CTA or DSA neck	Bow Hunter's syndrome

FCA focal cerebral arteriopathy, *HHT* hereditary hemorrhagic telangiectasia, *MELAS* mitochondrial encephalopathy, lactic acidosis, and stroke like episodes, *POLG1* DNA polymerase subunit gamma 1, *DADA2* deficiency of adenosine deaminase 2, *CTA* computed tomography angiography, *DSA* digital subtraction angiography

incident stroke in children, but further studies are needed to determine the risk of recurrent stroke [71]. Prothrombotic abnormalities tend to be more common in European-derived populations compared to other ethnic and racial groups, and whether these tests should be performed in all children with stroke is unknown.

MRI vessel wall imaging (VWI) is a diagnostic tool that utilizes special MR sequences to suppress the signal in areas within and around a blood vessel (flowing blood and CSF) to image the vessel wall. VWI requires a high spatial resolution and is typically performed on 3 T or higher scanners and with higher channel head coils. Imaging in multiple planes (2D and 3D) is required for optimal resolution of the vessel wall. Most protocols include pre- and post-contrast T-1 weighted studies to evaluate for enhancement within the vessel wall. The most common sequence used for blood and CSF suppression is a 3D turbo spin-echo sequence with variable flip angle refocusing pulses, which varies among vendors. VWI should be interpreted by individuals with experience in vessel wall imaging as age related, flow, and anatomical variation can sometimes mimic disease [160, 161]. MRI VWI has been shown to be helpful in the differentiation of intracranial arteriopathies [162]. Vessel wall enhancement is considered a marker of inflammatory vasculitis. A study by Dlamini and colleagues evaluated 26 children with AIS and found that distinct VWI patterns were associated with specific types of arteriopathy [163]. A study of 16 children with AIS found that strong vessel enhancement on VWI was associated with progressive arteriopathy [164]. However, a more recent study of 9 children with AIS and FCA who underwent VWI did not find an association with vessel enhancement and progression [165]. VWI studies can be long and require contrast agent and may therefore not be suitable for all children. Further studies are needed to determine the utility of VWI in children with AIS [165].

Finally, the role for genetic testing in pediatric stroke is expanding. Elucidation of the genetic cause of stroke can inform counseling, recurrence risk, and prognosis. It may also drastically change management strategies. For example, a diagnosis of deficiency of adenosine deaminase 2 (DADA2) may prompt discontinuation of antiplatelet therapies and initiation of TNF inhibitors [166, 167], as detailed below.

Therapeutics

Acute Therapies

IV Thrombolysis

The transformation of adult stroke care at the end of the twentieth century with the approval of IV thrombolysis for acute stroke and concurrent implementation of integrated stroke systems of care led to questions about the appropriateness of IV thrombolytics for childhood stroke. Several a priori considerations suggest that extrapolation from adult data may be inappropriate. Specifically, stroke etiologies differ between children and adults, with certain common childhood stroke etiologies not being clearly amenable to treatment with thrombolytic agents. Additionally, developmental changes in the coagulation cascade, termed "developmental hemostasis," should be considered, as younger children have lower levels of endogenous tPA and higher levels of plasminogen activator inhibitor-1 (PAI-1) compared with older children and adults [168–170], suggesting that different thrombolytic dosing may be needed based on age. Finally, as outcome after childhood stroke is generally better than after adult stroke in the absence of treatment, the risk–benefit balance may differ based on age.

The Thrombolysis In Pediatric Stroke (TIPS) trial was a multicenter prospective safety and dose-finding study of IV tPA in childhood stroke which unfortunately closed prematurely due to lack of participant accrual [171]. Nonetheless, TIPS resulted in important infrastructure development in participating sites, including protocols that allow for rapid, systematic diagnosis

and treatment of pediatric stroke [172]. TIPS also led to the TIPSTER study, which retrospectively analyzed the safety of IV thrombolysis for acute stroke in 26 children at prior TIPS sites [173]. The analysis yielded an estimated 2.1% rate of symptomatic intracranial hemorrhage after thrombolysis in children, suggesting IV thrombolysis for acute stroke is at least as safe in children when compared to adults [174].

