Received: 11 December 2018 | Revised: 17 January 2019 | Accepted: 30 January 2019

DOI: 10.1002/pbc.27665

REVIEW

WILEY Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology

Aspirin in childhood acute ischemic stroke: The evidence for treatment and efficacy testing

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Abstract

Aspirin is the most commonly prescribed antiplatelet agent worldwide, but evidence supporting its use varies by age and disease process. Despite its frequent use in childhood acute ischemic stroke prevention and management, major knowledge gaps exist about optimal pediatric aspirin use, particularly in this setting, where high-quality clinical trials are urgently needed. This review focuses upon the evidence for aspirin use in childhood acute ischemic stroke, includes a summary of aspirin pharmacology to highlight misconceptions and common clinical situations which may limit its efficacy, and discusses the techniques and potential role of laboratory monitoring of aspirin efficacy in children.

KEYWORDS

hemostasis and thrombosis, non-malignant hematology, pharmacology

1 | INTRODUCTION

Childhood stroke, although uncommon, often leads to prolonged or lifelong morbidity and early mortality. Aspirin (acetylsalicylic acid, ASA), widely prescribed for stroke thromboprophylaxis in adults,[1] accounts for nearly all prescribed antiplatelet therapy in children; however, evidence for using ASA in pediatric stroke cohorts and the applicability of adult data to pediatric situations is less clear.[2] Several publications have highlighted the incidence, risk factors, and significant impact of childhood stroke on patients, their families, and the healthcare system, yet strong evidence to guide management and prevention of childhood stroke in most cases is still lacking.[3–5] This review will focus upon the use of ASA for treatment and prevention of childhood acute ischemic stroke (AIS) by examining expert opinion-driven versus evidence-based practice guidelines and highlighting opportunities for future research.

2 | EPIDEMIOLOGY

A stroke, defined as an interruption of cerebral blood flow resulting in focal or global brain dysfunction, can be ischemic, hemorrhagic, or both. This review will focus on childhood AIS (age 29 days of life to 18 years) with brief comments on perinatal stroke, for which antithrombotic agents are rarely recommended.[6] The annual incidence of childhood AIS is estimated at 1.7 to 13 in 100 000 children in North America with in-hospital mortality around 3%.[7–10] AIS is more common than primary hemorrhagic stroke for all ages but accounts for 55% of all pediatric strokes compared with 80% to 85% in adults.[11] The risk profile for childhood AIS is also more varied than for adults.[12] For this reason, efforts have been made to standardize classification and diagnostic algorithms specific to childhood AIS using the Childhood Arterial Ischemic Stroke Standardized Classification and Diagnostic Evaluation (CASCADE) criteria.[13] In the registry-based, multicenter International Pediatric Stroke Study, 53% of childhood AIS patients had arteriopathy and 31% had a cardiac disorder.[14] Other risk factors included acute or chronic head and neck disorders, acute or chronic systemic conditions, prothrombotic states, or recent infections, with multiple risk factors often simultaneously present.[18] In a separate study, arteriopathy had a stroke recurrence hazard ratio of 5.0 (95% confidence interval, 1.8–14) compared with idiopathic stroke despite antithrombotic therapy.[15]

Strokes are relatively rare in children and adolescents and they can mimic more common disorders, so delays and misdiagnoses are common. Consequently, time-sensitive and potentially outcome-altering treatments in adults such as tissue plasminogen activator (tPA) or endovascular procedures remain experimental in pediatrics, partly because few children are recognized early enough for clinical trial eligibility.[16–19] A supportive care approach including ASA remains the standard for childhood AIS patients without sickle cell disease (SCD), though anticoagulation or alternative antiplatelet

