The Diagnosis and Acute Management of Childhood Stroke

CLINICAL GUIDELINE 2017

Australian Childhood Stroke Advisory Committee

The guideline for the diagnosis and acute management of childhood stroke has been

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ABBREVIATIONS & ACRONYMS

ACSAC	Australian Childhood Stroke Advisory Committee
ADC	Apparent Diffusion Coefficient
ADEM	Acute Disseminated Encephalomyelitis
AGREE II	Appraisal of Guidelines for Research & Evaluation
aPTT	Activated Partial Thromboplastin Time
BDNF	Brain Derived Neurotrophic Factor
CBR	Consensus Based Recommendation
CE	Contrast Enhanced
CNS	Central nervous system
COTS	Central Ohio Trauma System
CPSS	Cincinnati Prehospital Stroke Scale
CRP	C- reactive protein
CT	Computed Tomography
CTA	Computed Tomography Angiography
DBP	Diastolic Blood Pressure
DCE	Dynamic Contrast Enhanced
DWI	Diffusion Weighted Imaging
EEG	Electroencephalogram
EPI	Echo Planar Imaging
FLAIR	Fluid-Attenuated Inversion Recovery
FSE	Fast Spin Echo
g	grams
GA	General Anesthetic
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
IA	Intra-arterial
ICP	Intracranial pressure
ICU	Intensive Care Unit
IH	Intracranial Haemorrhage
IL	interleukin
INR	International Normalised Ratio
IPSS	International Pediatric Stroke Study
IV	Intra-venous
LMWH	Low Molecular Weight Heparin
MCA	Middle Cerebral Artery
MI	Myocardial Infarction
ml	milliliters
MMCAI	Malignant Middle Cerebral Artery Infarction
MMP	Matrix metalloproteinase
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MRV	Magnetic Resonance Venography
MTHFR	Methylenetetrahydrofolate reductase
NHMRC	National Health and Medical Research Council
PAI-1	Plasminogen Activator Inhibitor-1
PedNIHSS	Pediatric National Institute of Health Stroke Severity Scale
PFO	Patent foreman ovale
PPSC	Primary Paediatric Stroke Centre
PTT	Partial Thromboplastin Time
ROSIER	Recognition of Stroke in the Emergency Room
SAA	Serum amyloid A
SBP	Systolic Blood Pressure
SIGN	Scottish Intercollegiate Guidelines Network
SWI	Susceptibility Weighted Imaging
TIMPs	Tissue Inhibitors of Matrix Metalloproteinases
TIPS	Thrombolysis in Pediatric Stroke
TNF	Tumor Neurosis Factor
TOF	Time Of Flight
tPA	Tissue Plasminogen Activator
VIPS	Vascular Effects of Infection in Pediatric Stroke

1 PATHWAY OF CARE

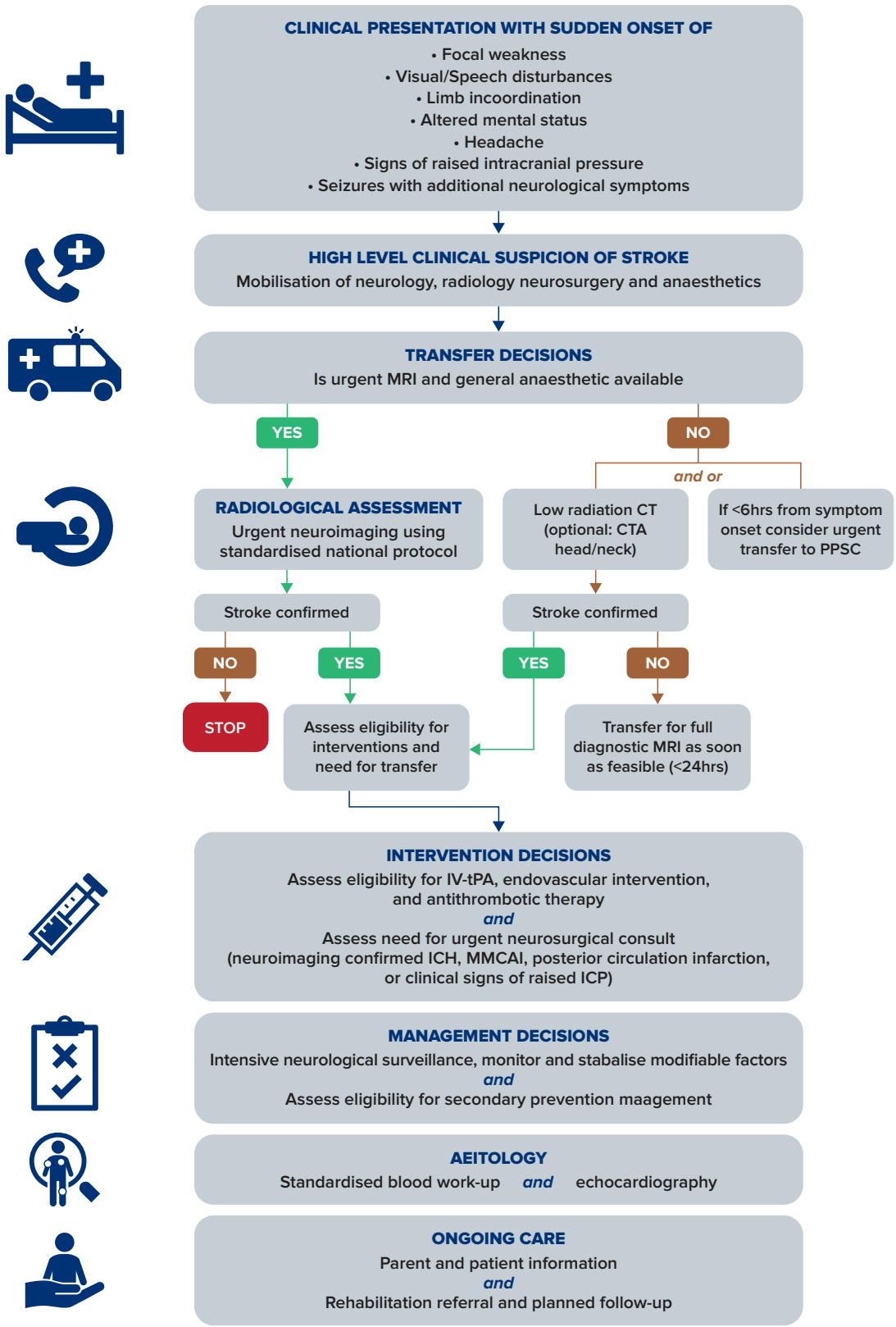

Figure 1. Quick Reference guide to the diagnosis and acute management of childhood stroke

Core components for implementation, blue circles; MRI, magnetic resonance imaging; CT, computed tomography; CTA, CT angiography; PPSC, primary paediatric stroke centre, MMCAI, malignant middle cerebral artery infarction; ICH, intracranial haemorrhage; ICP, intracranial pressure.

In children, stroke is among the top ten causes of death, is more common than brain tumours and is the leading cause of hemiplegic cerebral palsy in term born infants. Like adults 'time is brain' for children who suffer a stroke. Unlike adults, educational campaigns for childhood stroke are rare and scientific literature is scarce. Affected children carry resulting disabilities for a lifetime, at great cost to families, health services and most importantly the child's future.

2 INTRODUCTION

Stroke is a major cause of morbidity and mortality in children across the world. In developed countries, the reported incidence of stroke in children over one month of age ranges from 1.2 to eight per 100,000 per year (1-4). For neonates (less than 1 month of age) and preterm babies the incidence of stroke is significantly higher occurring one in every 2500 to 4000 live births (2, 4). In Australia, the actual incidence of childhood stroke remains unknown. In 2016 children accounted for approximately 22% or 4.88 million of Australia's total population, and 305,337 newborn babies were registered (5). The application of international incidence rates would therefore estimate there to be between 58 and 390 strokes in children, and between 76 and 122 strokes in newborn infants, each year in Australia. Systematic collection of patient data across tertiary paediatric centres is planned following implementation of the Clinical Guidelines to gather epidemiological data on the incidence, causes of, and outcomes following childhood stroke in the Australian population.

Childhood stroke has a mortality rate of five to 10% (6). More than half of the survivors have long-term neurological impairment and 10-20% suffer recurrent strokes. Stroke places significant demands on the health system, families and the community. The lifetime cost of adult stroke is approximately $44,000 in Australia. While there is no published data, the individual cost of childhood stroke is likely to be higher than adults. Firstly, childhood stroke survivors require life-long support for physical and neurological disabilities over several decades. Secondly, there is likely a greater associated loss of income for families and carers, and for the children themselves if they are unable to work as an adult. Studies from the US have estimated average costs of US$20,972 per patient for acute hospital care (7), US$47,929 for the first year of diagnosis, and a five-year direct cost of US$130,000 per patient (8). A comprehensive economic analysis should be a research priority as these costs are difficult to translate to the Australian population due to differences in healthcare systems.

Children with stroke differ from adults in terms of risk factors, underlying aetiologies and pathophysiology, and it is unknown whether children have different pharmacologic responses to reperfusion and secondary preventative therapies due to developmental differences in haemostatic systems. In addition, the outcomes and adverse effects of interventions following stroke in the immature brain are likely to be different to adults, with failure of achieve normal developmental milestones being as important as loss of function. Thus, while some care principles are relevant, direct application of adult recommendations to the treatment of children is inappropriate. The complexity in diagnosis and management of stroke in children is increased by the higher frequency of stroke mimics, variability in age of presentation, diversity of causes and of complex co-morbid conditions. These factors collectively necessitate child specific diagnostic and management regimes.

The diagnosis and acute management of childhood stroke depends on an experienced multidisciplinary paediatric team including emergency physicians, neurologists, neurosurgeons, neuroradiologists, haematologists, cardiologists, general and developmental paediatricians, anaesthetists, intensivists, rehabilitation, neuroscience nursing, allied health and educational specialists. This guideline was developed in response to the needs of professionals and families for a consistent approach to the diagnosis and acute management of childhood stroke in Australia. Successful implementation of these guidelines will allow for the collection of accurate national incidence and outcome data, identify priorities for future collaborative research and reduce variation in care across Australia's tertiary paediatric institutions.

2.1 Scope of the guidelines

These guidelines address the diagnosis and acute management of childhood ischaemic stroke and non-traumatic intracranial haemorrhagic stroke in a) children beyond the neonatal period (ages 29 days to 18 years) and b) neonates and children with congenital heart disease.

The guideline is not inclusive of:

- Adult stroke
- Cerebral sinovenous thrombosis
- Moyamoya disease
- Sickle cell disease
- Spinal stroke
- Perinatal stroke (unless in congenital heart disease patients)
- Traumatic intracranial haemorrhage
- The role of conventional adult stroke risk factors
- Pre-hospital care
- Discharge planning
- Ongoing medical care
- Rehabilitation

2.1.1 Target audience

This guideline is aimed at health professionals working in secondary level acute paediatrics, tertiary level paediatric neurology, neurosurgery, emergency medicine, cardiology, haematology and intensive care. In addition, it is anticipated that administrators, funders and policy makers who manage and deliver care for children with stroke will also find the guideline useful.

2.1.2 Purpose of the guidelines

The purpose of this guideline is to present evidence and/or expert consensus-based recommendations on the diagnosis and acute management of childhood stroke with the goal to:

- Reduce variation in care across Australian paediatric centers,
- Reduce time to diagnosis and treatment in the acute setting,
- Allow for accurate data collection on incidence, treatment and outcomes across Australia, and
- Facilitate collaborative research to improve outcomes for childhood stroke.

These guidelines provide a general approach to appropriate practice, subject to clinical judgment and patient preferences. In considering the implementation of these guidelines, health professionals are encouraged to identify the barriers and facilitators to evidence-based care within their institution to determine the best strategy. Where changes to current practice are required, initial and ongoing education is essential.

2.2 Guideline development methodology

To develop the Clinical Guideline for the Diagnosis and Acute Management of Childhood Stroke a panel of Australia's' leading clinical experts, scientists and guideline developers, representing all of Australia's leading tertiary paediatric centres, were assembled to form the *Australian Childhood Stroke Advisory Committee (ACSAC)*. A brief methodology is described below. More detail, including the committee governance, the disclosure of conflicts of interest, evidence summary tables, approaches used to develop and grade the recommendations and an implementation plan can be found in the document entitled: The Diagnosis and Acute Management of Childhood Stroke - Technical Document – 2017.

Briefly, the advisory committee agreed on a scope and priority areas. These documents informed the populations, interventions and comparatives, and outcomes for each of the clinical questions (Appendix 2). Literature was systematically identified from two databases, limited to English, the last 10 years and paediatric studies. Key relevant studies older than 10 years identified by the ACSAC were included. In the absence of randomised controlled trials in many areas of paediatric stroke, all levels of evidence were screened for inclusion. Final search strings for each question are shown in The Diagnosis and Acute Management of Childhood Stroke - Technical Document – 2017. In the absence of paediatric studies, adult literature was reviewed for its applicability. All literature was independently screened for inclusion and assessed for quality (using SIGN methodology (9)) by two committee members. Conflicting selections and assessments were resolved by a third reviewer. Where guidelines existed relevant to the clinical question they were independently assessed using AGREE II methodology together with systematic literature search from their date of completion. Evidence summary tables for selected literature informed the overview of relevant literature, which was graded by the quantity, quality, consistency, clinical impact, generalisability and applicability (using the National Health and Medical Research Council (NHMRC) system), for each clinical question. Drafted recommendations considered the above factors and were graded strong or weak in alignment with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (10). All evidence summaries and resulting recommendations were approved by the full committee. The subsequently drafted guideline underwent a period of targeted consultation. All comments and suggestions were collated and reviewed in blinded fashion by the committee. A consensus process was used to modify any recommendations. These guidelines will be updated within the next five years.

2.3 How to use this guideline

This guideline is an overview of the best available evidence translated into clinically relevant statements (recommendations). Recommendations were graded strong or weak, based on their benefit over harm to the patient (Table 1 and Table 2). The level of evidence next to the recommendation specifies the type of studies used to formulate the recommendation (Table 3). Where there was no available evidence but clinical experience clearly suggests benefit or harm to the patient, consensus-based recommendations and practice statements were formulated.

Table 1. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE)

Grade of Recommendation	Description
Strong	Benefits of implementing recommendation clearly outweigh drawbacks/harms
Weak	It is less clear that the benefits outweigh the drawbacks/harms
Practice statement	Expert opinion/advice for areas outside the search strategy, or where there is a lack of evidence on which to base a recommendation.

Table 2. Implications of GRADE recommendations

Implications for:	Strong recommendation	Weak recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Health professionals	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognise that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with patient values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
Policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Table sourced from GRADE developmental handbook 2013 (10).

Table 3. National Health and Medical Research Council Level of Evidence Matrix

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control • Interrupted time series with control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	A retrospective cohort study		A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case control
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/ post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

3 CHILDHOOD STROKE

3.1 Definitions

A paediatric stroke can be classified by stroke type, the age at which it occurred and the vessels involved. The three primary types are arterial ischaemic stroke, cerebral sinovenous thrombosis and haemorrhagic stroke. The timing of the stroke is classified as i) perinatal stroke, where diagnosis occurred or is presumed to have occurred between 28 weeks gestation and 28 days of life or, ii) childhood stroke, which is defined by stroke occurring between 29 days and 18 years of age. Within the literature paediatric stroke is also classified by the number of vessels and type of arterial territory involved.

Ischaemic stroke is defined as a sudden focal infarction of brain tissue diagnosed by neuroimaging or at autopsy and can result in arterial ischaemic stroke or venous infarction. An arterial ischaemic stroke occurs when there is sudden occlusion of one or more cerebral arteries. In adults, ischaemic stroke accounts for 75 to 85% of strokes. In children, arterial ischaemic stroke is also the most common subtype, accounting for just over half of all strokes (7, 11-13). Cerebral sinovenous thrombosis is defined by thrombosis within the superficial or deep venous system. It is a rarer type of stroke accounting for approximately one in four paediatric stroke cases, but is associated with significant morbidity and mortality (6, 14).

Haemorrhagic stroke is the result of bleeding from a ruptured cerebral artery or bleeding into the site of an acute ischaemic stroke. Haemorrhagic stroke can include intracerebral haemorrhage and less commonly subarachnoid or intraventricular haemorrhage. Haemorrhagic stroke is estimated to account for just under half of all childhood strokes (15), significantly more than the six to 15% reported in the adult population.