Currently, IV thrombolytic agents are administered in 5–7% of cases of childhood stroke in the USA [175, 176]. A recent serial cross-sectional study of admissions for childhood AIS identified using the Kids' Inpatient Database showed that IV tPA utilization in the USA significantly increased from 2.5 to 6.5% between 2005 and 2019 [176]. An analysis of the National Inpatient Sample similarly showed an increase in IV thrombolysis use from 1.6% between 2010 and 2015 to 5.5% between 2016 and 2019 [175]. Despite the increased use of thrombolytics for acute childhood stroke, the true benefit conferred by tPA in children, the ideal weight-based dosing, and the optimal time window for administration of IV tPA in children all remain unknown.

Mechanical Thrombectomy

Mounting observational data suggest that MT for acute stroke has a good safety profile in children. In the SaveChildS study, a recent retrospective cohort study of 73 children who underwent MT for acute AIS, only 1 patient developed symptomatic intracranial hemorrhage [177]. Given the concern about high rates of large vessel arteriopathies in childhood stroke, with theoretical increased risk of dissection, vasospasm, or vessel rupture in such cases, the authors noted that none of the 14 children with arteriopathies in SaveChildS experienced these complications [177]. A similar excellent safety profile was reported in an analysis of the National Inpatient Sample, which reported that in 190 children treated with MT, no patient suffered contrast-induced kidney injury nor periprocedural iatrogenic ischemia or hemorrhage [175].

While a growing body of evidence supports the feasibility and safety of MT in children, the efficacy remains less clear. For example, in the Save ChildS study, there was no control group to account for potential natural history of improvement. Nonetheless, children in the study who underwent MT had a reduction in median pediatric National Institutes of Health Stroke Scale Score (pedNIHSS) from 14 at admission to 4 at discharge. At 6 months from stroke, patients in this study had favorable neurologic outcomes, with 87% achieving a modified Rankin scale score (mRS) of 0–2. The results from the SaveChildS study are concordant with a meta-analysis of 113 children who were treated with MT for acute stroke [178]. In that analysis, over 90% of patients had favorable neurologic outcomes, though the role of publication bias must be considered.

More recently, a retrospective, population-based cohort study of childhood ischemic stroke in Australia demonstrated that children with large vessel occlusions who were treated with MT ($n=13$, with or without IV-tPA) had better functional outcomes compared with children with large vessel occlusions who were managed conservatively ($n=26$) [179]. The authors point out, importantly, that the absence of randomization or standardized MT selection criteria likely led to selection bias, and children who were treated with MT were older than those children managed conservatively, which may have driven, at least in part, the differences in outcomes.

In another recent analysis using the National Inpatient Sample by Dicpinigaitis and colleagues, 55.3% of children with acute ischemic stroke treated with MT had favorable outcomes at discharge [175], though the authors defined favorable as discharge to home or acute rehabilitation, which likely encompasses a broad range of functional outcomes. After propensity adjustment to address confounding by indication, patients treated with MT had higher rates of favorable functional outcomes compared to medically managed patients, though this did not reach statistical significance. Patients with greater dysfunction (NIHSS > 11) received a larger benefit from thrombectomy compared with controls, though this also did not reach statistical significance [175].

MT use is increasing in the USA, with recent data demonstrating that 3–4% of children admitted with acute AIS are treated with MT [175, 176]. Cross-sectional data derived from the Kids' Inpatient Database showed that MT was used in 1.2% of children admitted for AIS in 2009 and in 3.0% of similar children in 2019 [176]. A recent analysis of the National Inpatient Sample likewise showed an increase in MT utilization from 1.7% prior to publication of the landmark adult thrombectomy trials (2010–2015) to 4.0% in the post-thrombectomy era (2016–2019). In an Australian study of childhood ischemic stroke conducted between 2010 and 2019, a third of children with large vessel occlusion were treated with MT, with or without IV-tPA.