Abbreviations: ADP, adenine diphosphate; AIS, acute ischemic stroke; ARU, aspirin-resistance units; ASA, acetylsalicylic acid (aspirin); CAD, coronary artery disease; CASCADE, Childhood Arterial Ischemic Stroke Standardized Classification and Diagnostic Evaluation; CCAD, cervicocephalic arterial dissection; CHD, congenital heart disease; COX1, cyclooxygenase 1; COX2, cyclooxygenase 2; DAPT, dual antiplatelet therapy; FCA, focal cerebral arteriopathy; NSAID, nonsteroidal anti-inflammatory drug; PFA, platelet function assay; PPI, proton pump inhibitor; RS, Reye syndrome; SCA, sickle cell anemia; SCD, sickle cell disease; TCD, transcranial Doppler; tPA, tissue plasminogen activator; TXA_2, thromboxane A_2; TXB_2, thromboxane B_2; VAD, ventricular assist devices

TABLE 1 Expert guidelines for aspirin use in pediatric AIS

	RCPCH (2017)[a]	ACCP (2012)[a]	AHA (2008)[a]
Perinatal	NR	Secondary prevention after additional AIS: ASA or LMWH/UFH (grade 2C)	NR
Childhood	Secondary prevention, acute management: 5 mg/kg/day ASA (max 300 mg) within 24 hours of AIS diagnosis if no contraindications. Hold for 24 hours after tPA Secondary prevention, chronic management: Reduce dose to 1 mg/kg/day (max 75 mg) after 14 days	Secondary prevention, acute management: ASA or LMWH initially until embolic sources and dissection ruled out (grade 1C) Secondary prevention, chronic management (no dissection or embolic source): ASA for two years (grade 2C)	Secondary prevention (no SCD or hypercoagulable/recurrent embolic state): ASA 3–5 mg/kg/day for 3–5 years (grade IIa, C), reduce to 1–3 mg/kg/day if side effects present (grade IIb, C)
Cardioembolic	Secondary prevention: Consider antiplatelet versus anticoagulation	Primary prevention, Fontan: ASA or therapeutic UFH, followed by warfarin (grade 1C) Primary prevention, VAD: Therapeutic UFH plus ASA or ASA/dipyridamole within 72 hours of VAD placement; UFH should transition to LMWH or warfarin when clinically stable (grade 2C)	Secondary prevention: No patent foramen ovale, low/unknown risk of AIS: ASA $\geq$ 12 months (grade IIa, C)
Nonmoyamoya cerebral vasculopathy	NR	Secondary prevention: ASA or UFH/LMWH for 3 months (grade 1C)	Secondary prevention: UFH/LMWH, warfarin, or ASA for 3–6 months (grade IIa, C)
Moyamoya vasculopathy	NR	Secondary prevention: ASA plus revascularization (grade 2C)	Secondary prevention: Consider ASA after revascularization or if asymptomatic without planned surgical intervention (grade IIb, C)
Cervicocephalic arterial dissection	NR	NR	Secondary prevention: LMWH or warfarin or ASA for 3–6 months (grade IIa, C)
Sickle cell disease	Secondary prevention: Consider ASA only if cerebrovascular disease justifies use	NR	NR

Note: Expert consensus recommendations from the evidence-based clinical practice guidelines (most recent publication year in parentheses).[4,17,38]
Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; AIS, acute ischemic stroke; ASA, aspirin; LMWH, low-molecular-weight heparin; NR, no recommendation; RCPCH, Royal College of Paediatrics and Child Health; SCD, sickle cell disease; tPA, tissue plasminogen activator; UFH, unfractionated heparin; VAD, ventricular assist device.
[a]Grades of recommendations according to respective scoring system (Arabic or Roman numerals) are listed as available.

therapy is used for secondary thromboprophylaxis in certain situations.[3,11]