Despite increasing awareness, childhood stroke is often overlooked by health professionals and carers. This can be the result of limited stroke awareness in the paediatric population, the high frequency of stroke mimics, the diversity of presenting symptoms, the difficultly in examination and identification of subtle symptoms in young children, and delayed access to diagnostic neuroimaging expertise. Implementation of standardised protocols of care is expected to increase clinical suspicion of stroke, reduce missed and delayed diagnosis and help elucidate an accurate incidence of childhood stroke in Australia.

3.2 Risk factors

For adults, the influence of modifiable risk factors such as hypertension, hypercholesterolemia, smoking, obesity and diabetes on the risk of stroke are well understood. Despite some of these factors becoming more prevalent in older children, they are rare causes of childhood stroke. For many adults, risk factors are known before the event, however for children, approximately 50% of strokes occur when they have been previously well (12, 16). A wide range of presumptive risk factors are reported in association with childhood stroke (Table 4 (17)), however minimal high-quality evidence exists to suggest when and to which groups of children they apply. The more commonly reported risk factors include nonatherosclerotic arteriopathies, cardiac disorders, and infection, inherited or acquired coagulation abnormalities, malignancies, head and neck trauma, and sickle cell disease (17, 18). Importantly, multiple risk factors converge in more than 50% of children with stroke, however at least 10% remain idiopathic (16).

Childhood stroke risk factor profiles have been reported across various populations and cohorts. A review of risk factors in 676 children from the International Pediatric Stroke Study (IPSS) registry found geographical variation in the rates of arteriopathies, prothrombotic states and systemic conditions (16). Variation in factors for childhood stroke between populations and cohorts is not a new concept. For example, sickle cell disease is reportedly most frequent in African–American children, Moyamoya disease more frequent in Japan, coagulation disorders more frequent in Europe and cardiac disorders more common in Hong Kong (19). The relative contribution of specific conditions to childhood stroke varies across uncontrolled retrospective case series in cohorts from Turkey (20, 21), Korea (22), Switzerland (23), Saudi Arabia (24), Italy (25), China (26), India (27, 28), Taiwan (29), the United Kingdom (3), Denmark (1), Estonia (30, 31), Singapore (32), Pakistan (33) and Sweden (34). An understanding of the risk factors for haemorrhagic stroke in children is lacking. In retrospective case series and cohort studies arteriovenous malformation, aneurysms, cavernous malformations (35), and brain tumours bleeds have been associated with haemorrhagic stroke (15), however no aetiology is identified in up to 20% of cases (15).

In summary, a vast number of factors have been associated with childhood stroke. As it becomes increasingly clear that risk of childhood stroke is multifactorial the importance of high clinical suspicion and rapid, diagnosis by neuroimaging cannot be understated.

Table 4. Reported risk factors for childhood stroke

Category	Risk factors
Arteriopathy	Inflammatory and Post-Infectious: Focal cerebral arteriopathy, Post-varicella angiopathy, Primary CNS angiitis. Craniocervical arterial dissection. Moyamoya Disease.
Cardiac disorders	Congenital heart disease. Bacterial endocarditis.
Infection	Upper respiratory tract, herpes group viral, acute otitis media, bacterial or tuberculous meningitis, HIV.
Head/neck trauma	Post-traumatic dissection, intracranial trauma.
Hematologic and prothrombotic disorders	Protein C, protein S, antithrombin deficiency, factor V Leiden, pro-thrombin 20210, MTHFR mutations, antiphospholipid antibodies. Sickle cell disease. Iron deficiency anaemia.

Adapted from Swaiman's Pediatric Neurology 2017 (36) CNS, central nervous system; PFO, patent foremen ovale; HIV, human immunodeficiency virus; MTHFR, Methylene tetrahydrofolate reductase.

4 DIAGNOSIS OF CHILDHOOD STROKE

4.1 Presenting signs and symptoms indicating stroke

Clinical presentation of paediatric stroke varies depending on stroke type, vessels involved and the child's age. Indeed, variations in clinical presentation is cited as a factor in missed or delayed diagnosis. That said, some generalisations can be made as to how childhood stroke presents.

In 2011, The International Pediatric Stroke Study (IPSS) described the presenting features of 676 children diagnosed with arterial ischaemic stroke (16). In this cohort 80% percent presented with hemiparesis, 51% with speech disturbances, 52% with altered consciousness, 40% with a headache and 31% with seizures. Furthermore, the ACSAC conducted a collective review of 13 additional single centre retrospective datasets that showed; i) focal weakness in 63 to 100% of children (from eight studies (12, 16, 37-42), ii) headache in 16 to 45% (from six studies (12, 40-44), iii) altered mental state in 12 to 52% (from four studies (16, 40, 42); and iv) seizures in 11 to 58% in children (from 13 studies (12, 37-48). Children with cerebral sinovenous thrombosis present with even more diverse and non-focal symptoms including headache, seizures, lethargy, nausea, vomiting or signs of increased intracranial pressure.

Children with haemorrhagic stroke can also present with non-specific symptoms. There are however retrospective studies to suggest that vomiting and loss of consciousness are more common in haemorrhagic stroke in addition to headaches, altered mental status, whereas focal neurological deficits are more commonly seen in children with arterial ischaemic stroke (49-51).

There are also significant differences in clinical presentation depending on the child's age. Seizures are the most common presenting symptom in newborns but other non-specific symptoms include lethargy, apnoeic spells, or hypotonia. Focal neurological deficits may not develop later infancy. Older children can also present with non-specific symptoms but adult-like focal neurological defects are frequent. Like adults when symptoms last < 24 hours, they are defined as a transient ischaemic attack. Unlike adults, transient ischaemic attacks are uncommon in children compared to adults, with a US study finding that 4.8 children were admitted with stroke for every child with a transient attack (52).

4.2 Stroke mimics

Many conditions can mimic childhood stroke. Clinical differentiation by emergency staff, whilst challenging, is imperative to direct children to the appropriate pathway of care, improve time to diagnosis and avoid unnecessary diagnostic procedures.

Paediatric neurological emergencies that can present with stroke-like symptoms include status epilepticus, acute raised intracranial pressure, traumatic brain injury, central nervous system infections and demyelinating disorders (53). Although adult stroke is commonly diagnosed after the sudden onset of focal neurological symptoms including focal weakness, speech, sensory/visual disturbances or headache, this is not the case in children (54).

A study conducted at an Australian tertiary paediatric hospital involving 382 children found that migraine accounted for 28% of those presenting with sudden onset focal neurological symptoms, followed by new onset seizures in 15%, Bell's palsy in 10%, conversion disorders in 6% and ischaemic or haemorrhagic stroke in 7% (49). Features leading to a diagnosis of stroke were dependent on the subtype of stroke. Being previously well, face/arm weakness and the inability to walk at presentation were independently associated with an increased odds of stroke diagnosis (49). Other conditions such as post-infectious cerebellitis, posterior reversible leukoencephalopathy, inflammatory and demyelinating disorders, intracranial infection, metabolic stroke, tumours and drug toxicity have also been described as mimicking stroke in the inpatient setting (55).

Seizures are a common presentation for both ischaemic and haemorrhagic stroke. They occur in one-third to a half of children, which is significantly greater than in adults, where they are often used a predictor for diagnosing stroke mimics.

In summary, differentiation of stroke from mimics begins with clinical recognition of the most common presenting symptoms (Table 5), consideration of the child's age and a decisive decision for urgent neuroimaging. An accurate diagnosis, with early differentiation between stroke and mimics is crucial to allow for systematic review of interventions that improve long-term outcomes.

Table 5. Clinical presentation of stroke and stroke mimics in children

Condition	Typical onset of symptoms	Possible symptoms
Ischaemic stroke	Sudden	All neurological symptoms, particularly focal weakness, speech disturbance, sensory or limb incoordination, ataxia.
Cerebral sinovenous thrombosis	Sudden or Gradual	Headache, lethargy, nausea, vomiting or signs of increased intracranial pressure.
Haemorrhagic stroke	Sudden	All neurological symptoms, particularly headache, vomiting, altered consciousness.
Migraine	Gradual	Visual or sensory disturbance that usually resolves within 30 minutes, followed by headache.
Seizures / Todd's paresis	Sudden	Seizures with focal motor deficits.
Bell's Palsy	Sudden or Gradual	Isolated upper and lower facial weakness.
Conversion disorders	Sudden or Gradual	Neurological symptoms not conforming to neuroanatomical pathways, inconsistent or varying with examinations.
Syncope	Sudden	Loss of consciousness with an identifiable trigger, preceded by gradual visual obscuration, tingling or diaphoresis.
Post infectious cerebellitis	Gradual	Isolated cerebellar signs.
ADEM	Gradual	Encephalopathy, seizures and multifocal neurological deficits referable to multiple locations within the CNS.
Tumour	Gradual	Any neurological sign, altered consciousness and signs of raised intracranial pressure.

Adapted from Mackay et al 2016 (36); ADEM, acute disseminated encephalomyelitis; CNS, central nervous system.

Table 6. Recommendations for investigating stroke in children

Strong Recommendation
Children presenting with sudden onset of the following symptoms are at high risk of stroke and should undergo immediate neurological assessment and consideration of urgent neuroimaging; i) focal weakness (ii) visual or speech disturbances, (iii) limb incoordination or ataxia, (iv) altered mental status, (v) headache, (vi) signs of raised intracranial pressure, or (vii) seizures with additional neurological symptoms. Level of Evidence (III). References (12, 37-48).
Practice Statement
When taking a history, health professionals should consider all risk factors, ethnic origin, and family history, with attention to pre-existing conditions such as congenital heart disease, recent history of head or neck trauma, unexplained fever, recent infections (especially chicken pox), drug ingestion and anaemia or coagulation disorders.

Adult stroke recognition tools in their current form are unlikely to impact clinical recognition of stroke in the paediatric emergency department

4.3 Stroke recognition tools

Accurate and timely diagnosis of childhood stroke is essential to enable reperfusion therapies, prevent recurrence and minimise long term neurological damage. Unfortunately, long diagnostic delays before and after reaching hospital are all too common in childhood stroke (56, 57). One key reason cited for the in-hospital delays is limited stroke awareness among paediatric physicians. Stroke recognition tools use a combination of clinical symptoms and signs to aid physicians in distinguishing a stroke from other disorders, which mimic stroke. In adults, stroke recognition tools, which are widely used by pre-hospital emergency services, improve diagnostic accuracy, decrease time to diagnosis and thus increase access to reperfusion therapies to restore blood flow to salvageable brain at risk of infarction. In children however, the diagnostic accuracy and reliability of stroke assessment tools have been unclear.

A systematic review of the literature identified two studies in 2016 that retrospectively applied adult pre-hospital and emergency department stroke recognition tools to children. Mackay et al investigated the diagnostic accuracy and reliability of two such tools (Cincinnati Pre-hospital Stroke Scale (CPSS) and Recognition of Stroke in the Emergency Room (ROSIER)) to differentiate stroke from stroke mimics in 380 children presenting with brain attack symptoms. Both tools performed poorly in diagnosing all stroke types compared to the mimic diagnoses of migraine, first seizure, Bell's palsy and conversion disorders (58). In accordance, Neville et al demonstrated that the adult Central Ohio Trauma System (COTS) stroke scale was unable to distinguish ischaemic stroke from non-stroke focal neurological deficits when applied retrospectively to 53 children and age matched controls (59).

While limited in number these studies suggest that for children presenting to the emergency department with neurological symptoms or signs relevant for stroke, validated adult pre-hospital (CPSS and COTS), and emergency department (ROSIER) stroke recognition tools, do not accurately distinguish strokes from mimics. Further work is imperative to develop, validate and implement paediatric specific recognition tools to reduce the diagnostic delay in childhood stroke.

Table 7. Recommendations for the use of stroke recognition tools

Strong Recommendation	Against
In children presenting with neurological symptoms or signs relevant for stroke, the use of adult stroke recognition tools to differentiate childhood stroke from its mimics are not recommended in their current form. Level of Evidence (III-2). References (58, 59).	

4.4 Stroke severity score

The National Institutes of Health Stroke Scale (NIHSS) is a quantitative measure of stroke-related acute neurologic deficits, which has proven inter-rater reliability and predictive validity for outcome among adults. The paediatric modification (PedNIHSS), developed via consensus from paediatric and adult stroke experts, is adjusted according to the maturation of the child's neurological and cognitive function, considering their ability to comprehend instructions. Inter-rater reliability of the PedNIHSS has been assessed in a cohort of 25 children and was good to excellent for all items of the scale at mean of three days after symptom onset (60). The stroke scale is appropriate for use in children between two and 18 years of age and ideally should be performed upon arrival at the hospital, to determine eligibility for interventions.

Table 8. Recommendations for physical examinations in children with suspected or confirmed stroke

Strong Recommendation
In all children between the ages of 2 and 18 years, stroke severity should be assessed upon arrival to the hospital using the Paediatric National Institute of Health Stroke Scale to facilitate ongoing management. Level of Evidence (III, CBR), References (60).

4.5 Delayed diagnosis and stroke codes

Significant delays exist in the diagnosis of childhood stroke. Factors contributing to the delays include the low incidence, varying clinical presentations, limited access to urgent diagnostic neuroimaging, and poor awareness of childhood stroke among physicians and carers. Despite the reporting of detrimental delays from various international centres almost a decade, little progress has been made to reduce them, which precludes access to emergency interventions to minimise extent of brain injury.

The recommended time windows for thrombolysis and thrombectomy in adults are less than 4.5 and six hours respectively. Implementation of comprehensive stroke protocols together with national audits have shown that reducing time to diagnosis decreases costs and improves outcomes in adults (61).

Studies investigating time to diagnosis for children have reported both pre-hospital and in-hospital delays with the interval from symptom onset to stroke diagnosis ranging from six to more than 24 hours (37-39, 42, 56, 62-64). A retrospective review of 29 children in 2002 showed an average time to diagnosis of 35 hours (42). Six years later, a review of 50 children found that 32 did not access a paediatric neurologist in the first 24 hours, and time to clinical diagnosis ranged from less than six hours to more than 24 hours (39). The lack of stroke awareness among paediatric physicians was identified as factor for in-hospital delays in an assessment of 88 children with arterial ischaemic stroke where median time to diagnosis was almost 25 hours (37).

These significant delays are similar across international centres. In 81 children presenting to the Royal Children's Hospital Melbourne emergency department, the median time from onset to diagnosis was 21 hours for ischaemic stroke and 12 hours for haemorrhagic stroke (62). In England, a review of 96 children also reported a median time to diagnosis of more than 24 hours (56), and in Sweden and Singapore only 30 to 40% of children were diagnosed within six hours (32, 34).

There is a growing body of evidence to show that implementation of an immediate response protocol in paediatric emergency departments reduces the delay in diagnosis (38, 63, 65). In 2009 The Hospital for Sick Children in Toronto assessed 209 children with arterial ischaemic stroke and found median times to diagnosis of over 22 hours, with pre-hospital delays (symptom onset to arrival at hospital) at median of 1.7 hours and in-hospital delay (presentation to diagnosis) at 12.7 hours (38). They consequently implemented a four point stroke screening tool, where a stroke team is paged and urgent neuroimaging conducted on children that meet screening criteria (64). A subsequent analysis of 112 children pre- and post-implementation of the stroke protocol showed a significant reduction in diagnostic delays associated with increased use of MRI (64). Ladner and colleagues in 2016 subsequently reported an in-hospital time to neuroimaging of 94 minutes in 124 emergency cases where a paediatric acute stroke protocol was activated (63). DeLaroche and colleagues have shown that a mean time to neuroimaging of 17 hours was reduced to four hours after implementation of a paediatric stroke clinical pathway (65). Collectively, these studies demonstrate that time to neuroimaging and in-hospital diagnosis can be reduced with the implementation of standardised protocols in the emergency department.

In Australia, a recent study from the Royal Children's Hospital Melbourne of 19 children with arterial ischaemic stroke transported to the ED by ambulance reported a median pre-hospital delay of 71 minutes, compared to post arrival delays to radiological confirmation of diagnosis of 568 minutes (66).

In summary, the literature is consistent in that in-hospital factors contribute more to delayed diagnosis than pre-hospital factors. Thus, while increasing public awareness of stroke is important, there is a pressing need to implement evidence-based shared protocols, and decision tools that facilitate rapid stroke diagnosis following arrival to hospital.

Table 9. Recommendations to reduce time to diagnosis

Practice Statement
The development of a stroke "code" (i.e. an immediate response protocol) with an acute team including emergency physicians, neurologists, neuroradiologists, anaesthetists, haematologists, critical care teams, and neurointerventionalists or neurosurgeons (where indicated), may reduce time to diagnosis and should be a research priority within Australia's tertiary paediatric centers.