The boundaries of MT use in children have not yet been established. The time window to safely perform thrombectomy is generally extrapolated from adult data, but differences in collateral vasculature or other pediatric-specific factors may modify the time window in children. In a secondary analysis of 20 children in the SaveChildS study, MT between 7.8 and 16.2 h from symptom onset in the setting of a mismatch between clinical deficit and radiographic infarction was safe and associated with neurologic improvement, with reduction of pedNIHSS from 12 on admission to 2 at day 7 [180]. Several case reports even demonstrate good outcomes after MT when performed after 24 h from stroke onset [181–184]. Nonetheless, selection criteria for late-window MT are not yet well-established, and extrapolation from adult parameters may not be appropriate given concerns about differing penumbral thresholds in children compared with adults [185].

Similarly, the minimum age for MT eligibility in pediatric stroke is controversial [186, 187]. As there are no stent retrieval or aspiration devices designed specifically for children, questions frequently arise regarding the compatibility of devices designed for adults with the smaller pediatric cervicocerebral vasculature. While the head and neck vessels approximate adult size by the age of 5 years [188], access through the femoral arterial diameter may be more limiting [189]. Nonetheless, MT has been reported with good outcome in many children below 5 years of age [190], though very preliminary data suggest younger children may receive less benefit from thrombectomy compared with their older counterparts [177]. Other technical modifications related to tolerance of blood loss and safety of contrast and radiation exposure in young children should be considered [189]. Notably, thrombectomy in neonates is generally discouraged by pediatric stroke specialists, particularly given the inability in most cases to establish a clear time of stroke ictus and likelihood of higher risk of MT due to smaller vasculature [187].

As there are no randomized controlled data that allow for clear recommendations about when to proceed with MT in children, potential risks and benefits must be carefully weighed based on each individual patient's degree of disability, age, size, stroke etiology, comorbidities, and neuroimaging characteristics.

Acute Therapies in Special Populations

Moyamoya Disease Moyamoya disease is a progressive steno-occlusive arteriopathy of the intracranial vasculature beginning with the distal internal carotid arteries with compensatory collateral vessel formation. It can occur in isolation or with an associated condition including sickle cell disease, neurofibromatosis, and Down syndrome [42]. Moyamoya accounts for about 8% of childhood AIS and is associated with high rates of stroke recurrence [37]. The perioperative period is a particularly high-risk epoch for moyamoya-related stroke, which remains a challenge in moyamoya care due to the need for angiography and surgical management [191, 192]. While long-term stroke prophylaxis may include antiplatelet therapies and/or surgical revascularization, acute stroke is typically managed with augmentation of cerebral perfusion pressure with fluids and flat head of bed. Consideration can be given to vasopressors in the right clinical context, such as if the patient is hypotensive or there are other indicators of cerebral hypoperfusion [193]. Pain and agitation control is of paramount importance, as hyperventilation can lead to cerebral vasoconstriction, thereby exacerbating cerebral hypoperfusion [191]. Maintenance of normocarbia and normoglycemia and minimization of metabolic demand through normothermia and prompt seizure control are also important neuroprotective measures. The role of antiplatelet therapy and red blood cell transfusion in acute stroke in children with moyamoya needs further investigation. IV thrombolysis is contraindicated due to high risk of intracranial hemorrhage due to fragile collateral vasculature. Similarly, MT is typically not performed in children with moyamoya given increased risks of introducing a catheter into diseased vessels and low likelihood of benefit.

Sickle Cell Disease SCD is a major risk factor for childhood ischemic stroke [194]. The highest risk time for SCD-associated stroke is in the first decade of life [60]. By 20 years of age, 11% of individuals with SCD will experience a clinically evident stroke, and nearly a quarter of individuals with SCD have a stroke by age 45 years in the absence of preventative measures [60]. Recurrent stroke is also common in patients with SCD [195].

Any person with SCD presenting with acute neurologic deficits should be treated with an emergent blood transfusion, ideally an exchange transfusion when possible [196]. The role of IV thrombolysis and MT in children with SCD is less well-studied. In an analysis of the AHA/ASA Get With The Guidelines Stroke Registry, in adults with acute stroke who received thrombolytic therapy, rates of symptomatic intracranial hemorrhage were not higher in patients with SCD, and coexistent SCD did not impact the discharge outcome [197], suggesting that IV-tPA should not be withheld from adults with SCD. In adults with SCD and acute stroke, thrombolysis and thrombectomy should be considered, as they are for patients without SCD, followed by red blood cell exchange transfusion [198]. However, most pediatric stroke protocols exclude children with SCD from consideration for IV-tPA due to perceived high risk of intracranial hemorrhage related to high rates of moyamoya syndrome and intracranial hemorrhage in this population [199], particularly in the absence of proven benefit in children. The American Society of Hematology recommends against IV tPA for children with SCD [196]. There are no data on the risks or benefits of MT in children with SCD. It is the view of the authors that eligibility for MT should be considered using standard guidelines in children with SCD and large vessel occlusion, though special consideration must be made due to high rates of cerebral arteriopathies and moyamoya syndrome in children with SCD.