3 | ASPIRIN INDICATIONS FOR ADULT AIS

Despite the widespread prescription of ASA, evidence supporting its use varies by age and indication. Doses between 50 and 325 mg appear to provide similar benefit for adults.[20] Data support reduced morbidity and mortality in adults using ASA for primary stroke prevention after acute coronary syndrome,[21] severe or symptomatic atherosclerotic peripheral arterial disease,[22] and nonvalvular atrial fibrillation (though ASA is inferior to anticoagulation for this indication).[23] Secondary prevention of major vascular events with ASA in adults has also been demonstrated, but the risk of recurrence, especially early, remains high.[20] There is a low risk of hemorrhagic stroke with ASA use in appropriately selected patients. Alternative antiplatelet therapies such as ticagrelor,[24] clopidogrel,[25] and antiplatelet combinations[26] have also been studied in adults with stroke. Clopidogrel or dual antiplatelet therapy (DAPT, classically clopidogrel and ASA) may offer slight benefits over ASA alone, but bleeding risks limit their use. A major limitation for these data is that most adult studies focus on all-cardiovascular mortality as the primary outcome, which is a less relevant outcome in children.

4 | ASPIRIN INDICATIONS FOR CHILDHOOD AIS

Multiple ASA guidelines using varying doses for treatment and secondary prevention of childhood AIS have been published (Table 1).[3,11,27] Recommendations are based heavily upon expert opinion and frequently extrapolate from adult data, leading to wide variations in ASA use worldwide.[28] The evidence for efficacy, optimal dosing, safety, and treatment duration for either anticoagulation or ASA in childhood AIS is appreciably less robust than for adults, particularly outside of cardioembolic or vascular dissection indications, due to a lack of large, prospective, randomized clinical trials.[3,29]

5 | ASPIRIN INDICATION BY DISEASE SUBGROUP

5.1 | Large-vessel arteriopathy

Cerebral arteriopathy is a major childhood AIS risk factor. Recommendations for ASA use in patients with cerebral arteriopathy vary by etiology but mostly address large-vessel arteriopathy. Three paradigmatic large-vessel arteriopathies are discussed here: cervicocerebral arterial dissection (CCAD), focal cerebral arteriopathy (FCA), and moyamoya. A separate discussion of SCD-related stroke follows.

Arterial dissection can be spontaneous, secondary to head and neck trauma, associated with an underlying connective tissue disorder, or resulting from mechanical compression (e.g., Bow Hunter syndrome). In the absence of strong data, either anticoagulation or ASA is recommended for primary or secondary stroke prevention in pediatric CCAD, though surgical or endovascular intervention may be indicated for posttraumatic CCAD or with recurrent AIS.[30] Based on single-center pediatric CCAD case series, ASA is safe with a low risk of recurrent ischemia,[30] although hemorrhagic conversion risk may be higher in intracranial CCAD.[31]

FCA is a steno-occlusive phenomenon, usually of the anterior circulation, that can be transient or progressive. Progressive FCA has an AIS recurrence rate of nearly 25% within the first year, though significant residual stenotic disease can be a recurrence risk factor as well.[32] Along with traditional ASA or, less commonly, anticoagulant therapy, empiric adjunct corticosteroid use is increasing, though this requires further study.[33,34] ASA for FCA is often prescribed for at least a year or until disease stabilization or resolution, and the risk of recurrence is quite low if it resolves.[35,36] For more global vasculopathy such as central nervous system autoimmune vasculitis, ASA and immunosuppression are commonly employed together based on limited data.[37]

Moyamoya is a progressive large-vessel cerebral arteriopathy, where chronic parenchymal ischemia results in the characteristic "puff of smoke" angiographic morphology from neovascular collateralization. For pediatrics, it often presents with ischemia during the first decade of life and accounts for 6% of childhood AIS in North America.[38–40] Moyamoya management includes ASA and/or surgical revascularization, as the latter is not available at all centers.[41] Rarity and heterogeneity of both presentation and management have limited the strength of pediatric moyamoya data. Most publications are surgically focused but report similar long-term stroke outcomes for neurosurgical and medical approaches, especially long term.[42,43] Revascularization carries a 4% to 6% risk of periprocedural stroke or reversible ischemia.[44] Therefore, postoperative ASA (often 81 mg daily) is initiated early, but optimal treatment duration is unknown.[43] In adults, hemorrhagic stroke risk is not increased with ASA use in moyamoya and may actually be lower compared with no antiplatelet therapy.[45] What remains uncertain is whether this risk/benefit balance holds true for children, as well as whether ASA use is protective from hemorrhagic presentation of moyamoya in adult years. If revascularization cannot be performed, lifelong ASA thromboprophylaxis is generally recommended.[46]