Some children presenting to hospital with a stroke can wait more than a day for an accurate diagnosis

5 NEUROIMAGING

Neuroimaging is essential for the diagnosis of childhood stroke, and to differentiate stroke from stroke mimics. Technological advancements in neuroimaging offer numerous modalities and sequences to diagnose acute stroke in children including computed tomography (CT) with or without contrast, CT angiography, magnetic resonance imaging (MRI) magnetic resonance angiography (MRA), contrast magnetic resonance venography (MRV) and conventional catheter cerebral angiography. As previously discussed, in-hospital factors contribute more often to diagnostic delay than pre-hospital factors, and false negative imaging is a major contributor (37, 56, 67, 68). Here we present recommendations for neuroimaging for children with suspected stroke with the goal of standardising neuroimaging protocols across Australian paediatric institutions. In addition to aiding early diagnosis, national standardised protocols will also facilitate multicentre trials and research collaborations.

MRI is the most sensitive modality for diagnosis of acute arterial ischaemic stroke. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences can demonstrate the presence of acute cytotoxic oedema within minutes of stroke onset, and are more accurate, sensitive and specific for the early detection of acute ischaemic stroke, compared with other MRI sequences or CT imaging. The addition of MRA and MRV protocols facilitate identification of the site(s) of arterial or venous occlusions and gradient echo sequences, such as susceptibility-weighted imaging (SWI), provide information about presence of acute intracranial haemorrhage. Young children, particularly less than five years of age, are likely to require sedation or general anaesthesia to obtain an MRI. Thus, where sedation and MRI access is readily accessible a targeted stroke protocol is likely to confirm ischaemic or haemorrhagic stroke diagnosis. In many cases it will also identify; i) the site of vascular stenosis or occlusion; ii) presence of vascular malformations; and iii) arterial dissection, offering a greater chance of determining aetiology, risk of reoccurrence and selection of the most appropriate treatment interventions, at the time of diagnosis. In order to improve access to reperfusion therapies, some centres have advocated for the use of a limited set of sequences to allow rapid neuroradiological confirmation of stroke, whilst minimising the need for sedation. (63, 69, 70).

CT and MRI are equally sensitive for the detection of intraparenchymal blood. Thus, where signs and symptoms suggest haemorrhagic stroke, and access to sedation or MRI is delayed, a CT can be performed. The advantages of CT are that most children will not require sedation and they are readily available in most emergency departments. However, these benefits are largely outweighed by the limited sensitivity of CT in children with ischaemic stroke. CT can often miss the early sign of ischaemic infarction resulting in a delayed diagnosis, and therefore, cannot definitively differentiate between stroke and mimics in children. For example, in a cohort of 74 children with arterial ischaemic stroke CT did not diagnose stroke in 84% of cases, whereas 100% were diagnosed by MRI (37). A separate analysis of 71 cases of arterial ischaemic strokes that presented to the Royal Children's Hospital Melbourne over a 10 year period found that only 36% of children received MRI as first imaging, and while a CT scan was initially performed in 60% of children it was only diagnostic in 24% of cases (67). Furthermore, the reduced use of sedation in those undergoing CT was undermined by the need for 41 of these children with a negative CT requiring a subsequent MRI for definitive diagnosis (67). Further support comes from an English cohort of 96 children where CT only diagnosed 66% of cases (56, 64) that showed a reduction in diagnostic delays was associated with increased MRI usage due to 53% false negative CT (64).

The slightly increased lifelong risk of cancer in children exposed to radiation via CT is an additional concern (71). Finally, the increased prevalence of stroke mimics in children compared to adults (53-55), requires MRI to differentiate from other causes of focal deficits, and to allow diagnosis of other serious neurological disorders such as CNS demyelination, which are also poorly detected on CT imaging.

There is the potential for reperfusion therapies to improve outcomes for children with arterial ischaemic stroke (Chapter 9). The use of thrombolytic and endovascular interventions is highly time-dependent, thus, the establishment of rapid MRI protocols to confirm stroke diagnosis for children within the time frame for these interventions is imperative. A rapid protocol (of approximately 10-15 minutes, depending on MRI capabilities) is proposed here, based on a review of literature and expert opinion (Figure 2). Sequences including (i) axial DWI/ADC, (ii) axial gradient echo (such as SWI) for detection of haemorrhage, (iii) axial fast spin echo (FSE) or turbo spin echo (TSE) T2, iv) consideration of fluid-attenuated inversion recovery (FLAIR) if greater than 1 year of age, v) axial T1 and vi) time of flight (TOF) MRA, will allow for faster assessment for eligibility for thrombolytic or endovascular interventions. Where the rapid MRI does not diagnose stroke, there is the option to proceed with a full diagnostic protocol whist the children remains under general anaesthetic (Figure 2).

In children with suspected arterial abnormalities digital subtraction angiography may be required to better define the arterial lesion if the diagnosis is unclear on TOF MRA (72). Digital subtraction angiography is a safe procedure when performed by experienced angiographers (73). The role of vascular imaging for identification of non-atherosclerotic arteriopathies is discussed further in Chapter 5.

Table 10. Neuroimaging recommendations for diagnosing arterial ischaemic stroke

Strong Recommendation
In children with suspected arterial ischaemic stroke urgent brain magnetic resonance imaging (MRI) should be performed as the diagnostic imaging modality of choice. Level of evidence (I (adult), III-2 -IV paediatric). References (37, 56, 63, 67-69, 71, 74-76).
Weak Recommendation
In children undergoing MRI for suspected arterial ischaemic stroke *within* time frames for reperfusion therapies, a rapid imaging protocol including (i) axial DWI/ADC, (ii) axial gradient echo (such as SWI) for detection of haemorrhage, (iii) axial fast spin echo (FSE) or turbo spin (TSE) T2, iv) consideration of fluid-attenuated inversion recovery (FLAIR) if greater than 1 year of age, v) axial T1 and vi) time of flight (TOF) MRA, to inform ongoing management, is recommended. Level of Evidence (III-2, VI). References (63, 69).
Practice Statement
In children undergoing MRI for suspected arterial ischaemic stroke *outside* time frames for reperfusion therapies, a full diagnostic imaging protocol including (i) DWI/ADC, (ii) axial gradient echo (e.g SWI), (iii) axial T2, (iv) FLAIR if greater than one year of age), (v) 3D volumetric T1, (vi) TOF MRA, and consideration of perfusion imaging, is recommended.
Practice Statement
Intracranial vessel wall imaging (axial/coronal high resolution, pre- and post- contrast, fat-saturated T1 weighted imaging), contrast MRA, and axial/coronal fat saturated pre- and post- contrast T1 of the neck vessels, may also be considered for investigation of specific arteriopathies such as focal cerebral arteriopathy and cervical dissection.
Practice Statement
Hospitals providing tertiary care to children with presenting stroke symptoms should ideally have access to MRI facilities and radiologists with appropriate expertise to interpret these studies at all times to avoid diagnostic delays associated with CT scanning. When these facilities and expertise do not exist, centres should consider policies and protocols for rapid transfer.
Strong Recommendation
In children with suspected arterial ischaemic stroke where urgent MRI is not possible, CT imaging, including CTA and CT perfusion can be considered as an alternative, particularly in older teenagers. Level of Evidence (CBR).
Practice Statement
When CT is being performed, radiation exposure should be kept to the minimum required to produce diagnostic quality images, and protocols should be optimised for children of varying ages based on head size. Level of Evidence (III-2). References (71).

Table 11. Neuroimaging recommendations for diagnosing haemorrhagic stroke

Strong Recommendation
In children with suspected haemorrhagic stroke urgent brain MRI or CT should be performed. Level of Evidence (III-3). References (77).
Practice Statement
MRI and CT are equally sensitive in detecting intra-parenchymal blood. While MRI allows detection of vascular malformations and no radiation exposure, CT can be advantageous when a general anesthetic would otherwise be required, or the child needs urgent neurosurgical intervention.
Practice Statement
When CT is performed, radiation exposure should be kept to the minimum required to produce diagnostic quality images, and protocols should be optimised for children of varying ages based on head size. Level of Evidence (III-2). References (71).
Practice Statement
Vascular sequences such as an MRA or CTA should be performed and if the child is stable then a DSA should be considered.

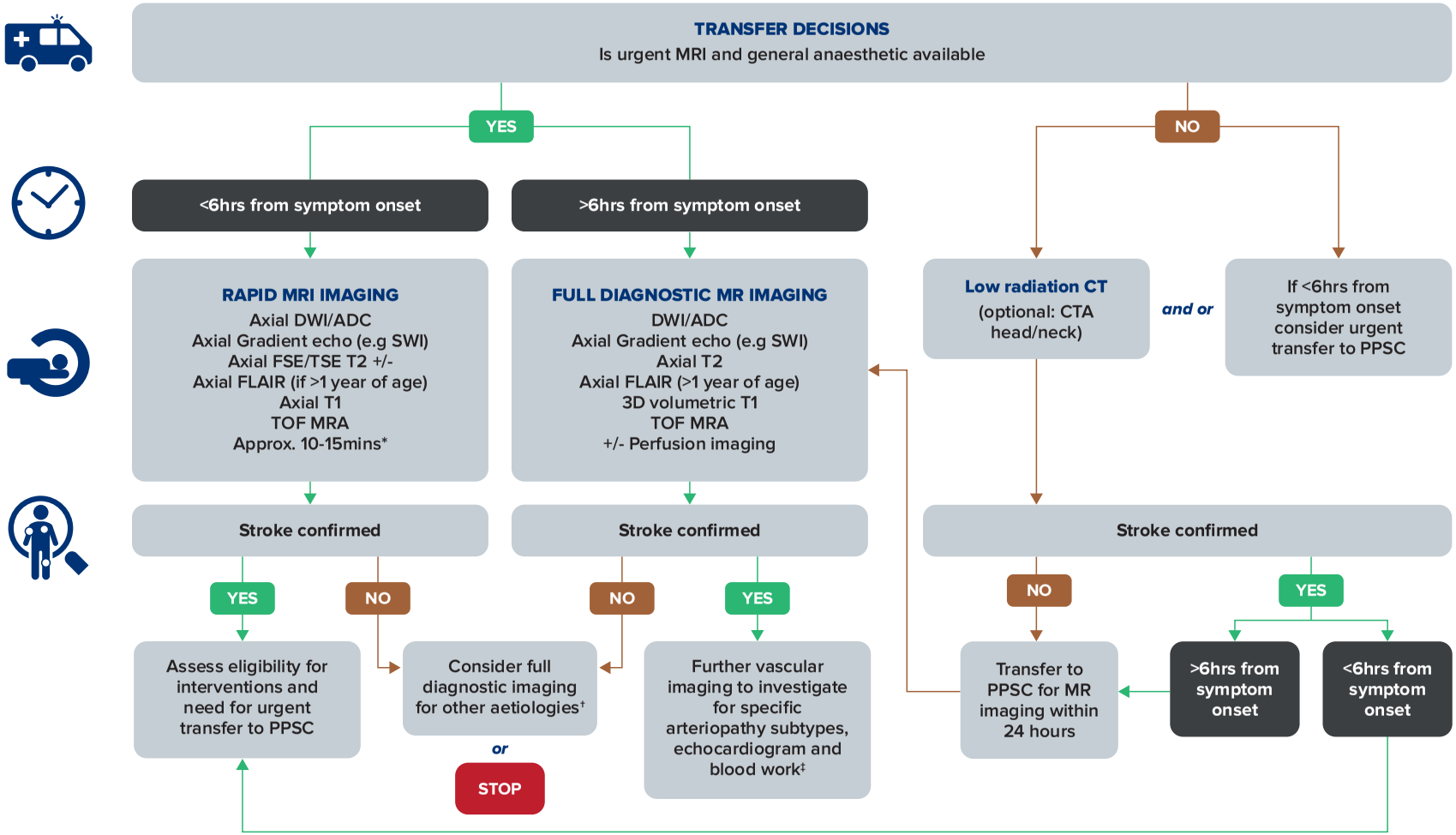

Figure 2. Imaging pathway for suspected childhood stroke (29 days to 18 years of age)

MRI, magnetic resonance imaging; DWI, diffusion-weighted images; ADC, apparent diffusion coefficient; SWI, susceptibility-weighted images; FSE, fast spin echo; TSE, turbo spin echo; FLAIR, fluid-attenuated inversion recovery; TOF, time of flight; MRA, magnetic resonance angiography; PPSC, Primary Paediatric Stroke Centre; CT, computed tomography; CTA, computed tomography angiography. *time may vary between scanners. †In children with alternative diagnoses, if attaining subsequent imaging will be difficult/traumatic (e.g. young children or those with intellectual disability) consideration should be given to complete a full diagnostic scan to elucidate aetiology. ‡ E.g. investigations for specific arteriopathies may include i) Intracranial arteriopathy using vessel wall imaging (axial/coronal pre- and post- contrast T1 weighted imaging) or ii) cervical dissection via contrast MRA and axial/coronal fat saturated pre- and post- contrast T1. § There are substantial difficulties associated with delivering contrast in young children, particularly using pump injection in the absence of general anaesthetic, and the skill required to attain images without movement error, teenagers 13-18 years of age. Note: Sequences are a guide and should be at discretion of the neuroradiologist.

6 INVESTIGATIONS

Neuroimaging confirms the diagnosis of stroke in children and can often identify a cause. However, in many children the cause of a stroke is multifactorial. Moreover, despite a thorough work-up aetiology remains unknown in 10 to 30% of children (78). In addition to the laboratory examinations recommended in the acute setting, there is evidence that additional investigations for arteriopathies (3, 16, 41, 79-88), cardiac disorders (3, 16, 41, 89-99), infection (45, 100-104) and iron deficiency (89, 105, 106) can help elucidate aetiology, and the risk of stroke recurrence.

While a broad range of factors have been described in association with childhood arterial ischaemic stroke in uncontrolled and mainly retrospective studies (107-118), the lack of control subjects means that these associations are largely presumptive. Data from larger prospective (3, 16, 23) and retrospective population based, or multicentre uncontrolled cases series, (79, 119) are summarised in Table 12.

Table 12. Risk factors for initial and recurrent stroke

Risk factor category	Mallick et al. (3)	Mackay et al. (16)	Bigi et al. (23)	Strater et al. (119)	Fullerton et al. (79)
Arteriopathy	29%	53%	36%	18%	24%
Cardiac disorders*	23%	31%	17%	12%	12%
Infection*	28%	24%		10%	23%
Acute systemic disorders	31%	22%			
Chronic systemic disorders (including anaemia*)	25%	19%			
Acute head & neck disorders (including trauma*)	19%	23%			
Chronic head & neck disorders	4%	10%			
Prothrombotic states	5%	13%	7%		7%
Atherosclerotic	2%	2%	11%		
Other		22%			7%
Idiopathic	17%	11%		60%	27%

Percentage of children in cohort studies presenting with each risk factor/aetiology.

6.1 Laboratory investigations in the acute setting

Laboratory examinations in the acute setting, including routine biochemistry, haematology and coagulation studies should be conducted as part of the initial evaluation.

Table 13. Initial laboratory investigations for suspected or confirmed childhood stroke

Strong Recommendation
Upon presentation, all children should undergo the following pathology; full blood count with differential, basic biochemistry (urea, creatinine, electrolytes, glucose), and a coagulation screen (international normalised ratio (INR)/ prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen). Level of Evidence (CBR).

6.2 Additional investigations

Additional investigations searching for risk factors, underlying comorbidities and biomarkers can assist in determining the cause and inform ongoing management for children. Here we review the evidence for additional investigations in arteriopathies, cardiac disorders, prothrombotic disorders, infection, iron deficiency and serum biomarkers.

Arteriopathies

Non-atherosclerotic arteriopathies can be divided into non-progressive (i.e. focal cerebral arteriopathies and arterial dissection) and progressive (i.e. Moyamoya, primary angiitis of the central nervous system, and sickle cell disease) disorders. Unilateral focal cerebral arteriopathy is the most common type of arteriopathy in childhood stroke accounting for almost one quarter of cases (80).

The presence of arteriopathy is the most important predictor of recurrent arterial ischaemic stroke. Early retrospective studies suggested a high risk of recurrent events in children with arterial ischaemic stroke. The five-year cumulative recurrence rate was 19% in a population-based case control study from the US (79)**.** Although there were no recurrences noted among children with normal vascular imaging, children with a vascular abnormality had a five year cumulative recurrence rate of 66% (79)**.** In another retrospective single centre study 79 of 212 (37%) children were reported to have recurrent events (82). However more recent prospective studies suggest a lower risk, with less than 13% of children having recurrent events (83-85). In support, the Vascular effect of Infection in Pediatric Stroke Study (VIPS) found a cumulative stroke recurrence rate of 6.8% at one month and 12% at one year (85). Two thirds of recurrences occurred within 12 months; presence of an arteriopathy was the sole predictor of recurrence, associated with a five-fold increased risk, compared to idiopathic stroke. Further analysis of the VIPS cohort found that arteriopathy progression increased the hazard of recurrent arterial ischaemic stroke by three-fold, with a one-year cumulative recurrence risk of 46% for those with progressive arteriopathy, compared to 25% in children without progressive arteriopathy (86). Predictors of recurrence are not reported in other studies, presumably due to the low number of patients affected (83, 84).