Systems of Care for Delivery of Acute Stroke Interventions

With increasing utilization of both IV thrombolysis and MT [175, 176], implementation of acute pediatric stroke protocols is critical to be able to deliver these interventions rapidly, safely, and effectively. Prior to the TIPS trial, which was initially funded in 2010, centers interested in pediatric stroke lacked systematic readiness to rapidly diagnose and

treat childhood stroke [172]. In defining staffing, neuroimaging, and ordering criteria necessary to administer IV tPA, TIPS set standards that led to the emergence of the primary pediatric stroke center [172]. More recently, a survey of pediatric stroke specialists showed that at least 41 pediatric centers in the USA and Canada have established acute stroke protocols [200]. Another survey demonstrated that most pediatric hospitals surveyed have stroke protocols to be able to deliver IV tPA and thrombectomy, but respondents did not agree on precisely what the protocols should contain and how they should be actualized [201]. That survey study also highlighted the need for development of standardized pre-hospital screening tools for pediatric stroke.

Multiple acute pediatric stroke protocols and accompanying data on time to stroke diagnosis have been published [146–148, 202–204], with average time from presentation to neuroimaging/diagnosis ranging from 1.3 to 10.5 h. This starkly contrasts to adult data, which boasts median door-to-needle times of around an hour for the past decade [205, 206]. An analysis from a US hospital showed that the major source of pediatric stroke diagnostic delays was late presentation to the emergency department, suggesting that future interventions aimed improving community recognition of stroke symptoms could help alleviate these delays [203]. Though ongoing improvements in time to pediatric stroke diagnosis are needed, a recent Australian study of pediatric large vessel occlusions showed that the majority presented early enough to be eligible for MT (69% presented within 6 hours of symptom onset and 90% within 24 hours) [179].

Neuroprotection

Most children with stroke will not be candidates for IV thrombolysis or thrombectomy; however, prompt stroke diagnosis remains critical so neuroprotective measures can be implemented early. Neuroprotective measures aim to salvage penumbral tissue through optimization of oxygen and glucose delivery to at-risk tissue and minimization of metabolic demand through prompt fever and seizure control. Though there are limited data to support specific neuroprotective measures in children, strategies are generally adopted from the adult stroke literature [43].

In a retrospective multivariate analysis of modifiable physiologic parameters in 98 children with acute AIS, hyperglycemia was associated with worse neurologic outcomes, but fever and hypertension were not [121]. Based on this study as well as extrapolation from adult data, a recent scientific statement from the AHA/American Stroke Association (ASA) recommends treatment of hyperglycemia to achieve blood glucose < 180 mg/dL as well as avoidance of hypoglycemia [43].

Another retrospective study of 53 children with AIS showed that hypertension in the first 72 hours after stroke ictus was associated with higher in-hospital mortality, but not with neurologic disability [207]. The association between hypertension and childhood ischemic stroke and in-hospital mortality was supported by an analysis that identified children with ischemic stroke and hypertension using ICD codes in a large national database [208]. Importantly, hypertension may not be directly harmful but instead may be a compensatory mechanism to support cerebral perfusion in children with more severe presentations including large vessel occlusions and cerebral arteriopathies. Optimal blood pressure management in children after stroke remains an important knowledge gap [43].