5.2 | Sickle cell cerebral arteriopathy

Stroke risk in SCD predominates in the subset of patients with hemoglobin SS and hemoglobin S-beta^0 thalassemia, classified together as sickle cell anemia (SCA). Risks include overt stroke, estimated at 11% incidence in children, and radiographically but not clinically detected silent stroke (39% incidence by age 18 years).[47] Both large- and small-vessel arteriopathy occur. Similar to other arteriopathies, AIS is the more common stroke presentation in children, especially in those with moyamoya, but unlike other populations, ASA is rarely used due to hemorrhagic stroke concerns that increase with age.[48,49] Strong evidence guides SCA stroke prevention, including early hydroxyurea initiation, screening by transcranial Doppler (TCD) examinations, and chronic red cell transfusions (or possibly hematopoietic stem cell transplantation) for those at high risk for primary or secondary stroke.[50,51] One small pediatric SCA series reported a stroke recurrence risk of 0.58 per 100 patient years when receiving ASA in conjunction with chronic transfusion, with one hemorrhagic stroke occurring two years after the initial AIS.[52]

5.3 | Cardioembolic

About one third of children with AIS have a cardiac disorder, 59% of which are congenital.[53] Thromboembolic risk reduction strategies generally target extra- or intracardiac shunts and baffles, foreign surfaces, and flow alterations that increase thrombosis risk. Congenital and acquired cardiac disease thromboprophylaxis strategies have been more rigorously evaluated than in most other pediatric AIS etiologies, with preventive approaches differing based upon the perceived and historical risk of thromboembolism.[54–56] Complex surgical correction of single-ventricle physiology with a Fontan procedure is associated with thrombosis and stroke rates up to 19% despite warfarin or ASA thromboprophylaxis.[57] In an international randomized trial of 111 patients comparing post-Fontan ASA (5 mg/kg/day) to warfarin (target international normalized ratio goal 2.0–3.0) over two years, thrombosis occurred in 14% of the ASA group versus 24% in the warfarin group ($P = 0.45$) with no thromboembolic recurrences or strokes.[58] In contrast, a bidirectional Glenn procedure has a relatively low risk of thromboembolic sequelae (less than 3%) and extended thromboprophylaxis is not generally prescribed.[3,59]

Expert panels strongly advise empiric antiplatelet therapy (ASA or DAPT) in conjunction with anticoagulation after implantation of ventricular assist devices (VAD).[60] Stroke risk is substantial, regardless of the device used, though device-specific pharmacologic recommendations may differ. In a study of 28 children with left-sided or biventricular assist devices or total artificial hearts, stroke incidence was 25% despite therapeutic monitoring and dose-adjusted ASA, along with anticoagulation and dipyramidole without clopidogrel.[61] However, aggressive antiplatelet therapy appears to be beneficial. One pediatric study using the Berlin Heart EXCOR VAD found that triple antiplatelet therapy (ASA, dipyramidole, and clopidogrel) using high, weight-based dosing targets reduced stroke incidence by 84% compared with DAPT (ASA and dipyramidole), titrated based on

thromboelastography (TEG) with platelet mapping.[62] The triple therapy cohort experienced less significant bleeding as well.