Silent infarction has been shown to occur in up to 11% of children undergoing surveillance imaging (82). The presence of arteriopathy (in addition to previous transient ischaemic attack, bilateral infarction, prior diagnosis and leucocytosis) has been independently associated with the incidence of clinically overt or silent re-infarction (82).

Moyamoya disease is an occlusive cerebrovascular disorder characterised by the angiographic appearance of an abnormal vascular network at the base of the brain. Moyamoya accounts for a significant percentage of arteriopathies in children, and is more commonly found in Asian populations. Moyamoya is often associated with recurrent stroke, cognitive deterioration and seizures. Sickle cell disease is often associated with cerebral vasculopathy, particularly affecting the distal internal carotid or proximal middle arteries, increased risk of recurrent strokes and transient ischaemic attacks. The diagnosis and management of patients with Moyamoya or Sickle cell disease is not covered here and readers are referred to other international guidelines (78, 120).

There is minimal literature to support the imaging modality by which vascular abnormalities should be detected. One study (88) that compared MRA with conventional angiography in 36 children found that MRA was diagnostic in patients with large vessel stenosis and occlusion. Conventional angiography was abnormal in four of nine children with normal MRA, and identified abnormalities which were not detected on MRA in 13 children, altering management in 11 patients. Another study of 24 children found that distal vascular lesions and the degree of arterial stenosis were better detected on conventional angiography in 34% children and MRA overestimated the degree of stenosis in 25% of children (87).

In summary, non-atherosclerotic arteriopathies are important causes of paediatric stroke. They have been identified in 18 to 53% of children (3, 16, 41, 79). Unilateral focal cerebral arteriopathy, dissection and Moyamoya disease are the most commonly identified subtypes of arteriopathies (80, 81). Stroke in the context of arteriopathy has substantial implications for clinical treatment, concerning ongoing radiological surveillance, and choice of medical or surgical therapies for specific arteriopathy subtypes. While the level of evidence is low, studies are consistent in demonstrating an association between arteriopathies and initial stroke event, and risk of recurrence of childhood arterial ischaemic stroke.

Table 14. Recommendations for investigating arteriopathies

Strong Recommendation
Vascular imaging (MR or CT angiography) of the intracranial and neck vessels is recommended in all children with confirmed arterial ischaemic stroke. Level of evidence (II-IV). References (3, 16, 41, 79-81).
Strong Recommendation
Ongoing radiological surveillance is recommended in children with cervical or cranial arteriopathies, due to the association with increased risk of recurrent events. Level of evidence (II-IV). References (79, 82-86).
Weak Recommendation
Conventional angiography may be considered in cases where diagnostic uncertainties persist following MR or CT angiography. Level of evidence (III). References (87, 88).

Cardiac disease

Congenital heart disease accounts for a significant percentage of childhood strokes (16, 121). In mixed congenital heart disease cohort studies, the incidence of preoperative stroke is reportedly between 10 and 31% (3, 16, 41, 89), with the increased risk postulated to be associated with measures of brain dysmaturation at birth. The ability to diagnose cardiac disorders prenatally, together with advancements in surgical techniques, and observations that stroke events often occur in-hospital, make this cohort an important target for primary prevention.

Congenital heart defects, particularly complex cyanotic lesions, account for the majority of clinically recognised strokes (90, 91). A case control study of 412 children reported a 19-fold increased stroke risk in children aged > 28 days with congenital heart disease. The risk was even greater for children with a history of cardiac surgery although many of these events were unrelated to, or occurred more than five years from surgery (92).

Stroke risk varies by cardiac lesion and procedure. Up to two thirds of events take place in the periprocedural period (90, 91, 99). Cardiac surgery carries a 1:185 to 1:217 risk of symptomatic arterial ischaemic stroke risk (91, 94). Periprocedural stroke risk also varies by diagnostic category, being significantly more common in children with cyanotic congenital heart disease undergoing palliation surgery than children with cyanotic heart disease undergoing biventricular repair or acyanotic heart disease (91). Cardiac catheterisation carries a 1:588 to 1:700 risk of symptomatic arterial ischaemic stroke (91, 96). The relationship between stroke and balloon atrial septostomy, which is performed prior to arterial switch surgery for transposition of the great arteries, is unclear (97, 98).

Atrial septal aneurysms and patent foramen ovale are potential risk factors for cryptogenic stroke in young adults (95) but there are no case control or cohort studies in children, and therefore, their role in causation remains unclear.

In one study independent risk factors for recurrent stroke in 135 children with congenital heart disease of which 27% had recurrent events were identified as the presence of a mechanical valve, prothrombotic condition and infection at the time of stroke (99).

Table 15. Recommendations for additional cardiac investigations

Strong Recommendation
Echocardiography and ECG should be performed in all children with arterial ischaemic stroke. Level of evidence III-IV. References (3, 16, 41, 89-99).
Practice Statement
The role of isolated patent foreman ovale in cryptogenic childhood stroke is unclear but it is reasonable to perform contrast echocardiography with a Valsalva manouevre to detect a paradoxical right to left shunt.
Practice Statement
There is insufficient evidence to determine the superiority of trans-oesophageal echocardiography (TOE) over trans-thoracic echocardiography (TTE) but TOE should be considered if TTE does not allow adequate visualisation of the left atrial appendage.

Iron deficiency

Iron deficiency anaemia is present in up to 40% of childhood arterial ischaemic stroke (89). However, a direct association with stroke has only been investigated in two case control studies to date (105, 106). In the first study from Canada, iron deficiency anaemia, together with thrombocytosis, was significantly more common among stroke patients than controls (53% versus 9% for patients and 47% versus 16% for controls). The association between iron deficiency anaemia and stroke remained significant in a regression analysis, however an interaction with thrombocytosis was not identified. The second study involved 21 childhood stroke cases from Egypt (106). Authors noted iron deficiency anaemia in 57% of cases, and previously healthy children who suffered stroke were 3.8 times more likely to have iron deficiency than control children. In contrast to the first study, there was a significant interaction between iron deficiency and thrombocytosis. Iron deficiency anaemia has a peak prevalence between the ages of one to three years but it is unclear from cohort studies whether the association holds true for older healthy children whom suffer a stroke.

Table 16. Recommendations for iron deficiency investigations

Strong Recommendation
A full blood count and iron studies should be performed in all children with suspected stroke at presentation. Level of evidence (III-IV). References (89, 105, 106).

Prothrombotic disorders

In reviewing the role of prothrombotic disorders causing an initial stroke, two meta-analyses were identified (122, 123). The larger systemic review involved 22 studies and 1,764 children, assessing the impact of thrombophilia on the first stroke episode as a primary outcome. Whilst the findings supported the investigation of thrombophilia markers, their impact on patient outcomes and stroke recurrence remained inconclusive (122).

Collectively, the reviews suggest genetic prothrombotic factors associated with childhood stroke may include Factor V Leiden, prothrombin G20210A, methyl tetrahydrofolate reductase (MTHR), lipoprotein (a) and protein C deficiency. Acquired prothrombotic factors including antiphospholipid antibodies and lupus anticoagulant were also associated with increased risk of stroke. However, antithrombin deficiency and protein S deficiency were not (122, 123). Only two studies were identified which address the role of prothrombotic disorders in recurrent stroke and findings are inconsistent and remain to be fully elucidated (82, 119).

A study examining the role of plasma homocysteine including 24 Thai children with arterial ischaemic stroke and healthy controls found that children with plasma homocysteine above the 95th percentile had an increased odds ratio for developing ischemic stroke (124).

Additional case cohort and control studies have investigated the role of genetic polymorphisms for a variety of factors including TNF-α-308 G>A, VCAM1 c.1238G>c, VWF cleavage protease ADAMTS13, plasminogen activator inhibitor-1, interleukin-6 -174G/C, cytochrome b-245 alpha C242T, glutathione peroxidase, E-selectin 98G>T, protein Z ATG haplotype, glutathione peroxidase promoter, and CTLA-4 and CD28. However, results vary and findings are yet to be replicated in multiple patient populations (107-118).

In summary, the evidence for investigation of genetic and acquired prothrombotic disorders is inconsistent and inconclusive. Reported findings are unfortunately influenced by methodological limitations including lack of concurrent controls, highly selected patient populations and the use of adult reference ranges which do not consider developmental differences in haemostatic factors. Studies also failed to confirm abnormalities on follow-up testing, which is imperative given that fractional assays are reduced in the setting of an acute thrombotic event or administration of anticoagulation.

Table 17. Recommendations for prothrombotic disorder investigations

Weak Recommendation
Investigation of prothrombotic makers (Anticardiolipin Ab(ACLA), lupus anticoagulant, antithrombin, protein C, protein S, activated protein C resistance, Factor V Leiden, prothrombin G20210A and MTHFR TT677 mutations) and serum homocysteine is reasonable in children with radiologically confirmed stroke, where aetiology remains to be fully elucidated. Level of Evidence (I-IV). References (82, 119, 122, 124).
Practice Statement
For children with confirmed stroke who undergo prothrombotic screening in the acute setting, a second screen should be performed sub-acutely, due to fractional assays (antithrombin, protein C, protein S) being reduced in the setting of an acute thrombotic event or related to anticoagulation.
Practice Statement
Investigations for lupus anticoagulant, antithrombin, protein C, protein S, and activated protein C resistance should be conducted before the initiation of anticoagulation.
Practice Statement
Many children have transient ACLA/LAC immediately after stroke. Clinically significant ACLA/LAC should still be present on repeat testing 3-6 months post event.

Infection

Population based case control studies have confirmed that recent infection is associated with an increased risk of stroke. One retrospective population study reported a four-fold increased odds of stroke (100). Further evaluation in the same population confirmed that the strongest association between infection and arterial ischaemic stroke was observed for infectious visits ≤ three days prior to stroke, with respiratory infections accounting for 80% of infections (100).

Varicella infection was first implicated as a risk factor for childhood stroke almost 20 years ago. In one study, seven of 11 children with strokes (64%) had varicella within the nine month period prior to the stroke, compared to four of 44 children (9%) in the control group (104). In another study, 22 of 70 consecutive children with arterial ischaemic stroke had varicella infection in the preceding year compared with 9% published rates of varicella in the healthy population (45). A more recent case series from the United Kingdom used anonymized electronic health records from four primary care databases to identify individuals who had documented clinical chickenpox and stroke or transient ischemic attack (TIA). Five hundred and sixty eligible participants (including 60 children) were identified who experienced chickenpox and a stroke or TIA during follow-up. Among children, there was a four-fold increased risk of stroke in the six months after chickenpox. No increased risk was observed seven-12 months post chickenpox (102).

The role of infections has been prospectively investigated in the VIPS study. This study confirmed that infection in the week prior to stroke was reported in 18% of cases, compared to three percent of controls, conferring a 6.3-fold increased risk of arterial ischaemic stroke, with upper respiratory infections the most common. (101). Equally important was the observation that childhood immunisation was protective against stroke. Among the 187 cases with acute and convalescent blood samples, 85 (45%) showed evidence of acute herpes virus infection; herpes simplex virus 1/2 and varicella (103). Serological evidence of acute herpes group virus infection doubled the odds of childhood stroke, after adjusting for age, race, and socioeconomic status.

In summary, the literature reviewed consistently demonstrates an association between recent infection and childhood arterial ischaemic stroke. Serological evidence of herpes group virus infection, specifically varicella and herpes simplex 1 are associated with increased odds of stroke.

Table 18. Recommendations for infection investigations

Strong Recommendation
A history of recent infection (within the preceding 6 months), particularly varicella infection should be sought in children with suspected or confirmed stroke. Level of evidence (II-III3). References (45, 100-104).
Practice Statement
Serological testing for infectious pathogens is reasonable to consider but the risk benefit ratio of CSF analysis for detection of active infection or treatment with antiviral agents are unclear.

Serum Biomarkers

There is an increasing number of low quality studies investigating serum biomarkers of inflammation and hypercoagulability, and the differences in serum biomarker profiles for specific aetiologies in childhood stroke. In a US study of 50 children with arterial ischaemic stroke, D-dimer and C-reactive protein (CRP) were frequently elevated in acute stroke and decreased over time (125). In another Canadian study, markers of adult stroke (IL-6, IL-10, GM-CSF, IL-1Ra), in addition to novel markers Eotaxin, IL-12p40, IL-15, MIP-1, were found to be elevated (126). A Swiss study investigated 23 different metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs), endothelial factors, vascular cell adhesion proteins and cytokines in 12 children with arterial ischaemic stroke, comparing the results to healthy age matched controls (127). Acute elevations of serum MMP-9, TIMP4, IL-6, IL-8, and CRP were noted in 12 children with arterial ischaemic stroke, compared to seven controls but no time trend was identified with follow up testing (127).

A multicentre study investigating four immune mediators in children, including CRP, serum amyloid A (SAA), myeloperoxidase, and tumour necrosis factor (TNF)-α, found that the cardioembolic stroke group had higher concentrations of C-reactive protein and myeloperoxidase compared to idiopathic group. Both cardioembolic and arteriopathic groups had higher serum amyloid A compared to idiopathic group. In the arteriopathic (but not cardioembolic) group, higher C-reactive protein and serum amyloid A predicted recurrent arterial ischaemic stroke (86).

A British study used immunomagnetic bead extraction and flow cytometry techniques to investigate the role of circulating endothelial cells and microparticles, as markers of endothelial injury, cellular activation, and microparticle-mediated thrombin generation, in a cross-sectional convenience population of 46 children with arteriopathies (128). Circulating endothelial cells and microparticles of endothelial or platelet origin were raised in children with recurrent arterial ischaemic stroke at diagnosis, and remained high over time in a subgroup with follow up data, compared to those with no recurrence and controls.

Microparticle-mediated thrombin generation was enhanced in children with recurrent stroke compared to those with no recurrence, suggesting that a state of chronic endothelial activation and injury, platelet activation and increased MP-mediated thrombin generation, may be determinants of arterial ischaemic stroke recurrence (128). An analysis of the same cohort using flow cytometry, investigated the relationship between the number and function of circulating endothelial progenitor cells, levels of brain-derived neurotrophic factor (BDNF) (which mobilises haematopoietic progenitor cells and promotes revascularisation in ischaemic injury), and arterial ischaemic stroke recurrence. Thirty-five children with arterial ischaemic stroke and cerebral arteriopathy were studied of which 10 had recurrent arterial ischaemic stroke. Circulating endothelial progenitor cell levels were significantly higher in recurrent arterial ischaemic stroke, compared to non-recurrent arterial ischaemic stroke patients and controls but endothelial progenitor cell angiogenic function was significantly reduced. Levels of BDNF were significantly higher in recurrent stroke cases, compared to non-recurrent stroke patients and controls. These findings suggest an endothelial repair response in recurrent arterial ischaemic stroke could be an attempt to mediate vascular repair. Endothelial progenitor cell function was, however, impaired, suggesting the suboptimal response may contribute to childhood arterial ischaemic stroke recurrence (129). Limitations of these studies included the cross-sectional nature, therapeutic heterogeneity across subjects and non-standardised timing of sample collections.

In summary, the evidence for serum biomarkers is limited by small sample sizes, lack of data on reproducibility and limited follow up data. The clinical impact of a positive result, in the absence of other associations such as infection, arteriopathy or cardiac disease, is slight. The usefulness as predictors of a specific stroke aetiology or increased risk of recurrence, cannot be determined.

Table 19. Recommendations for investigation of serum biomarkers

Weak Recommendation	Against
In children with arterial ischaemic stroke measurement of biomarkers CRP, d-dimer and serum amyloid and myeloperoxidase are unlikely to influence management directly. There is insufficient evidence to support testing for more specific serum biomarkers for inflammation, systemic vasculitides or genetic polymorphisms. Level of Evidence (II-III-3). References (125-129).	

7 PRIMARY PAEDIATRIC STROKE CENTRE CARE

Providing optimal and equitable care to all children who suffer a stroke in Australia is a goal with many challenges. For *adults* treated by multidisciplinary teams in a dedicated stroke-unit there is substantial evidence demonstrating benefits on both morbidity and mortality (130). Importantly, these benefits are independent of age, gender, stroke type or severity (130). As a result, various resources have been developed to support the implementation of best practice stroke care for adults, including frameworks for Acute Stroke Services and Performance Indicators and National Clinical Care Standards (131, 132). The 2015 Acute Stroke Clinical Care Standards from the Australian Commission on Safety and Quality in Health Care states that the strong evidence that specialised stroke units, staffed with a multidisciplinary team of stroke specialists, improves patient outcomes and reduces mortality, provides rationale for the recommendation that '*all adult stroke patients should be admitted to hospital and treated by an interdisciplinary team, and 'where presenting to non-stroke unit hospitals patients should be urgently transferred to the nearest stroke unit hospital*' (132). Australian adult stroke units are defined by a minimum set of criteria and services and are categorised into comprehensive stroke centres and primary stroke centres (Table 21, (131)).