Stroke Prevention

Stroke Prevention in Sickle Cell Disease

Primary Prevention Development of evidence-based primary prevention measures in childhood SCD has been incredibly successful. Without implementation of preventative measures, 11% of individuals with SCD will experience an overt stroke by 20 years of age [60]. Stroke risk in SCD can be stratified using TCD, a non-invasive bedside test that measures cerebral blood flow velocities [209]. In the 1998 Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial, treatment of high-risk children (as stratified by TCD) with chronic transfusion therapy resulted in a 92% reduction in stroke risk compared with standard care [210]. Annual TCD screening is therefore recommended for screening all children with HbSS disease or HbSβ^0 thalassemia between the ages of 2 and 16 years [196, 211]. For children who meet TCD criteria for high stroke risk, monthly blood transfusions are recommended to maintain HbS level < 30% and hemoglobin > 9.0 g/dL. In environments where regular blood transfusion therapy and chelation therapy are not available or practical, hydroxyurea therapy can be considered as an alternative [196]. A retrospective trend analysis of the Nationwide Inpatient Sample and Kids' Inpatient Database showed that incidence rates of hospitalization for stroke in children with SCD decreased by 45% after publication of the STOP trial and hydroxyurea licensure in 1998, suggesting that these measures had been effective in primary stroke prevention in SCD [212].

Chronic transfusion therapy is associated with serious long-term morbidity, including alloimmunization, transfusion reaction, iron overload, and infection risk. High associated costs and burden to families and patients also limit adherence. Therefore, studies subsequent to STOP have examined when and how transfusions can be safely discontinued. In 2005, the STOP2 trial evaluated children with SCD with high stroke risk based on TCD screening but without severe

cerebral arteriopathy who had normalized cerebral blood flow velocities after at least 30 months on transfusion therapy [213]. Participants were randomized to either continue or discontinue transfusion therapy. Discontinuation of transfusions resulted in high rates of reversion to abnormal TCD readings (14 of 41 participants who had transfusion discontinued) and overt stroke (2 of 41 participants, mean 4.5 months after last transfusion) [213]. Subsequently, the 2015 TCD With Transfusions Changing to Hydroxyurea (TWiTCH) trial was a randomized, open label, non-inferiority trial that enrolled children 2–16 years old with abnormal TCD results but without severe cerebral arteriopathy who had received transfusion therapy for at least a year [214]. Participants were randomized to either continue transfusion therapy or transition to hydroxyurea. There were no differences in 24-month TCD velocities between the groups, suggesting that in children with SCD without cerebral arteriopathy, hydroxyurea may be a reasonable substitute for chronic transfusions after at least 1 year of transfusions [214]. Notably, participants in the study were on transfusion therapy for an average of 4 years, so the optimal duration of transfusion therapy prior to transition to hydroxyurea remains unknown.

Silent cerebral infarctions in children with SCD have been associated with cognitive impairment, recurrent silent infarction, and progression to overt stroke [62]. In the silent cerebral infarct (SIT) trial, children with silent cerebral infarcts who were treated with transfusion therapy, as opposed to standard observation, had lower rates of subsequent overt stroke or recurrent silent infarction [215]. Therefore, the American Society of Hematology recommends obtaining a screening brain MRI at least once in early school age children with HbSS or HbSβ^0 thalassemia once they are able to tolerate the imaging without sedation [196]. If silent cerebral infarcts are identified, secondary prevention measures, such as chronic transfusion therapy or hematopoietic stem cell transplantation, as well as neuropsychological evaluation, can be considered.

Despite effective and safe screening and prevention methods, there are substantial barriers to the widespread use of these measures. According to Medicaid claims data from 2010 to 2011, less than 25% of children in Maryland received the recommended annual TCD screening [216]. A recent national survey of SCD clinicians found only a 46% adherence to TCD screening guidelines, and low adherence was associated with practice barriers including lack of support staff or time [217]. Another study found that 22% of caregivers of children with SCD had no knowledge of TCD screening and that 42% were unaware that screenings were recommended annually [218]. Additionally, the lack of sufficient specialty SCD clinics impedes access to SCD-specific care for many individuals [219]. Importantly, as SCD affects largely Black Americans, racial disparities may play a role in poor access to care, with prior studies suggesting that differences in insurance coverage and systemic racism, among other factors, may play a role [220, 221].