5.4 | Perinatal stroke

Perinatal stroke (occurring from 20 weeks gestation up to 28 days postnatally) is a different entity than in older children. It is much more common, with an incidence of 1 in 1600 to 3000 live births, but recurrence is much rarer because typical risk factors, such as the stress of the birth process, are limited to the perinatal period.[63] Although secondary thromboprophylaxis is generally not indicated for perinatal stroke, a few etiologies (e.g., CCAD or CHD) bridge perinatal and childhood AIS and merit pharmacologic management as in older children.[64] Recurrent AIS after perinatal AIS requires a thorough evaluation of etiology and may be an indication for ASA or anticoagulation.

5.5 | Treatment for AIS recurrence

AIS recurrence risk is high, up to 16% in one prospective study.[15] This is especially true in those with CHD and arteriopathy, where both early and late recurrences are common even with secondary thromboprophylaxis.[65–67] One case–control study in children with CHD found a 27% risk of stroke recurrence after 10 years.[65] A recent retrospective study of childhood arteriopathic stroke found that initial CASCADE classification was correlated with recurrent stroke risk and arteriopathic progression.[13,67] For recurrent childhood AIS on ASA, recommendations are either to change antiplatelet agents (usually to clopidogrel) or to switch to anticoagulation.[3] DAPT (ASA and clopidogrel) is less favored due to an elevated hemorrhagic risk with minimal added benefit, similar to adults.[68,69]

5.6 | Aspirin pharmacology

ASA irreversibly acetylates cyclooxygenase 1 (COX1), likely in a dose-independent manner, and to a much lesser extent, cyclooxygenase 2 (COX2). Platelets constitutively produce COX1, while inducible COX2 is present on newly formed platelets, monocytes, and endothelial cells, generally in inflammatory settings.[70] Both COX pathways generate thromboxane A_2 (TXA_2), leading to platelet activation, but COX2 mechanisms are relatively ASA insensitive.[71] ASA, rather than its metabolites, is the active form for COX1 inhibition but it has a very short plasma half-life of 15 to 20 minutes.[72] This short half-life means that ASA's effect may be limited in situations associated with thrombocytosis or rapid platelet turnover and that dose modifications may provide minimal improvement.[70,73] Platelet function may also be paradoxically increased despite ASA use in the setting of acute or chronic inflammation, diabetes mellitus, or metabolic syndrome.[74–76]

After rapid absorption from the stomach and small intestine, ASA is quickly hydrolyzed to salicylic acid by gastrointestinal mucosal and plasma esterases. Absorption is delayed, and potentially suboptimal, for enteric-coated ASA[77] or for ASA that is delivered distal to the stomach (e.g., through a jejunal feeding tube). A broader overview of factors that may reduce ASA absorption and/or effectiveness can be found in Table 2. Salicylic acid is conjugated in the liver to salicyluric acid as well as glucuronidated to an ester and other metabolites whose transport in blood is heavily dependent on plasma proteins. Metabolites are mostly excreted via urine, largely as salicyluric acid. These metabolic processes are saturable, and overdoses can lead to prolonged exposure and potentially toxic effects including tinnitus, hyperventilation, metabolic acidosis, hyperpyrexia, or death.[72]

TABLE 2 Modifiable potential causes of suboptimal antiplatelet efficacy

Possible etiologies	Reason for diminished effect
Nonadherence	Side effects may limit use
Testing error	Specific timing/handling of samples needed for accuracy
Concurrent NSAID use	NSAIDs may antagonize antiplatelet effects, especially if taken before ASA
Concurrent antacid use	Increased gastric pH decreases absorption
Enteric coating	Absorption can be delayed and/or decreased
Postpyloric dosing	Absorption is decreased at increased pH
Acute/chronic inflammation	Often involves platelet hyperreactivity and TXA_2-independent mechanisms for platelet aggregation
Obesity/metabolic syndrome	Obesity increases platelet reactivity and decreases ASA responsiveness

Abbreviations: ASA, aspirin; NSAID, nonsteroidal anti-inflammatory drug; TXA_2, thromboxane A_2.