There are, however, no data to directly demonstrate the benefit of paediatric stroke units. Upon review of the literature, two studies (63, 64) were found to demonstrate the benefit of an Emergency Department acute code stroke protocols. Collectively these studies show that implementation of emergency "code stroke" protocols for children are associated with i) reduced time to secondary preventative treatment, ii) increased usage of MRI as first imaging modality, iii) shortened delay to completion of MRI imaging, and iv) improved access to hyper acute therapies. Recommendations for the development of "code stroke" protocols are detailed in Chapter 4.

The ACSAC has developed consensus-based recommendations for the elements of service required to certify a hospital as a Primary Paediatric Stroke Centre (PPSC), drawing on key components of adult primary and comprehensive stroke centre. The development of PPSC's across Australia will help elucidate whether children can benefit from care in dedicated stroke units to the same extent as adults. The established adult framework was used as a benchmark with differences between the adult and paediatric centres being clearly outlined. The variations between *adult* primary centres criteria, and those recommended for children, are explained by differences in pathophysiology, presentation, frequency, staffing constraints and international recommendations from leading paediatric stroke institutions. Firstly, access to advanced MRI imaging in all primary childhood stroke centres is imperative due to high rates of false negative arterial ischaemic stroke diagnosis using CT imaging (Chapter 5). Access to, or development of transfer protocols for, neurosurgical care is of importance due to the increased frequency of haemorrhagic stroke in children compared to adults. Access to rapid transient ischaemic attack (TIA) assessment services is deemed of less importance in children as TIAs are less frequent, the adult assessment tools are not validated in children, and neuroimaging via MRI is the gold standard to differentiate between childhood strokes and mimics (Chapter 4). While the efficacy and safety of tissue plasminogen activator (tPA) remains to be fully elucidated, and is not currently approved for use in children (Chapter 9), non-availability of tPA treatment should not currently exclude institutions from qualifying as stroke centres. Access to, and collaboration with, other paediatric services is, however, of great importance given that congenital heart disease and vascular malformations are common aetiologies of childhood stroke. Regular audit activities are of less importance, until paediatric centres begin collecting data in alignment with the Australian Stroke Data Tool.

Table 20. Recommendations for primary paediatric stroke centre care

Strong Recommendation
All children with stroke should be admitted to paediatric centers meeting criteria for a primary paediatric stroke center. Level of Evidence (Adult I) (Paediatric, CBR).
Practice Statement
Where clinically appropriate, transfer protocols should be developed for children presenting to non-primary stroke center institutions, to enable an urgent transfer to certified Primary Paediatric Stroke Centre hospital.
Practice Statement
A key worker (ideally stroke nurse/coordinator) should be appointed as point of contact for family, to provide appropriate information and support, and to ensure data collection for national auditing.

Strong Recommendation

Parents/carers and children should be provided with the appropriate level of stroke literature. Level of Evidence (CBR, IV). References (133, 134).

Table 21. Elements of service for adult and paediatric stroke care centres

Element of service	Comprehensive stroke centre	Primary stroke centre	Primary paediatric stroke centre*
Organised pre-hospital services (includes use of validated screening tools by paramedics, & pre-notification systems).	✓	✓	✗
Coordinated emergency department systems (e.g. code stroke)	✓	✓	✓ / #
Coordinated regional stroke systems (includes protocols for hospital bypass, transfer to stroke centres)	✓	✓	✓ / #
Stroke Unit	✓	✓	✗
Onsite CT brain imaging (24/7)	✓	✓	✓
Carotid imaging	✓	✓	✗
Advanced imaging capability (e.g. MRI/MRA, catheter angiography).	✓	optional	✓ (24/7)
On-site neurosurgical services (e.g. for hemicraniectomy due to large middle cerebral artery infarcts)	✓	optional	✓ / β
Delivery of intravenous tissue plasminogen activator (tPA)	✓ (24/7)	✓	optional
Ability to provide acute monitoring up to 72 hours	✓	✓	✓
Dedicated stroke coordinator position	✓	✓	✓/ γ
Dedicated medical lead	✓ / γ	✓	✓
Access to ICU	✓	✓	✓
Rapid TIA assessment services	✓	✓	✗
Provision of telehealth services for acute assessment and treatment.	✓	optional	optional
Coordination with rehabilitation service providers	✓	✓	✓
Early assessment using standardised tools to determine individual rehabilitation needs and goals.	✓	✓	✗
Routine involvement of carers in rehabilitation process	✓	✓	✓
Routine use of guidelines, care plans and protocols	✓	✓	✓ / #
Regular data collection and stroke specific quality improvement activities	✓	✓	✗
Access and collaboration with other services (cardiology, palliative care, vascular)	✓	optional	optional
Regional responsibility	commonly	optional	commonly
Parent/carer and children provided with appropriate level of literature			✓

Table adapted from National Acute Stroke Services Framework 2015 (131). * Consensus based recommendations on the elements of service relevant to childhood stroke to qualify as a primary paediatric stroke centre. β, if neurosurgical services are not available the institution should have developed transfer protocols; γ, if a stroke coordinator not available institution should have a dedicated medical lead who has a primary focus on stroke (stroke centre director). #, upon successful implementation of recommendations within this guideline.

8 MODIFIABLE FACTORS AND ACUTE STABILISATION

The medical stabilisation of modifiable factors in children with suspected or confirmed stroke aims to minimise brain injury, prevent reoccurrence and optimise neurological outcome. Current practice is primarily based on findings from trials conducted in adults and other critically ill paediatric cohorts. A systematic search of the benefits and harms of several neuroprotective measures retrieved a small number of lower level papers, in contrast to multiple well-conducted clinical trials in adults. The available evidence for managing blood pressure, serum glucose levels, fever, hydration and the use of supplemental oxygen was reviewed to develop recommendations that aim to standardise care, facilitate collaborative research and allow data collection to improve understanding of the modifiable elements that may improve neurological outcome in children with stroke.

8.1 Blood Pressure

Persistently elevated blood pressure (hypertension) in children is commonly defined as an average systolic and/or diastolic blood pressure that is ≥ 95th percentile on at least three separate occasions. Pre-hypertension is classified as ≥90th percentile over three readings (135) (Table 23). Unlike adults, overt stroke in children with hypertension alone is rare.

The acute hypertensive response that commonly occurs post stroke in adults has been associated with increased risk of death and dependency (136). However a large meta-analysis of nearly 13,000 ischaemic stroke patients (137), a Cochrane review of randomised control trials involving more than 17,000 stroke patients (138) and randomised controlled trials of 1,000 patients with acute cerebral haemorrhage consistently showed no benefit to aggressively lowering of blood pressure on death or functional outcome (137-139). The 2017 Stroke Foundation clinical guidelines for adults recommend that all patients with acute stroke should have their blood pressure closely monitored in the first 48 hours after stroke onset. Patients eligible for thrombolysis should have their blood pressure reduced to below 185/110 mmHg before treatment and in the first 24 hours after treatment. Adult patients with acute ischaemic stroke with blood pressure >220/120/mmHg should have their blood pressure cautiously reduced over the first 24 hours. In adults, intensive blood pressure lowering in the acute phase of care is not recommended. Direct extrapolation of these findings to children is inappropriate due to the significant aetiological and age dependent differences in children's cardiovascular and coagulation systems (121, 140). The incidence of acute hypertensive responses in children and the effect of lowering blood pressure on functional outcome remains to be fully elucidated.

In assessing the evidence on blood pressure control in the acute setting of childhood stroke, three retrospective cohort studies were identified (141-143). Brush and colleagues retrospectively analysed a cohort of 90 children diagnosed with ischaemic stroke and found a trend towards increased mortality at 12 months and an increased relative risk of in-hospital death if the child experienced high blood pressure (141). However, in this study, the method and timing of measurements were not controlled, and due to diagnostic delays, some measures may have been taken up to five days post stroke. In contrast, Grelli et al respectively analysed 98 children diagnosed with arterial ischaemic stroke and concluded that hypertension was not associated with infarct size, poor clinical outcome or mortality (142). This cohort was notably different from the normal population with 15% of children already taking antihypertensive agents due to known cardiac disease. Finally, the largest retrospective analysis involving 2,590 children diagnosed with arterial ischaemic stroke, where 156 were reported to have elicited an acute hypertensive response, found that hypertension was associated with increased mortality and length of hospital stay (143). In this cohort, the mean age was considerably older and perhaps the increased frequency of hypertension in children with comorbidities contributed to the significant risk of hospital stay and outcome.

Despite the difficulty of obtaining reliable measures in anxious or distressed children, blood pressure should be monitored to avoid significant hypertension and hypotension, or compromised cerebral perfusion pressure. A significant knowledge gap remains regarding the effect of blood pressure reduction where an acute hypertensive response is measured in children with haemorrhagic stroke.

Table 21. Recommendations for acute blood pressure management

Strong Recommendation
In children with suspected or confirmed stroke, blood pressure should be closely monitored in the acute setting. Level of Evidence (CBR).
Weak Recommendation
In children with suspected or confirmed arterial ischaemic stroke, the reduction of significantly and persistently elevated blood pressure can be considered in the acute setting. Level of Evidence (III). References (141-145).
Practice Statement
In children with suspected or confirmed haemorrhagic stroke, blood pressure reduction can be considered, however benefits remain uncertain.
Practice Statement
If the decision is made to treat hypertension, there should be close and ongoing monitoring of blood pressure with avoidance of long-acting agents and hypotension.

Table 23. Range of blood pressure measurements in infants and children

SBP/DBP (mmHg)				
Age	**Boys**		**Girls**	
	50th*	**95th***	**50th***	**95th***
1	80-89/34-37	98-106/54-58	83-90/38-42	100-107/56-60
2	84-92/39-44	101-110/59-63	85-91/43-47	102-109/61-65
3	86-95/44-48	104-113/63-67	86-93/47-51	104-110/65-69
4	88-97/47-52	106-115/66-71	88-94/50-54	105-112/68-72
5	90-98/50-55	108-116/69-74	89-94/52-56	107-113/70-74
6	91-100/53-57	109-117/72-76	91-98/54-58	108-115/72-76
7	92-101/55-59	110-119/74-78	93-99/55-59	110-116/73-77
8	94-102/56-61	111-120/75-80	95-101/57-60	112-118/75-78
9	95-104/57-62	113-121/76-81	96-103/58-61	114-120/76-79
10	97-106/58-63	115-123/77-82	98-105/59-62	116-122/77-80
11	99-107/59-63	117-125/78-82	100-107/60-63	118-124/78-81
12	101-110/59-64	119-127/78-83	102-109/61-64	119-126/79-82
13	104-112/60-64	121-130/79-83	104-110/62-65	121-128/80-83
14	106-115/60-65	124-132/80-84	106/112-63-66	123-129/81-84
15	109-117/61-66	126-135/81-85	107-113/64-67	124-131/82-85
16	111-120/63-67	129-137/82-87	108-114/64-68	125-132/82-86
17	114-122/65-70	131-140/80-89	108-115/64-68	125-132/82-86
1-3 months	65-85/35-55		65-85/35-55	
3-6 months	70-90/33-65		70-90/33-65	
6-12 months	80-100/40-65		80-100/40-65	

SBP, systolic blood pressure; DBP, diastolic blood pressure; * blood pressure ranging from 5th - 95th percentile of height. The 90th percentile blood pressure is 1.28 standard deviations over the mean. Adapted from the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents (135) and the guidelines for basic paediatric neurological observation (146).

8.2 Glucose

Both hyper- and hypoglycaemia can adversely affect the developing brain. Hyperglycaemia in children is commonly defined as two consecutive readings of blood glucose greater than 7.8 to 8.3 mmol/l. In adults, a high proportion of stroke patients present with hyperglycaemia, even in the absence of pre-existing diabetes. Hyperglycaemia is associated with poorer outcome in adults but there is a large body of evidence showing increased complication rates and no clear benefit from intensive or tight glycaemic control with intravenous insulin in the acute setting (147, 148). In assessing the effect of glycaemic control and outcome in children with acute stroke, only one paper was identified. To facilitate the development of recommendations relevant articles in children with traumatic brain injury and other critical illness were therefore reviewed (142, 149-154).

In a retrospective analysis of 98 children diagnosed with arterial ischaemic stroke by (142), blood glucose levels were collected on 94 children from admission to day five of their hospital stay. Hyperglycaemia, defined as > 200mg/dL, was recorded in 17 children of which three received insulin therapy. Three other children recorded hypoglycaemic levels (<60mg/dL), however it is unknown if children were fasting at the time of measurement. Despite the lack of information around fasting, authors identified hyperglycaemia as an independent predictor of poorer outcome at six months (142).

Results of randomised controlled trials conducted in paediatric intensive care units show no clear benefit or harm of tight glycaemic control. A randomised trial involving 1,369 paediatric intensive care patients showed no significant effect on the primary clinical outcomes between patients randomised to tight versus conventional glycaemic control (154). In contrast, a trial assessing the harm of hypo- and hyperglycaemia on neurocognitive outcome, found that tight glycaemic control to age appropriate normoglycaemic levels did not worsen cognitive outcome in 569 paediatric intensive care patients followed up at four years, despite being associated with increased incidence of hypoglycaemia (150).

Hyperglycaemia defined as > 120 or 180 mg/dL has been associated with increased morbidity over the short term in critically ill children with meningococcal sepsis (149). Furthermore, in children with traumatic brain injury, hyperglycaemia has been associated with poorer outcome when it persists beyond the initial 48 hours (152), and when measured perioperatively in those undergoing urgent craniotomy (151). Finally, a retrospective cohort analysis of 271 children admitted to intensive care units with traumatic brain injury found that only severe blood glucose elevation (>200mg/dL) was associated with increased risk of poorer outcome measured by the Glasgow Outcome Score (153).

Table 24. Recommendations for acute glucose management

Strong Recommendation
In all children with suspected or confirmed stroke, blood glucose levels should be closely monitored in the acute setting. Level of Evidence (CBR).
Weak Recommendation
In all children with suspected or confirmed arterial ischaemic stroke, targeting a normal blood glucose can be considered. Level of Evidence (II). References (142, 149-153, 155, 156).
Weak Recommendation
In all children with suspected or confirmed haemorrhagic stroke, targeting a normal blood glucose can be considered, however the benefits remain uncertain. Level of Evidence (CBR).
Weak Recommendation
If the decision is made to treat, an intensive approach to the maintenance of tight glycaemic control is not recommended. Level of Evidence (CBR). Supporting reference (154).

8.3 Temperature

Fever, defined as body temperature greater than 37.5 degrees Celsius, can be an important indicator of infection or developing sepsis, is commonly reported in children presenting with acute stroke. The absolute benefit over any harm for treating fever with paracetamol has been demonstrated in adult stroke (157, 158), and while the use of paracetamol in children to control fever is safe and commonly prescribed, short or long-term neurological benefits from controlling fever in children with stroke remain to be elucidated.

In Grelli's cohort analysis of 98 children diagnosed with arterial ischaemic stroke 37 had a fever within the first five days post stroke (of which 95% were treated), but no association was found between fever and neurological outcome at three months (142). No other studies were found to address fever in relation to neurological outcome in children with acute stroke.

There are of course good biological reasons and supporting evidence in other paediatric cohorts to suggest fever may adversely affect neurological outcome after injury. Hyperthermia leads to a hypermetabolic state where the demand for oxygen and glucose is increased. In the setting of ischaemic stroke, where substrate delivery is impaired, fever can intensify this imbalance, which may lead to further injury. Evidence for tight fever control and therapeutic cooling is conflicting in other paediatric cohorts. In children with traumatic brain injury fever has been associated with longer hospital stays in children (159), however, therapeutic hypothermia has not been shown to improve neurological outcomes above tight fever control (160). In contrast, the benefit of therapeutic hypothermia is well established in neonates with hypoxic ischaemic encephalopathy. The relevance of these findings to children with stroke remains unknown. A prospective study of 15 neonates diagnosed with encephalopathy and perinatal stroke found that none of the neonates treated with hypothermia (n=5) experienced seizures, compared with those not therapeutically cooled (161). As prolonged and recurrent seizures are associated with worse cognitive outcomes in children with stroke, this small study lends support to trials aimed at investigating the benefits of therapeutic hypothermia in paediatric stroke.