Finally, there are emerging data that initiation of hydroxyurea in asymptomatic SCD patients may have a role in stroke prevention, though further investigation is needed. The BABY HUG trial demonstrated that early initiation of hydroxyurea mitigated the rise of cerebral blood flow velocities on TCD [222]. In the SCATE study, fewer children on hydroxyurea, compared with standard care, had conversion from conditional to abnormal TCD velocities [223], though the study was concluded prematurely due to slow patient accrual.

Secondary Prevention After incident stroke, two-thirds of individuals with SCD will have recurrent stroke [195]. Chronic transfusions are standard of care for secondary stroke prevention, but long-term transfusion therapy confers significant risks. In one study of 10 patients with SCD whose transfusions were halted an average of 9.5 years after stroke, 50% of participants had an ischemic event within 12 months of transfusion discontinuation [224]. In 2012, the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial investigated hydroxyurea plus phlebotomy as an alternative to transfusions with chelation therapy for recurrent stroke prevention in participants with SCD, prior clinical stroke, and iron overload [225]. SWiTCH was unfortunately terminated early due to statistical futility for the composite endpoint, as there was equivalent liver iron content in the two groups. Though the stroke endpoint was within the non-inferiority margin, there were no strokes in the 66 participants in the transfusion group, but 10% of the 67 participants in the hydroxyurea group experienced stroke [225]. Transfusions with chelation therefore remain standard of care for prevention of stroke recurrence in children with SCD.

Optimization of other stroke risk factors is also an important component of stroke prevention in children with SCD. Of note, the role of antiplatelet therapy in stroke recurrence prevention in patients with SCD remains unclear, and other stroke risk factors as well as the presence of arteriopathy must be considered when making decisions about antithrombotic therapy initiation.

Antithrombotic Therapies

The decision to start antithrombotic therapy, choice of agent, timing of initiation, and duration of therapy are highly dependent on the cause of the stroke and patient-specific factors such as age and comorbid conditions. After perinatal stroke, antithrombotic therapy is rarely indicated, as the stroke risk factors that converge to cause the vast majority of perinatal strokes are generally confined to the perinatal

period. In contrast, antithrombotic therapy is a mainstay of secondary prevention after childhood stroke [157].

The type of antithrombotic therapy chosen after childhood stroke varies both by stroke etiology and geographic region [226]. When the stroke etiology is determined to be cardioembolic or due to a thrombophilia, anticoagulation is typically recommended [43]. In the case of cervical arterial dissection, there are no pediatric data to guide the choice of antithrombotic agent, and there remains equipoise in adults as well [227, 228]. The presence of an intraluminal thrombus may prompt the clinician to opt for anticoagulation, while a large associated stroke may make antiplatelet therapy more appropriate. Antiplatelet agents are typically recommended for cryptogenic stroke and moyamoya. However, in the absence of strong evidence supporting a specific antithrombotic agent choice for most causes of pediatric stroke, optimal stroke prevention strategies remain unknown.

In the setting of acute stroke, the general approach is to initiate antithrombotic therapy only after the risk of recurrent stroke exceeds the risk of hemorrhagic transformation of the infarcted tissue. When anticoagulation is deemed necessary, initiation of a heparin infusion with neuroimaging once therapeutic to evaluate for hemorrhagic transfusion before transition to a longer-acting anticoagulant is reasonable. The choice of anticoagulant, which includes low molecular weight heparin, warfarin, or direct oral anticoagulants, should be based on stroke etiology and patient-specific factors. Antiplatelet agents, including aspirin and clopidogrel, can generally be initiated earlier than anticoagulation after incident stroke.

Duration of antithrombotic therapy depends on the stroke cause. In cryptogenic childhood stroke, expert consensus is to continue antithrombotic therapy for 2 years, as most stroke recurrences occur within this time frame [43].

Immunomodulatory Therapies

Steroids and other immunomodulatory therapies may play a role in stroke prevention in children with inflammatory, infectious/post-infectious, and genetic arteriopathies [229]. The most accepted use of these therapies is in primary central nervous system (CNS) angiitis, though specific regimens vary between institutions [230, 231]. In children with FCA, some evidence suggests that corticosteroids may improve outcomes when added to antithrombotic therapy [232]. This is an area of interest given emerging evidence of inflammation in the pathogenesis of FCA, though the pathophysiology of FCA is an area of ongoing investigation [165, 233]. Several studies are currently ongoing to evaluate the role of steroids in the treatment of FCA.