6 | ASPIRIN SIDE EFFECTS

Bleeding is the most common side effect of ASA. Gastrointestinal bleeding is attributed to both decreased prostaglandin synthesis in the gastric mucosa resulting in gastritis and an antiplatelet effect from irreversible COX1 inhibition. Pediatric data describing overall bleeding risks with ASA are limited, but the reported incidence ranges from 2% to 33%, with the highest risks associated with central venous catheter or chest tube sites after cardiac surgery.[78,79] Pediatric estimates of ASA-associated gastrointestinal bleeding are even more elusive, because most large studies address bleeding in side-effect reporting rather than as a primary outcome.[80] A large case crossover study in French children, ages 2 months to 16 years, who had had at least 1 dose of ASA or a nonsteroidal inflammatory drug (NSAID), calculated an adjusted odds ratio of drug exposure in upper gastrointestinal bleeding of 7.3 for ASA and 10 for ibuprofen.[81] A retrospective report of 58 children with Sturge-Weber syndrome who were treated with low-dose ASA (3–5 mg/kg/day) noted that six had increased bruising or epistaxis, one had an allergic rash, one had hematemesis, and one developed a subdural hematoma following minor head trauma.[82]

Concurrent use of anticoagulants or other antiplatelet agents such as clopidogrel or dipyramidole confounds the attributable bleeding risk of ASA, but the overall risk is higher. The risk of major gastrointestinal bleeding can be attenuated with proton pump inhibitor (PPI) therapy,[83] though laboratory-based assays also suggest PPIs may

decrease ASA effectiveness, possibly by altering absorption, as was shown in adults with coronary artery disease (CAD).[84] Concurrent NSAID use may competitively interfere with ASA and decrease platelet function inhibition.[85] Celecoxib, a selective COX2 inhibitor, does not appear to have the same competitive interaction.[86]

Reye syndrome (RS), a disturbance of mitochondrial metabolism causing significant and potentially fatal hepatic fatty degeneration and encephalopathy, has been associated with ASA use during an antecedent influenza-like illness or varicella in children. Its incidence has markedly decreased from the 1960s to 1970s, likely from a combination of diminished ASA use in children altogether and improved recognition of "Reye-like" metabolic disorders.[87] Although RS has not been reported during ASA use for AIS prophylaxis, proactive approaches such as encouraging influenza and varicella vaccination and minimizing the use and duration of high-dose ASA (>20 mg/kg) may decrease the risk for developing RS.[88] If symptoms should arise, ASA should be discontinued promptly.

7 | ASPIRIN TESTING

The morbidity and mortality of childhood AIS are undoubtedly compounded by recurrent stroke; therefore, it seems prudent to ensure that ASA treatment is "therapeutic."[15] However, this can be a challenge. Dosing and monitoring are more standardized for anticoagulated pediatric patients, but the utility of, and correct method for, monitoring ASA therapy is less clear. Test development and validation for laboratory-based measurements of ASA efficacy have been driven almost exclusively by adult cardiovascular disease outcomes.[89] Some ASA tests evaluate platelet function, such as ex vivo platelet aggregation specific to COX1 or global platelet aggregation inhibition, while others measure TXA_2 metabolites (Table 3).[90] The different methods for defining and measuring ASA efficacy may explain much of the variability in published estimates of "therapeutic" ASA efficacy and spark debate about the relevance of therapeutic ASA monitoring.