Table 25. Recommendations for acute fever management

Strong Recommendation
In all children with suspected or confirmed stroke temperature should be closely monitored in the acute setting. Level of Evidence (CBR).
Weak Recommendation
In all children with suspected or confirmed stroke, targeting a temperature less than or equal to 37.5 degrees via administration of paracetamol is recommended. Level of Evidence (III). References (142, 162).
Practice Statement
Use of paracetamol in the setting of acute stroke is perceived to be low risk.
Practice Statement
The efficacy of therapeutic hypothermia in children with stroke has not been elucidated and it should not be administered outside clinical trials.

8.4 Oxygen supplementation

The theoretical rationale for administration of supplemental oxygen following head injury or stroke is to minimise secondary injury by raising the oxygen tension in an hypoxic brain, improve mitochondrial function and limit infarct size (163). However, if the patient is not hypoxic, it is biologically plausible that hyperoxia may increase the formation of oxygen free radicals, induce cerebral vasoconstriction and reduce cerebral blood flow. Thus, the routine practice of administrating oxygen to non-hypoxic patients with stroke is questionable with regard to effects on functional outcome and mortality.

In adult studies, routine oxygen supplementation has not been associated with reduced disability of mortality, or shown to significantly improve neurological outcomes in patients that are not hypoxic (164-166). No studies addressing outcome differences in children with stroke, with or without oxygen supplementation, were identified. Evaluation of efficacy for oxygen supplementation in children with stroke should be a research priority.

Table 26. Recommendations for oxygen supplementation

Strong Recommendation	
In all children with suspected or confirmed stroke oxygen levels should be closely monitored in the acute setting. Level of Evidence (CBR).	
Weak Recommendation	**Against**
In all children with suspected or confirmed stroke, oxygen supplementation is not recommended unless monitoring demonstrates hypoxia (≤ 93%). Level of Evidence (III). References (Adult (164-167)).	
Practice Statement	
Supplemental oxygen is considered reasonable in hypoxic children, however evidence is of low quality and quantity with the effect on functional outcomes uncertain.	

8.5 Hydration

Dehydration results in elevated plasma osmolality levels and decreased cerebral perfusion pressure, which may lead to increased risk of abnormal blood clotting and stroke. Patients with known cerebral arteriopathies (e.g. Moyamoya disease) are counselled to avoid dehydration, however, clinical trials investigating the effect of dehydration and administration of fluids in childhood stroke is lacking and should be a research priority. In adults, a retrospective analysis of over 3000 patients found dehydration was associated with worse modified Rankin Scale (higher rates of neurological impairment) upon discharge in cases with ischaemic stroke, but not with haemorrhagic stroke (168). No comparable studies in children were identified.

Table 27. Recommendations for fluid administration

Strong Recommendation
In all children with suspected or confirmed stroke hydration status should be closely monitored in the acute setting. Level of Evidence (CBR).
Weak Recommendation
In children with suspected or confirmed stroke and dehydration, optimisation of hydration status is reasonable. Level of Evidence (III-2). References (Adult (168)).
Practice Statement
In children with suspected or diagnosed stroke, nothing should be administered orally until swallowing status is assessed.

8.6 Seizures

Seizures are a common clinical presentation of childhood stroke. The relative risk of seizures in acute childhood stroke is 18 fold higher compared to adults (46). Seizures can occur acutely as a symptom of stroke, in the early, or late post stroke (remote) periods. Seizures are more frequent in children compared to adults with stroke, and more frequent again in younger compared to older children.

There is an increasing body of consistent literature demonstrating the harmful effects of stroke associated seizures on short and long-term outcomes. In 2012, Singh et al published a cohort analysis of 77 children with stroke and found that five of 21 children who presented with acute seizures went on to develop remote seizures, compared to none of the 44 that presented without an acute seizure (48). The association between acute seizures and subsequent development of remote seizures, is further supported by cohort analyses from the Kaiser Permanente (169) and the International Pediatric Stroke studies (170). Of the 305 children analysed from the Kaiser Pediatric Stroke Study, 27% who experienced acute seizures were younger and four times more likely to have a remote seizure over a four year follow-up period (169). Acute seizures were a strong independent predictor of late onset seizures and active epilepsy, with acute seizures having a 25% cumulative risk of active epilepsy. In 2016, data on 114 children in the IPSS registry showed that younger children were at significantly higher risk of acute seizures and epilepsy after stroke. At one year, 10% of children were being treated for epilepsy. This study importantly demonstrated a 30-fold increase in the risk of epilepsy in children that experienced prolonged or recurrent acute seizures (170).

Prolonged seizures have been also associated with the onset of malignant middle cerebral artery infarction (MMCAI) which is the most common cause of acute stroke specific mortality in adults. MMCAI is heralded by rapid neurological deterioration, usually with within 72 hours of stroke onset, due to the space occupying effect of cerebral oedema. In 66 children diagnosed with acute stroke at one centre, prolonged seizures during the first 24 hours was a significant independent predictor of MMCAI (171). All 12 children that developed MMCAI aged over two years had initial seizures longer than five minutes in duration.

Other studies have confirmed the harmful effect of seizures in childhood stroke. The Swiss Neuropediatric Stroke Registry showed significantly lower overall cognitive outcomes, as measured by the modified Rankin Scale, in a subgroup of 99 children with arterial ischaemic stroke who experienced acute and persistent seizures (172). In another cohort of arterial ischaemic stroke patients, 25%-41% experienced seizures with seizures more frequently in younger children, and were associated with the development of remote seizures and increased risk of epilepsy (173, 174). Finally, epilepsy has been reported in 13% of children with spontaneous intracerebral haemorrhage after a follow-up period of two years. In this cohort elevated intracranial pressure requiring acute intervention was identified as a significant risk factor for seizures and onset of epilepsy (175).

In summary, children that present with acute seizures have an increased risk of developing remote seizures and epilepsy. This risk is significantly increased in younger children and with recurrent or prolonged seizures. Collectively, studies show a deleterious effect on outcome following stroke and support treatment in the setting of prolonged or recurrent seizures. Identification of clinically silent seizures requires continuous electroencephalogram monitoring, however the implementation may not be feasible in many institutions. Furthermore, the prevalence and consequences of electrographic versus electroclinical seizures is unknown. In comatose children (aged two months to 17 years) admitted to paediatric intensive care unit subclinical seizures were found to be very uncommon (176).

Table 28. Recommendations for acute seizure management

Weak Recommendation
In all children with suspected or confirmed stroke, recurrent or prolonged symptomatic seizures should be treated with anticonvulsant medication in the acute setting. Level of Evidence (III-2 III-3). References (46-48, 169-172, 174, 175).
Practice Statement
In the setting of acute stroke and symptomatic seizures, use of relatively non-sedating intravenous / oral anticonvulsants such as Levetiracetam or Phenytoin, is perceived to be low risk.
Practice Statement
Seizure recurrence in the setting of acute stroke may herald stroke extension, cerebral oedema or haemorrhagic transformation and should therefore prompt urgent neurological review.

Acute stabilisation of modifiable factors in childhood suspected of or diagnosed with stroke

- Nothing by mouth (until swallowing status assessed)
- Identify and treat prolonged or recurrent seizures
- Optimise cerebral perfusion by maintaining good blood pressure
- Correct dehydration to maintain circulation volumes
- Maintain normal range of blood sugar levels
- Treat fever and infection

9 REPERFUSION THERAPIES

Intravenous and endovascular thrombolytic therapies have revolutionised the management of ischaemic stroke in adults, reducing the severity of disability and mortality rates. For adults, the recommendations for eligibility and efficacy of interventions are based on multiple large randomised controlled trials. There are no such trials in children. Furthermore, the significant pathophysiological differences between paediatric and adult stroke preclude direct extrapolation of these recommendations to children. Due to the absence of randomised evidence for benefit, thrombolytic agents are not approved by the Therapeutic Goods Administration for use in Australian children with acute ischaemic stroke. Despite this, there are a growing number of international publications reporting use of these interventions. Thus, there is a strong impetus for development of primary paediatric stroke centres, and formulation of paediatric protocols with clear guidelines around eligibility and exclusion criteria, to allow some children to access off-label treatment, whilst minimising risk of complications.

9.1 Intravenous tissue plasminogen activator

Recombinant tissue plasminogen activators (tPA) bind to fibrin within a thrombus and convert plasminogen to plasmin which leads to local fibrinolysis. A systematic review of 27 trials, involving 10,187 adults has shown that tPA use is associated with reductions in disability and mortality (177). This and other large randomised controlled trials underpin the licencing of intravenous (IV)-tPA in adults presenting with acute ischaemic stroke within 4.5 hours of symptom symptoms (178). To date, there are no published randomised controlled trials for use of IV-tPA in children, and its effectiveness and safety remain to be fully elucidated. Despite evidence of benefit over risk in adults, many factors make extrapolation of these results to children inappropriate, including differences in pathophysiology, aetiology, developmental differences in the fibrinolytic system (such as lower endogenous plasminogen levels and higher plasminogen activator inhibitor-1 (PAI-1) levels (179) (180)), and the differences in cerebral blood flow which may mean that different tPA doses are required for clot lysis in children.

In 2006, the Stroke Progress Review Group, commissioned by the National Institute of Neurological Disorders and Stroke concluded that there was an urgent need for safety and efficacy data for therapies in paediatric stroke. As a result, the National Institutes of Health funded the Thrombolysis in Pediatric Stroke (TIPS) study, a five-year multicentre international phase II dosage finding and safety study of tPA in children. The study aimed to determine the maximal safe dose of intravenous tPA among three doses (0.75. 0.9, 1.0 mg/kg), administered within 4.5 hours from onset of acute arterial ischaemic stroke, in children aged two to 17 years (181). End points were symptomatic intracranial haemorrhage at 36 hours, neurological outcome at three months, and determination of pharmacokinetic properties of tPA in children. Recruitment commenced in October 2012 but the National Institutes of Health closed the trial in December 2013 due to lack of patient accrual. Ninety-three children were screened as potential candidates for tPA, forty-three (46%) of whom had confirmed stroke. Of these, (i) 21 had contraindications to treatment, (ii) five had a PedNIHSS score <6, (iii) 10 were radiologically-confirmed diagnoses beyond the 4.5-hour time window, (iv) two did not have angiographic evidence of vascular occlusion, (v) two had sickle cell disease, (vi) one arrived within the time window but failed anaesthesia, and (vii) one missed the time window by 15 minutes because of scanning delay (182).

The long delays to diagnosis of childhood stroke, increased frequency of stroke mimics, reduced access to urgent neuroimaging, and lack of dedicated stroke care teams within paediatric centres all contribute to childhood stroke often being diagnosed outside the time window for IV-tPA. Delay to stroke diagnosis is probably the most important factor limiting access to reperfusion interventions. A retrospective population study from Greater Cincinnati/Northern Kentucky assessed tPA eligibility in 29 children (183). Only one child (3% of the total) was eligible for thrombolysis. Three of the 29 children presented within 3.5 hours, but two had relative contraindications to tPA (based on adult criteria). These findings however, need to be interpreted with caution because the investigators assumed that radiological confirmation of diagnosis would occur within 60 minutes. The reality is that paediatric studies show there are much longer delays to diagnostic imaging in routine clinical practice (Chapter 4). A study from the United Kingdom found that none of 107 patients seen at a paediatric hospital were eligible for thrombolysis (184) with the main barriers being delayed diagnosis, delayed transfer to the tertiary centre, age and medical comorbidities. However, this study site did not adhere to predefined consensus criteria for thrombolysis proposed by the International Paediatric Stroke Study group limiting the validity of the conclusions.

Despite unknown efficacy, two guidelines have provided recommendations for use of tPA in children with stroke (78, 185). The American College of Chest Physicians Guidelines recommend against tPA outside a clinical trial (Grade 1B: risk clearly outweighs benefit). The American Heart Association guidelines state that “until there are additional published safety and efficacy data, tPA generally is not recommended for children with arterial ischaemic stroke outside a clinical trial (Class III: evidence or general agreement that the procedure or treatment is not useful/effective and in some cases, may be harmful, Level of Evidence C: Consensus opinion of experts) (78). However, there was no consensus about the use of tPA in older adolescents who otherwise meet standard adult tPA eligibility criteria and neither guideline provides recommendations for endovascular therapies.

9.1.1 Use of IV-tPA in children with stroke

Despite the variation in recommendations and lack of high-quality evidence, children are being treated with IV-tPA. The US Nationwide Inpatient Sample captured data from 995 hospitals in the United States found that 1.6% of 2,904 paediatric stroke cases were treated with tPA between 2000 and 2003 (186). No treatment complications were reported, but the cost of hospital stay, inpatient mortality and dependency at discharge were higher in children who received tPA. The study was unfortunately unable to assess factors influencing tPA administration (186). Another U.S. study searched the National Kids Inpatient Database from 1998-2009 and found only 0.7% of children (67 from 9,257) with acute arterial ischaemic stroke had received tPA (187). In this cohort, the overall rates of thrombolysis per three-year interval increased from 5.2 per 1000, to 9.7 per 1000, with the increase mainly being seen in non-paediatric hospitals. Thrombolysis treated children were significantly older with longer hospital stays (11 versus six days), and an adjusted analysis showed that higher hospital mortality was predicted by intracerebral haemorrhage, hypertension, and heart failure but not by thrombolysis (187).

A review of centres contributing data to the International Pediatric Stroke Registry, found that 2% (15 from 687) children received tPA (9 intravenous and six intra-arterial) but that treatment often failed to comply with recommended adult guidelines. Time to administration ranged from two to 52 hours for intravenous, and 3.8 to 24 hours for intra-arterial tPA (188). Only seven were treated within a 4.5-hour time window. Symptomatic intracranial haemorrhage occurred in 26% of patients, much higher than the 7% bleeding rates reported in adult trials. Two children died and only one of the 13 remaining survivors was neurologically normal at discharge. When results were compared to ten cases previously described in the literature, children in the registry were significantly younger, treatment was more often delayed, and outcome was poorer, suggesting a previous publication bias towards cases with shorter treatment lag and better outcomes (188). Finally, one paper presented outcomes from a cohort of 24 children with basilar artery strokes, including 11 with basilar artery occlusion (189). All were managed with “conservative” medical treatments, defined as aspirin or anticoagulation or no thrombotic treatment. Half were reported normal or suffering mild deficits at follow-up. The authors concluded that neurointervention may not be justified in the paediatric population because there were no deaths with conservative medical management, and outcomes appeared to be better than those reported in adults. There was however no direct comparison group in this study.

A systematic review of the literature from 1994 to 2016 identified a total of 28 cases of paediatric arterial ischaemic stroke treated with IV-tPA alone. The literature included individual case studies and cases within a review of subjects recruited to the International Pediatric Stroke Study (Table 37, Appendix 1). In the 28 children treated with IV tPA alone, 13 strokes were due to cardioembolism. Nineteen (68%) children were treated within a 4.5-hour time window and pedNIHSS was > four in all seven children where data were provided (Table 37, Appendix 1). IV-tPA dosage was 0.9mg/kg in 13 patients, less than 0.9mg/kg in four patients, and details were not provided in the remainder. In cases treated within the 4.5-hour time window recommended for adults, two were neurologically normal, nine had mild deficits, six had moderate or severe deficits at variable time points following treatment, and no information was provided in three children. Two children developed intracranial haemorrhage.

The inconsistencies and variations in reporting baseline stroke severity, aetiology, time to treatment, neuroimaging findings, outcomes (with most failing to used validated measures), and adverse events preclude the identification of clear quantifiable metrics for a cohort of children that may benefit from thrombolysis. These limitations reiterate the need for a national registry to collect standardised datasets to aid selection of children that will benefit.

Table 29. Recommendations for the use of IV-tPA in childhood stroke

Weak Recommendation
IV-tPA may be appropriate in specific children. Consensus on potential eligibility criteria include: (i) two to 17 years of age, (ii) radiologically confirmed arterial stroke with absence of haemorrhage, (iii) paediatric stroke severity score ≥ 4 and ≤ 24, and (iv) treatment can be administrated within 4.5hrs from known symptom onset. However, the absence of high-quality evidence means that benefit over harm to these children cannot be accurately assessed, Level of Evidence (III, IV). References (181, 188, 190-208) (Table 37).
Strong Recommendation / **Against**
Administration of IV-tPA in children with confirmed stroke should not be considered where the time from symptom onset is unknown or greater than 4.5 hours. Level of evidence (I-III). References (177, 181, 188).
Weak Recommendation
Where administration of IV-tPA is being considered for children with stroke, eligibility and protocols should align with previously developed international consensus based standards, and adult protocols where appropriate (e.g.in teenagers 13-18 years). Level of Evidence (CBR). Supporting references (182), Table 30.
Practice Statement
Where administration of IV-tPA is being considered for children with stroke, an experienced team of neuro-interventionalists, haematologists and neurologists within a Primary Paediatric Stroke Centre or Comprehensive Adult Stroke Centre should be involved. Professionals should take a cautious approach, appreciating that the safety and efficacy in children remains to be elucidated.