Anti-TNF therapy is the mainstay of therapy in children with DADA2, which is a genetic small and medium size vasculitis that results in early lacunar strokes in addition to manifestations of systemic vasculitis [166]. Available data suggest that TNF inhibition may be effective in reducing the risk of stroke in children with DADA2 [166, 167]. Importantly, patients with DADA2 are at risk for hemorrhagic stroke, and thus, antithrombotic therapy is generally not recommended.

PFO Closure

The pathophysiologic role of PFO in childhood stroke remains undetermined, but multiple recent adult studies showed that PFO closure reduces recurrent stroke risk in a subset of young adults with cryptogenic strokes when compared with medical management alone [54–57]. Based on these studies, the American Academy of Neurology 2020 practice advisory suggests that PFO closure can be considered for patients under 60 years old with a PFO and embolic-appearing infarct in the absence of another stroke mechanism [234]. In a recent prospective observational single-center study, children with cryptogenic stroke had a higher frequency of PFO compared with children with stroke of known etiology and with children who had echocardiograms for benign cardiac concerns, which hints at a potential causative relationship between PFO and childhood stroke [58]. Nonetheless, which children would benefit from PFO closure after cryptogenic stroke remains unknown, and further investigation is necessary [235].

Surgical Revascularization in Moyamoya Arteriopathy

Children with moyamoya are at high risk of occurrent and recurrent stroke [28, 37, 137]. The mainstay of long-term stroke prevention in moyamoya is revascularization surgery, which can be done via a direct anastomotic bypass or via an indirect non-anastomotic approach, the latter of which is more commonly performed in children. In a retrospective analysis of 174 children with moyamoya enrolled in the IPSS, children who had revascularization surgery were less likely to experience stroke recurrence [37]. Observational single-center data also suggest that revascularization surgery confers protection from ischemic stroke in children with moyamoya [236, 237].

Though revascularization surgery decreases the long-term risk of stroke, there is a risk of perioperative complications, especially ischemic stroke and TIA. Reported incidence of perioperative ischemic events for children with moyamoya undergoing revascularization surgery ranges from 4 to 20% [192, 237–240]. Therefore, selecting patients in whom these risks are outweighed by the long-term benefits of surgery is critical. Some data suggest that radiographic progression and the presence of biomarkers such as the ivy sign may help stratify risk of clinical disease progression and identify patients likely to benefit from surgery [241,

242]. The ivy sign is characterized by leptomeningeal fluid-attenuated inversion recovery (FLAIR) hyperintensity or contrast enhancement on T1-weighted images that looks like ivy growing along the sulci and subarachnoid space [243]. It represents engorgement of the pial vasculature and/or slow flow in leptomeningeal collateral vessels and is thought to indicate cerebral hypoperfusion and elevated stroke risk. Common comorbid conditions may also modify stroke risk, with recent data demonstrating that children with neurofibromatosis type 1 generally have milder disease, while associated Down syndrome and SCD portend a more aggressive course [42, 244].

Increasingly, patients are being diagnosed with moyamoya before they experience stroke or TIA. This occurs typically when patients with commonly associated conditions, such as neurofibromatosis and SCD, are screened with neuroimaging, or when patients present with non-ischemic symptoms such as headache. In two distinct single-center retrospective studies, 12–14% of asymptomatic children with moyamoya developed clinical ischemic stroke over an average follow-up time of 5–6 years, though more children (36–54%) developed radiographic progression [41, 241]. Therefore, the role and most optimal timing of surgery in children with asymptomatic moyamoya remain unclear.

Once appropriate patients are selected for surgery, identification of high-risk patients and meticulous perioperative management, which includes rigorous blood pressure management and maintenance of normocarbia, is critical to minimizing risk of perioperative infarction [191, 192]. When revascularization is performed at high-volume moyamoya centers, length of stay and costs are decreased without more complications [245].