The gold-standard test for ASA effect is light transmission platelet aggregometry, which measures TXA_2-dependent platelet function using platelet-rich plasma and a platelet agonist. Whole blood aggregometry using electrical impedance has also been used, at least in part because test blood volume requirements are lower.[91] The platelet function analyzer (PFA-100, Siemens Medical Solutions USA, Inc., Washington DC) and VerifyNow ASA tests (Accriva Diagnostics, San Diego, CA) are whole blood, point-of-care tests of platelet inhibition by ASA. The PFA-100 uses dual collagen-epinephrine- and collagen-adenine diphosphate (ADP)-coated cartridges, as well as high shear force, and measures the time for activated platelets to occlude an aperture (closure time). Prolongation of the collagen-epinephrine closure time, but not collagen-ADP, would be consistent with ASA effect. VerifyNow ASA measures light impedance in aspirin resistance units (ARUs) in whole blood exposed to fibrinogen-coated polystyrene beads and arachidonic acid reagent.[90] VerifyNow ASA has been validated for predicting ASA responsiveness in adults with CAD and has more recently been tested in pediatric cardiac surgery patients.[92,93] Studies of VerifyNow ASA have shown sufficient platelet inhibition from ASA ranging between 79% and 94% after adult and pediatric stroke,[94,95] but this testing platform has also shown poor agreement with other platelet function tests, including in some of the same studies.[96]

Detection of TXA_2 metabolites is another ex vivo evaluation of ASA efficacy.[97] Serum thromboxane B_2 (TXB_2) is a stable metabolite that reflects ASA effect on COX1 inhibition, which is relatively platelet-specific. Urinary 11-dehydroxy-TXB_2, a stable downstream metabolite, reflects both COX1 and COX2 pathways of platelet activation and has been shown to predict adverse cardiac events in adults with previous cardiovascular disease.[98] Although less specific for ASA, this may be physiologically relevant in inflammatory or postoperative states and could explain some discordance with other ASA-specific functional tests of platelet inhibition.[94] Whether functional, biochemical, or both methods of evaluating ASA efficacy provide the most comprehensive view of "on-therapy" ASA platelet inhibition remains to be demonstrated.

"Aspirin resistance" is a term that has been employed in two contexts. One definition uses one or more of the ex vivo functional tests or metabolite measurements described previously to demonstrate inadequate TXA_2 synthesis inhibition and/or subsequent platelet aggregability in a patient who is on ASA. This laboratory ASA resistance, which may not be associated with clinical events, has also been called "pseudoresistance," though "high on-treatment platelet reactivity" may be a better designation.[99] Clinical ASA resistance occurs when a patient has ischemic events despite ASA therapy. The term "ASA resistance" in this context suggests a pharmacologic failure. It is important to recognize that platelet aggregation is a complex process with multiple triggers, not all of which are COX1- or even TXA_2-dependent, such that optimally dosed ASA may still have limited effectiveness. Treatment adherence would also impact results.

Aside from recent studies of VerifyNow ASA in CHD patients,[93] pediatric data about ASA efficacy testing has been quite limited (Table 3). It is unclear whether monitoring laboratory-based ASA efficacy is precise, accurate, or more effective than optimizing clinical medication adherence practices. Even in adult studies, poor agreement among testing modalities casts shadows on the clinical relevance of therapeutic ASA monitoring beyond a limited number of indications.

8 | RECOMMENDATIONS

With limited data to guide use of ASA in childhood AIS, a pragmatic approach is recommended. ASA dosing of 1 to 5 mg/kg rounded to the nearest half-tablet should be adequate in most instances as an initial approach, though at our institution, the maximum dose is usually 81 mg in children. Absorption should be optimized and drug interactions limited, as highlighted in Table 2. Because many interacting medications can be obtained over the counter, potential interactions from common drugs should be discussed with patients and families, and any new medications or homeopathic agents should be reviewed by a qualified expert, such as a pharmacist. The utility of ASA efficacy testing after an index AIS is unclear, given the limited data and discordance among tests, and it is not our standard practice to do so. Randomized,