Table 30. Eligibility and protocol when considering use of IV-tPA in children with stroke

Criteria	Inclusion
Age	• 2 to 17 years of age.
Acute arterial ischaemic stroke	• Stroke radiologically confirmed by; (a) MR showing acute stroke on diffusion imaging plus MRA showing arterial partial or complete arterial occlusion of the corresponding intracranial artery OR (b) CT and CT angiogram confirmation showing a normal brain parenchyma or minimal early ischemic change plus partial or complete arterial occlusion of the corresponding intracranial artery. (c) No evidence of any intracranial haemorrhage.
PedNIHSS	• ≥ 4 and ≤ 24.
Time	• Treatment can be administered within 4.5 of stroke onset.
Co-morbidities	• Children with seizure at onset may be included as long as they fulfil the criteria above.
Additional exclusion criteria	
Safety related exclusions	• Unknown time of symptom onset. • Pregnancy. • Clinical presentation suggestive of subarachnoid haemorrhage, even if head CT or head MRI scan is negative for blood. • Patient who would decline blood transfusion if indicated. • History of prior intracranial haemorrhage. • Known cerebral arterial venous malformation, aneurysm, or neoplasm. • Persistent SBP > 15% above the 95th percentile for age while sitting or supine. • Glucose < 50 mg/dl (2.78 mmol/l) or > 400 mg/dl (22.22 mmol/l). • Bleeding diathesis including platelets < 100,000, PT > 15 sec (INR > 1.4) or elevated PTT > upper limits of the normal range. • Clinical presentation is consistent with acute myocardial infarction (MI) or post-MI pericarditis that requires evaluation by cardiology prior to treatment. • Stroke, major head trauma, or intracranial surgery within the past 3 months. • Major surgery or parenchymal biopsy within 10 days. • Gastrointestinal or urinary bleeding within 21 days. • Arterial puncture at noncompressible site or lumbar puncture within 7 days. Patients with cardiac catheterization via a compressible artery are not excluded. • Patient with malignancy or within one month of completion of treatment for cancer. • Patients with an underlying significant bleeding disorder. Patients with a mild platelet dysfunction, mild von Willebrand Disease or other mild bleeding disorders are not excluded.
Stroke related exclusions	• Mild deficit (PedNIHSS < 4) at start of tPA infusion. • Severe deficit suggesting very large territory stroke, with pre-tPA PedNIHSS > 24, regardless of the infarct volume seen on neuroimaging. • Stroke suspected to be due to subacute bacterial endocarditis, MoyaMoya, sickle cell disease, meningitis, bone marrow, air or fat embolism. • Previously diagnosed primary angiitis of the central nervous system or secondary CNS vasculitis. Focal cerebral arteriopathy of childhood is not a contraindication.
Neuro-imaging related exclusions	• Intracranial haemorrhage (HI-1, HI-2, PH-1 or PH-2) on MRI or CT. • Intracranial dissection (defined as at or distal to the ophthalmic artery). • Large infarct volume, defined 1/3 or more of the complete MCA territory involvement diagnosed by MRI, due to increased risk of ICP.
Drug Related exclusions	• Known allergy to recombinant tissue plasminogen activator. • Patient on anticoagulation therapy must have INR ≤ 1.4. • Patient who received heparin within 4 hours must have aPTT in normal range. • LMWH within past 24 hours (aPTT and INR will not reflect LMWH effect).
Protocol	
	• Maximum dose reached at 90 kg body weight. • IV tPA dose to be given over one hour; ten percent of the total dose as a bolus over 1 minutes with the remaining 90% over the subsequent 59 minutes.

Adapted from Thrombolysis in Pediatric Stroke (TIPS) study (182). A more detailed protocol for administration can be found in supplementary files (182). MR, magnetic resonance; MRA, magnetic resonance angiography; CT, computerised tomography; SBP, systolic blood pressure; INR, international normalized ratio; PTT, prothrombin time; MI, myocardial infarction; PedNIHSS, paediatric version of the NIH Stroke Scale; tPA, tissue-type plasminogen activator; CNS, central nervous system; PH, parenchymal haemorrhage; IH, intracranial haemorrhage; MCA, middle cerebral artery; ICP, intracranial pressure; LMWH, low-molecular-weight heparin; aPTT indicates activated partial thromboplastin time.

Quantitative metrics guiding patient selection for IV-tPA in children diagnosed with stroke

- **Age of child**
- **Time since onset of symptoms**
- **Stroke location and severity**
- **Underlying pathophysiology**
- **Neuroimaging findings**

9.2 Endovascular therapy

The objective of endovascular therapy in arterial ischaemic stroke is prompt recanalisation of occluded vessels and the restoration of cerebral blood flow. Stroke patients who present outside the time frame, or have contraindications to IV-tPA may benefit from endovascular therapy, which in this section refers to IA-pharmacological thrombolysis or mechanical thrombolysis/thrombectomy using endovascular devices.

Endovascular therapy in adults

Five randomised open-label placebo-controlled endovascular trials with almost 1,300 patients, using newer generation clot retrieval devices, have been published since December 2014 (209-214). All studies used imaging to select patients with anterior circulation large vessel occlusions and small ischaemic cores, who were most likely to benefit from endovascular treatment. Treatment was given within a six to 12-hour time window from symptom onset. The primary outcome was functional status, as defined by the modified Rankin score at 90 days, in all but one study (210). The studies showed consistent treatment benefit across all primary and secondary clinical outcomes with a 14% to 31% difference in achieving a good functional outcome between the interventional and control groups. The number needed to treat to achieve one additional good outcome is from three to five patients (210, 215). There were no significant differences in rates of adverse outcomes of death or symptomatic haemorrhage. There were also consistent findings in favour of treatment for imaging outcome measures including reperfusion and recanalization. Thus, there is strong evidence underpinning recommendations for endovascular thrombectomy within six hours of stroke onset in adults (216).

Endovascular therapy in children

There are no published clinical trials of endovascular therapy in childhood stroke, and the efficacy and safety of treatment in adults cannot be directly extrapolated to children due to a range of factors discussed previously. Despite this, the 2015 American guidelines for endovascular treatment provide a recommendation for the use of endovascular treatments in children (217). The consensus based recommendation states that *endovascular therapy with stent retrievers may be reasonable for some patients <18 years of age with acute ischemic stroke who have demonstrated large-vessel occlusion, in whom treatment can be initiated (groin puncture) within six hours of symptom onset, noting that the benefits are not established in this age group* (217). This consensus-based recommendation is likely influenced by the growing number of published case studies in children, often beyond the recommended time window for adults (Table 37, Appendix 1).

In 2017 a review of the Kids' Inpatient Database in the US identified 38 children that underwent endovascular therapy from a total of 3,184 children diagnosed with arterial ischaemic stroke (218). Endovascular therapy was defined as endovascular thrombectomy or embolectomy procedures. The analysis revealed that treated children were significantly older and more commonly had existing cardiac comorbidities. Administration of tPA was significantly more common in the endovascular treatment group, which is expected given the similarities in eligibility criteria for both interventions. Interestingly, endovascular therapy was not associated with increased critical care usage or neurosurgical intervention compared to children with stroke not treated. There was however, a trend towards increased intracranial haemorrhage, but perhaps due to small numbers, this did not reach statistical significance. Whether endovascular therapy was performed within the suggested time window was not reported. Importantly, a multivariate analysis, adjusted for age, found no difference in length of hospital stay or mortality rate between those not treated with endovascular therapy and those receiving the procedure (218).

In reviewing the case study literature, there is also support for the safety of endovascular therapy in children. This 'evidence' for safety should however be interpreted with caution due to the high level of bias associated with published case studies. It is plausible that children undergoing of interventional procedures with less favourable outcomes have not been published.

A total of 32 cases of paediatric arterial ischaemic stroke treated with endovascular therapies were identified, including individually published case studies and cases within a review (219) (Table 37, Appendix 1). Thirteen children were treated with IA-tPA; six were treated beyond 4.5 hours, including two with basilar artery occlusion. Outcomes were reported in 11 from 13 patients, with two reported as normal, and three citing intracerebral haemorrhage (Table 37, Appendix 1).

Thirty-two children were treated with mechanical clot retrieval, either alone (n=22), or in combination with (i) IV-tPA following (n=5), (ii) IA-tPA (n=3), or (iii) IA urokinase (n=2 children). One third of the cohort reported cardioembolic stroke as the mechanism, with all cases having evidence of vessel occlusion or thrombosis pre-treatment. Importantly, only 13 from 32 children (41%) were treated within the six-hour time window recommended for adults. There were similar proportions of children with basilar thrombosis in cases treated within and beyond six hours. Complete procedures (n=17) or partial procedures (n=8) resulted in recanalisation in the majority of cases. Fourteen (44%) reported normal outcomes, with vasospasm occurring in two children and wire migration in another child. Three children suffered intracerebral haemorrhage and one child required a posterior fossa craniectomy for oedema (Table 37, Appendix 1).

In summary, a total 67 studies on endovascular therapy were reviewed, including one case control study, and case reports for 82 children. The case report data has considerable variation in time to treatment, recanalisation rates and outcomes. Treatments administered included (i) IV-tPA alone in 28 children, (ii) IA-tPA alone in 13 children, (iii) IA-urokinase alone in eight, or (iii) IA-streptokinase alone in one child, (iv) endovascular therapy with mechanical clot retrieval alone in 22 children, or in combination with (v) IV-tPA (n=5), (vi) IA-tPA (n=3), or (vii) IA-urokinase (n=2) children (Table 37, Appendix 1).

The median age of treated children was 10±5 years. The youngest patient was 2.5 months, only 11 (13%) were less than < five years and 31 (38%) were less than 10 years of age. Circulations affected included anterior circulation in 49, posterior circulation in 27, both circulations in two, and not stated three children. Cardiac embolism was the most commonly identified stroke mechanism, in 34 (42%) children, followed by dissection in 10, other arteriopathy in four or not specified arteriopathy in 3, other risk factors in 6, unknown mechanism in 24, and no information was provided for 1 child. Standardised measures of pre-intervention stroke severity were not provided for 42 children. Modified Rankin Score was reported in two children, and PedNIHSS ranged from two to 36 in a further 37 children; only one child had a PedNIHSS < four (Table 37, Appendix 1).

The effect of interventions is difficult to interpret due to variations in reporting of a) baseline data, b) outcomes at follow-up, and c) description or severity of deficits. A standardised clinical assessment measure was used in 37 (45%) of cases but some used the Modified Rankin scale, which is not validated for children. In total, 16 (20%) were normal at discharge. Three children died. Treatment complications included intracranial haemorrhage in five children, malignant cerebral oedema occurred in one child, requiring decompressive craniotomy, vasospasm occurred in two children and the wire broke and migrated in one child.

In summary, the evidence for use of IA- tPA and endovascular therapy in childhood arterial ischaemic stroke is inconsistent largely due to heterogeneity in stroke mechanism aetiology, age, time to treatment, stroke severity, imaging findings (infarct characteristics and vessel status), and reports of outcomes and adverse events. In particular, many case reports fail to standardise measures of stroke severity (the pedNIHSS) and outcome (the Modified Rankin Scale or Pediatric Stroke Outcome Measure). As for IV thrombolysis, there is a high likelihood of publication bias. These factors, in combination with a lack of clinical trials prevent clear conclusions on the safety and efficacy for all children presenting with stroke.

Congenital cardiac disease is a known risk factor for childhood stroke (Chapters 6 and 12). Given that one third of cases reviewed here were of cardiac origin, together with the rising number of complex of cardiac procedures being performed in Australia, research should also focus on the potential role of neuro-interventions in the paediatric cardiac population.

Table 31. Recommendations for use the of endovascular therapy in childhood stroke

Weak Recommendation	
Endovascular therapies may be appropriate in some children meeting adult eligibility criteria, defined as radiologically diagnosed ischaemic stroke caused by large vessel occlusion and where treatment can be initiated within six hours since onset of stroke symptoms. The absence of high quality paediatric evidence, together with differences in underlying pathophysiology means that benefit over harm for children cannot be accurately assessed. Level of Evidence (III-2, IV). References (218, 220-241).	
Practice Statement	
Where endovascular mechanical thrombolytic interventions are being performed in children, professionals should consider the uncertainty around potential for injury to intimal and medial vessel walls with the use of large catheters and stent retrievers, and the differences in underlying pathophysiology.	
Strong Recommendation	**Against**
In children with stroke where time of onset of symptoms is unknown or greater than six hours, adult evidence suggests that endovascular therapy inclusive of IA-tPA and mechanical clot retrieval should not be considered. Level of Evidence (Adult II). References (209-214).	

* Endovascular thrombectomy should be performed by an experienced neurointerventionist with recognised training in the procedure (Conjoint Committee for Recognition of Training in Interventional Neuroradiology CCINR.org.au).

10 ANTI-THROMBOTIC THERAPY

Anti-thrombotic therapy aims to prevent recurrence and progression of arterial ischaemic stroke, but the use of these drugs in children differs from that in adults. Differences in the epidemiology of thromboembolism, the dynamic haemostatic system in growing children, differences in drug clearance capabilities, difficulties attaining vascular access for delivery and age-related variations in stroke recurrence, limit the applicability of adult evidence to children. The most recent clinical guidelines, American College of Chest Physicians Clinical Guidelines on Antithrombotic Therapy in Neonates and Children, published in 2012, present specific recommendations for CVST, Moyamoya syndrome, arterial ischaemic stroke (185). Here we review new evidence published since 2012 and provide recommendations for the timing and use of anticoagulation, antiplatelet and steroid therapy in children with radiologically confirmed ischaemic stroke.

10.1 Anticoagulation and antiplatelet therapy

In adults, there is high-level evidence to support recommendations for antiplatelet therapy upon exclusion of haemorrhage (242, 243) and against the use of anticoagulation in patients without cardioembolism (214, 243). In children, there are currently no randomised controlled trials published on the efficacy of anticoagulation or antiplatelet therapy in children with stroke and as such heparin, LMWH or Vitamin K antagonists are not approved by the Therapeutic Goods Administration for use in Australian children with acute ischaemic stroke. Furthermore, a large number of antithrombotic drugs used are off-label or unlicensed, reiterating the importance of understanding efficacy, impact and activity of these drugs in children, compared to adults.

Despite the absence of controlled trials, there is a body of literature supporting the safety of using anticoagulation and antiplatelet therapy in children with stroke (122, 189, 244-251). Eight studies were identified describing the use of anticoagulation or antiplatelet therapy in children with arterial ischaemic stroke, of varying aetiologies, including a systematic review (122), five cohort studies (189, 246, 248-251) and a case series (247).

Three studies were found to compare treated and untreated cases (189, 247, 248). A case series of 22 children with arterial ischaemic stroke and bacterial meningitis (247) found recurrent episodes in i) none of the children that were treated with unfractionated heparin, ii) in 40% of the children treated with Aspirin and iii) in 57% of the children that were not treated. There was no incidence of bleeding reported in this cohort (247). A retrospective study of 37 children treated with anticoagulation therapy also reported no episodes of bleeding with use of the anticoagulants unfractionated heparin, LMWH and warfarin, but a recurrent infarction rate of 14% (250). The third study was a prospective study of 27 children with basilar artery stroke whom were treated with Aspirin or anticoagulant medications. Good outcomes were reported in five from nine receiving no therapy, four from six with anticoagulation therapy alone, and three from seven patients receiving Aspirin and anticoagulation (189).

A prospective study examining the safety of anticoagulation in 215 children with arterial ischaemic stroke found a 4% increase in risk of symptomatic intracranial haemorrhage (248). Finally, a cohort study examining the safety of clopidogrel in 17 children with arterial ischaemic stroke with Aspirin intolerance reported no recurrent infarction, and two bleeds over a median duration of three years (251).

In the CADISS trial, which involved 250 adults with cervical arterial dissection, patients were randomised within seven days of symptom onset to anticoagulant or antiplatelet therapy (252). Authors found a low overall (2%) risk of recurrent stroke and no difference in efficacy of antiplatelet versus anticoagulant agents. There was one major bleeding event recorded in the anticoagulant group. This study confirmed the findings of previous observational studies that there is a low risk of recurrent strokes in adult cervical arterial dissection.