Rehabilitation and Management of Stroke Sequelae

Rehabilitation is a critical aspect of stroke treatment that targets the physical, occupational, language, cognitive, and behavioral sequelae of stroke and aims to optimize function and independence [246, 247]. Unlike after adult stroke, strategies for pediatric rehabilitation differ by age and depend on the child's developmental level and degree of brain maturation. Concepts such as neuroplasticity and emerging deficits must be considered when evaluating optimal timing, dose, and intensity of therapies [248].

Constraint-induced movement therapy (CIMT) is a therapeutic approach in which the less impaired limb is restrained, promoting functional use of the more-impaired side. Several small studies in children with hemiparesis demonstrate improvements in spontaneous use, efficiency, and dexterity of the more impaired arm after CIMT [249, 250]. Bimanual therapy has also been evaluated with promising results and may be able to achieve benefits comparable to CIMT [251, 252]. Optimal timing of CIMT and bimanual therapy initiation after perinatal stroke are areas of active investigation.

Non-invasive brain stimulation is another area of active investigation [253]. Several small, randomized trials of repetitive transcranial magnetic stimulation (rTMS) in children with chronic stroke have demonstrated benefits of this technique compared with sham controls, particularly when paired with other therapeutic techniques [254–257]. In the largest pediatric rTMS trial to date, the combination of rTMS and CIMT together with intensive therapy provided the greatest benefit compared with intensive therapy paired with either rTMS or CIMT [256]. A randomized controlled trial evaluating the effect of the addition of transcranial direct current stimulation (tDCS) to intensive therapy on motor function in children with perinatal stroke-related hemiparesis failed to demonstrate a benefit in objective motor function, but subjective gains were evident 1 week after intervention [258]. Before non-invasive brain stimulation techniques can be used clinically, optimal modalities, stimulation parameters, and timing of therapy, as well as concurrent therapies and patient selection criteria, need to be established.

The best evidence supporting these novel therapies in children after stroke is primarily aimed at improving motor outcomes. Nonetheless, monitoring for language, cognitive, and behavioral dysfunction after stroke is critical. When deficits are identified, implementation of therapies, educational resources, and school accommodations can help optimize school function. For example, children with a history of stroke are at risk for attention-deficit/hyperactivity disorder (ADHD) [259]. ADHD can be medically managed when identified, thereby limiting the impact on a child's daily life. Emerging evidence is beginning to elucidate a potential role for non-invasive brain stimulation as an adjunct therapy for post-stroke aphasia in adults, though the use of brain stimulation to treat aphasia after childhood stroke is limited to case reports [260, 261].

Post-stroke care should also entail monitoring for fatigue, depression, and anxiety, all of which may interfere with participation in therapies as well as quality of life. Though data on post-stroke fatigue after childhood stroke are limited, fatigue is common in young adults after stroke and is associated with worse functional outcomes [262]. Post-traumatic stress disorder and depression are also common in parents of children who suffer stroke [263]; assessing the family unit for mental health consequences of stroke could lead to improved long-term care after childhood stroke.

Epilepsy is common after perinatal and childhood stroke, and development of epilepsy in the first year after stroke is associated with worse neurologic outcomes [127, 128, 264]. Development of epilepsy is also associated with poorer quality of life after childhood stroke [128]. Optimal epilepsy management is critical, as seizure freedom is

associated with higher likelihood of functional independence after childhood stroke [128].

Conclusions and Future Directions

Diagnostic and therapeutic advances in pediatric stroke have led to improved care for infants and children with stroke, but important knowledge gaps persist. Further advances in neuroimaging techniques, such as VWI and arterial spin labeling MRI, may provide better diagnostic capabilities in the future. Therapeutically, feasibility and safety data for IV thrombolysis and MT for childhood stroke are mounting, but high-quality evidence for efficacy of these therapies is lacking. Optimal dosing and type of thrombolytic agents and selection criteria for IV thrombolysis and MT have yet to be defined. Great advancements have been made in stroke prevention in children with SCD, but the optimal transfusion-sparing regimen remains undefined. Other knowledge gaps in stroke prevention include the role of immunomodulatory therapies for FCA, ideal long-term antithrombotic strategies, and the role of PFO closure in pediatric stroke. Finally, further evaluation of rehabilitation strategies including non-invasive brain stimulation and constraint-based therapies may allow for improved outcomes after pediatric stroke.

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