TABLE 3 Laboratory tests used for aspirin efficacy

	Sample and volume	ASA resistance frequency (%)[a]	Operator dependence	Point of care	Limitations	Confounders	Evaluated in stroke patients[b]	Pediatric studies[a]
Functional platelet inhibition								
Light transmission aggregometry	270 μL platelet-rich plasma + 30 μL agonist	1–22	Yes	No	Not platelet function-specific, labor-intensive, dependent on pH, temperature, fibrinogen, and anticoagulant for sample	Drugs affecting platelets (NSAID, PPIs, SSRIs), caffeine, smoking, platelet count, time after collection	Yes	Yes
Whole blood aggregometry (multiplate)	300 μL whole blood	8–20	No	No	Not platelet function-specific	Platelet count, high HCT, anticoagulant used, time between collection/test	Yes	Yes
PFA-100	900 μL citrated venous blood	10–49	No	Yes	Sensitive to non-ASA drugs affecting platelet activity or vWF levels, no pediatric standardization	Platelet count, high HCT, time after collection, vWF levels, other antiplatelet agents, clotting factor deficiencies	Yes	Yes
VerifyNow ASA	2 mL whole blood	6–28	No	Yes	No pediatric standardization	High HCT, platelet count, improper volume collected for sample, GpIIb/IIIa inhibitor use	Yes	Yes
TEG with platelet mapping	360 μL whole blood	5–80	Yes	Yes	Poor sensitivity to detect moderate changes in platelet function, no pediatric standardization	High HCT, anticoagulants or antiplatelet agents, platelet count, improper sample collection method or delayed processing	Yes	Yes
Biochemical TXA_2 metabolite production								
Serum TXB_2	Serum	8–29	Yes	No	No pediatric standardization	SSRIs, PPIs, incubation time and temperature, poor processing	Yes	Yes
Urinary 11-dehydroxy-TXB_2	6 mL clean catch urine	25–100	No	No	Not platelet function-specific, no pediatric standardization	Production from extraplatelet sources, inflammation	Yes	Yes

Abbreviations: ASA, aspirin; HCT, hematocrit; NSAID, nonsteroidal anti-inflammatory drug; PFA, platelet function assay; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; TEG, thromboelastography; TXB_2, thromboxane B_2; vWF, von Willebrand factor.
[a]Clinical testing data not specific to stroke.
[b]Clinical studies not specific to pediatric stroke.

controlled clinical trials are needed to answer this question, especially in noncardiac patients who are at high risk for recurrence. If patients experience transient ischemic attacks and/or overt stroke recurrence on ASA, we recommend an in-depth review for potential unanticipated interactions or nonadherence. If the decision is made to continue ASA, efficacy testing using the best available test could be considered.

9 | CONCLUSIONS AND FUTURE DIRECTIONS

Childhood AIS has risk factors and presentations that differ markedly from adult AIS, but there are a paucity of evidence-based prevention and management guidelines. The morbidity and mortality of AIS

and potential costs to patients, families, and society argue for continued research into more effective primary and secondary stroke prevention strategies. Although ASA remains the most commonly used antiplatelet agent in pediatrics, the optimal dose, interval, indications, and monitoring strategies are unclear. Childhood AIS management and prevention suffer from the same challenges that face other rare pediatric diseases: a worldwide overreliance on adult data (for a disease with largely nonoverlapping etiologies) with rare high-quality investigations and a dearth of good outcome measures. The gaps in strong evidence for efficacy, questions about the role of ASA-independent platelet reactivity, the impact of developmental hemostasis, and the unclear utility of ASA monitoring in pediatric AIS argue most persuasively that high-quality research is needed to optimize our understanding of ASA use in pediatric AIS.

ACKNOWLEDGMENTS

None.

FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

FUNDING SOURCE

None.

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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How to cite this article: Boucher AA, Taylor JM, Luchtman-Jones L. Aspirin in childhood acute ischemic stroke: The evidence for treatment and efficacy testing. *Pediatr Blood Cancer*. 2019;66:e27665. https://doi.org/10.1002/pbc.27665