While there is limited data, it is reasonable to assume safety of anticoagulation and antiplatelet therapy, based on current findings unable to find an increased risk of bleeding. Evidence regarding the role of therapy in recurrent stroke is varied, but may suggest benefit of treating with unfractionated heparin, compared to Aspirin or no treatment (250). In the absence of consistent high-quality evidence current practice includes administration of anticoagulation upon exclusion of haemorrhage until the exclusion of dissection or embolism as a cause of stroke (185). The rationale is to reduce the risk of recurrent stroke while investigating for aetiology. An alternative argument suggests initial use of Aspirin, because the potentially increased risk of bleeding should be considered, and that formal anticoagulation should only be administered after embolism or dissection as proven (120). The biological rationale in favour of initial heparinisation is that recurrent strokes are most likely to occur within the first 48-72 hours if there is dissection or embolus.

10.2 **Steroid therapy**

Current or past infection or inflammatory disease may be associated with increased risk of stroke. One proposed mechanism is through inflammation of the cerebral arteries. Varicella zoster virus, enterovirus, herpes virus and pneumonia have all been identified as risk factors for childhood arterial ischaemic stroke (Chapter 6). In particular, varicella zoster virus, which is known to replicate in the arteries, has been reported as a risk factors for cerebral infarction (104, 197, 253-255). A comprehensive review of the role of infection in risk of stroke can be found in Chapter 6. The inflammatory immune response that occurs as a result of an ischaemic insult further contributes to tissue damage. A study of 12 children has suggested that children with arterial ischaemic stroke exhibit elevated inflammation makers (matrix metalloproteinase-9, tissue inhibitors of metalloproteinase-4, interleukin six and eight and C-reactive protein) compared to control (127). Thus, as infection is a common aetiology in childhood stroke, steroid therapy may play a great role in prevention and damage compared to adults.

Two papers that addressed the use of steroids in children with arterial ischaemic stroke were identified. A systematic review of 32 observational studies and two trials involving 152 children reported a weak benefit for the use of steroids in in some subtypes of arteriopathy, and in tuberculous and bacterial meningitis related arterial ischaemic stroke (256). It was noted that the studies reviewed had no internal controls or comparison groups, and that the data presented provide very weak evidence for the association between treatment and outcomes. The authors concluded that there was little robust evidence either in favour or against the use of immunotherapy in childhood arterial ischaemic stroke. In contrast, a case series of four children with varicella related stroke reported good outcomes without the use of steroids (253), however the small case number, bias associated with case studies and lack of control data limits the interpretation of these findings.

Table 32. Anti-thrombotic and steriod therapy for children with arterial ischaemic stroke.

Weak Recommendation
Anticoagulation and antiplatelet therapy are safe in children with arterial ischaemic stroke after the exclusion of haemorrhage. Level of Evidence (III, IV). References (122, 189, 246-251).
Weak Recommendation
In children with arterial ischaemic stroke anticoagulation should not be administered within 24 hours of receiving neurovascular intervention. Level of Evidence (adult I). References (257).
Weak Recommendation
For all children with arterial ischaemic stroke, after exclusion of haemorrhage, unfractionated heparin, low molecular weight heparin or Aspirin is recommended as an initial therapy until the exclusion of dissection and embolic causes. Level of Evidence/References - adapted from (185).
Weak Recommendation
In children where an arterial ischaemic stroke is NOT caused by cardioembolism or dissection, daily aspirin is recommended for a minimum of 2 years. Level of Evidence/References - adapted from (185).
Weak Recommendation
In children with arterial ischaemic stroke secondary to cardioembolism treatment with low molecular weight heparin or Vitamin K antagonist is recommended for a minimum of three months. Level of Evidence/References - adapted from (185).
Weak Recommendation
In children with arterial ischaemic stroke secondary to dissection, treatment with low molecular weight heparin or Vitamin K antagonist is recommended for a minimum of 6 weeks. Ongoing treatment should be dependent on neuro-radiological assessment of stenosis severity and recurrent ischaemic episodes. Level of Evidence/References - adapted from (185).
Weak Recommendation
In children where the cause of arterial ischaemic stroke is NOT cardioembolic or dissection, the addition of steroids to antiplatelet therapy may be considered in some subgroups of children with infection and arteriopathy related aetiologies. Level of Evidence (I-IV). References (253, 256).

11 INTRACRANIAL PRESSURE AND DECOMPRESSIVE CRANIECTOMY FOR ACUTE ARTERIAL STROKE

Raised intracranial pressure is uncommon in paediatric patients with arterial ischaemic stroke. It is, however, important to consider raised intracranial pressure in selected paediatric patients with arterial ischaemic stroke, since timely intervention may be lifesaving and reduce morbidity. The two most relevant clinical scenarios are extensive middle cerebral artery infarction (so-called malignant middle cerebral artery infraction [MMCAI]), and infratentorial stroke with oedema, brainstem compression and obstructive hydrocephalus. The limited paediatric population data suggests one to 12 percent of children with arterial ischaemic stroke develop MMCAI and raised intracranial pressure (171, 258, 259). Once the sutures fuse and the skull is closed, the relatively larger proportion of intracranial volume occupied by brain and lesser by cerebrospinal fluid and intravascular blood in the healthy paediatric brain, compared to older adults, sets the scene for raised intracranial pressure secondary to stroke-induced space-occupying cerebral oedema.

11.1 Recognition of intracranial pressure

Early recognition of the patients at risk of raised intracranial pressure can be difficult and requires a high level of clinical suspicion. The most important indicators for raised intracranial pressure with both supra- and infratentorial infarcts are deteriorating level of consciousness and the worsening of neurologic dysfunction.

In adults, MMCAI occurs in 10 to 20% of MCA strokes. Aids to predict progression and elevated intracranial pressure revolve around the large volume of the stroke and include; i) clinical parameters of forced eye and head deviation, ii) > 50% middle cerebral artery territory affected on initial CT scan, and iii) midline shift and diffusion weighting imaging volume > 145ml (260, 261). Large volume and multiple posterior fossa strokes, the degree of mass effect on imaging and lower cranial nerve dysfunction may also help predict progression and elevated intracranial pressure in adults (262, 263).

Comparable data pertaining to children is limited. One retrospective review of children treated with decompressive craniectomy after stroke suggested some factors predictive of MMCAI in adults are not consistent in the paediatric population (264). A recent retrospective study, focussing children with MMCAI, reviewed 66 children from one institution with middle cerebral artery stroke, of whom 12 (18%) developed MMCAI syndrome (265). Compared to children that did not progress to MMCAI, those with MMCAI were older (>2 years), presented with significantly higher serum glucose and had larger volume strokes by neuroimaging (modified PedASPECTS > 3.5 (266)), with combined involvement of cortex, white matter and basal ganglia (171). In a multivariate analysis, seizures longer than five minutes and more severe neurologic dysfunction, measured as higher initial PedNIHSS scores (>7.5), were independent predictors of developing MMCAI syndrome (265).

Although identifying which children will go on to develop raised intracranial pressure as a result of a stroke is difficult, early recognition is key to effective management. The limited paediatric literature is consistent with The Canadian Stroke Code (267), a key review (260) and The Brain Trauma Foundation guidelines for raised intracranial pressure in children (268), all of which advocate for initial supportive care, early neurosurgical referral and consideration of decompressive craniectomy in selected patients. Initial supportive care includes admission to an intensive care setting, 30 degrees elevation of the head of the bed, good oxygenation, adequate hydration and maintenance of euvolaemia, nil oral intake, temperature control (avoiding hyperthermia), prevention of hypotension and control of seizures in deteriorating patients and those at risk of MMCAI.

Table 33. Recognition of intracranial pressure associated with actue stroke

Strong Recommendation
Early recognition of the minority of paediatric patients with acute stroke who may develop raised intracranial pressure should prompt initial supportive care and early neurosurgical referral for consideration of decompressive craniectomy. Level of Evidence (IV). References (258, 264, 265).
Practice Statement
The most important indicators for raised intracranial pressure with both supra- and infratentorial infarcts are deteriorating level of consciousness and worsening of neurologic dysfunction. Due to the small space between the cranial vault and brain parenchyma children with large infarcts require close monitoring for signs and symptoms of raised intracranial pressure in the days following the stroke.
Practice Statement
Children presenting with a PedNIHSS score ≥8 or seizures greater than five minutes, should remain under close surveillance, as these are reported independent predictors of paediatric MMCAI. Elevated serum glucose at presentation and larger volume strokes on neuroimaging with combined involvement of cortex, white matter and basal ganglia in children older than two years are also risk factors for development of MMCAI. Level of Evidence (CBR, III-3). References (265).
Practice Statement
Initial supportive care includes intensive neurological surveillance, 30^0 elevation of the head of the bed, good oxygenation, adequate hydration and maintenance of euvolaemia, nil oral intake, temperature control (avoiding hyperthermia), prevention of hypotension but toleration of mild hypertension and control of seizures.
Practice Statement
Early neurosurgical referral is important for consideration of decompressive craniectomy and placement of intracranial pressure measuring devices. Although reliable measurement of raised intracranial pressure may be important, the placement of measuring devices or sustained medical management should not delay the more effective treatment option of timely decompressive craniectomy.

11.2 Decompressive craniectomy

Increased intracranial pressure decreases cerebral blood flow and impairs cerebral perfusion pressure, which inhibits oxygenation of healthy/non-ischaemic brain tissue. The main aim of decompressive surgery is to remove a part of the cranium to enable outward swelling of ischaemic tissue, and without compromising healthy brain tissue, normalise intracranial pressure. Here we review the literature on the use of decompressive craniectomy in the setting of MMCAI, posterior circulation ischaemic strokes including post tPA treatment.

In the adult literature five high-quality, randomised trials of patients treated with decompressive craniectomy for severe cerebral oedema and raised intracranial pressure associated with extensive MCA infarcts (269-273) and four systematic reviews (261, 274-276) report effective reduction of raised intracranial pressure after decompressive craniectomy. Collectively these studies indicate a marked reduction in mortality with an absolute reduction in risk of death of about 50% compared to medical treatment alone. They also show overall improved disability measured by modified Rankin Scale, although the data suggest that surgical intervention decreased mortality at the expense of increased degrees of disability. Younger age and surgical intervention within the first 48 hours (perhaps more marked with surgery within the first 24 hours or first six hours (261)) after stroke were associated with better prognosis. The limited paediatric literature regarding decompressive craniectomy in children with MMCAI provides concordant and possibly more optimistic results than the adult series.

Suboccipital decompressive craniectomy in patients with posterior circulation ischaemic stroke and raised intracranial pressure should also be considered. Despite minimal literature in adults and children the pathophysiology and rationale behind benefits of decompressive craniectomy are similar to MMCAI. In adults, a systematic review of 283 patients found that preoperative level of consciousness correlated with outcome (277) and implied that early decompression or pre-emptive decompression (if the latter patients could be accurately selected), at onset of neurologic symptom progression or deterioration in consciousness, would be optimal. Two studies (262, 263) also noted good outcome after medical treatment alone in patients whose level of consciousness did not deteriorate. Taken together, these data also indicate the need for close clinical observation in the first few days after stroke to identify progression and institute timely decompressive craniectomy. One relevant paediatric paper identified four children with space-occupying cerebral oedema attributed to severe ischaemic infarction of the posterior cerebral arterial circulation and echoes the adult observations detailed above (278).

Given the likelihood that more paediatric stroke patients will be treated with emergent thrombolysis in the future, the efficiency of decompressive craniectomy post-acute treatment is relevant. There are currently no published paediatric studies that address this question. Four adult retrospective observational reports indicate that decompressive craniectomy can be safely undertaken after initial, emergent treatment with tPA (279-282). These studies report initial treatment with tPA in 91 patients with MMCAI who subsequently underwent surgery, and 74 patients treated with decompressive craniectomy not initially treated with tPA. Surgery was typically performed more than 24 hours after treatment with tPA. Post-operative bleeding complications were not more frequent in patients treated with tPA, and mortality and functional outcomes were comparable.

Efficacy in children

There is a growing body of low-level evidence suggesting decompressive craniectomy may provide increased benefit in children compared to adults. This hypothesis originated from a 2004 systematic review of 138 patients that reported younger age was a significant factor in predicting improved functional outcome (283). Indeed, the differences between adults and children are significant and it is plausible that direct translation of adult recommendations may not be best practice in paediatrics. Firstly, there is preliminary evidence to suggest children have improved mortality rates post decompressive craniectomy (reviewed in (264, 265, 284, 285)). Secondly, the time window for improved outcomes in children may extend beyond the recommended 48 hours for adults (265, 285). Finally, one retrospective study of decompressive craniectomy for all neurologic emergencies in adults and children reported "the cost of neurosurgical treatment for a quality-adjusted life year as acceptable" (286), which might be predicted to be more benefit in children with longer life spans after the procedure.

Unlike the adult data, there are no controlled trials of decompressive craniectomy in paediatric stroke patients. The identified paediatric studies include six retrospective observational series (258, 259, 264, 265, 287, 288) and 11 case reports (reviewed in (264, 284, 285). These studies report 39 paediatric patients treated with decompressive craniectomy for severe cerebral oedema associated with MMCAI. Recognising that many published cased studies may be biased towards positive outcomes, all 38 of 39 (97%) paediatric patients treated with decompressive craniectomy survived, which is better than the reported 78% survival in adult trials (275). Furthermore, the outcome among paediatric survivors was "good to moderately good", with most survivors ambulant with normal speech (264, 265), consistently better than reported in adult literature. Three papers included information of patients with a similar clinical scenario not treated with decompressive craniectomy (258, 259, 265), among whom only three from nine survived.

Intra and post-operative considerations

There are currently no paediatric studies assessing the efficacy or timing of monitoring intracranial pressure in the setting of MMCAI. One retrospective, uncontrolled study of 12 adults with MMCAI treated with decompressive craniectomy reports the role of intracranial pressure monitoring placed at the time of surgery (289). They showed nine from 12 patients had recurrent, intermittent elevation of intracranial pressure despite surgical intervention. They also found head elevation and medical therapies to reduce intracranial pressure including sedation modification, osmotherapy cooling and especially drainage of cerebrospinal fluid from external ventricular drains were effective in treating episodes of raised pressure. The study was not aimed at assessing outcome, but based on first principals, improved treatment of raised intracranial pressure would be expected to improve and not worsen outcome. Adult literature also suggests that monitoring intracranial pressure is useful in guiding therapy and improves short-term survival in patients undergoing decompressive craniectomy for traumatic brain injury (290, 291).

A systematic review of 10 clinical trials with 237 patients assessed the effect of optimal head elevation on intracranial pressure post craniotomy (292). Findings showed that 30-45 degrees elevation is optimal for decreasing intracranial pressure, and that any elevation is better than zero degrees. Only a minority of the patients were children.

A systematic review of mostly adult literature showed that complications related to both the craniectomy and replacement of the bone during cranioplasty for MMCAI are common and include post-operative intra and extra-parenchymal haemorrhage, contra-lateral haemorrhage, haemorrhagic transformation of infarction, infectious, inflammatory and wound healing complications and cerebrospinal fluid disturbances (293). One systematic review of the paediatric literature was limited by paucity of data, but revealed frequent resorption after cranioplasty with stored bone (35%) but infrequent bone resorption with fresh autograft of rib or calvaria (5%), titanium (0%) and methyl methacrylate (0%) (294). They did not present any findings on the management of intracranial pressure.

In summary, the adult data is high-quality, extensive and supportive of decompressive craniectomy for MMCAI. The paediatric data is observational and uncontrolled, although the study by Andrade et al (171) specifically focusses upon MMCAI in MCA infarction. Collectively, the evidence suggests that morbidity and mortality outcomes after decompressive craniectomy for raised ICP with arterial ischaemic stroke may be better for children than adults, warranting further investigation whilst providing support for intervention.

Table 34. Recommendations for decompressive craniectomy in childhood stroke

Strong Recommendation
Decompressive craniectomy should be considered for children with malignant ischaemic MCA (or ICA) territory infarction. Level of Evidence (III, IV). References (258, 259, 264, 265, 284, 285, 287, 288).
Weak Recommendation
Suboccipital decompressive craniectomy should be considered for children with posterior circulation ischaemic strokes and raised intracranial pressure or decreasing level of consciousness. Level of Evidence (IV). References (262, 263, 277, 278).
Weak Recommendation
Decompressive craniectomy may be considered 24 hours after treatment with intravenous thrombolytic therapy (e.g. tPA). Level of Evidence (IV). References (279-282).
Strong Recommendation / **Against**
Placement of an intracranial pressure monitor and subsequent time to assess pressure should not delay decompressive craniectomy. Level of Evidence (CBR).
Weak Recommendation
Placement of an intracranial pressure measuring device at the time of decompressive craniectomy, should be considered for paediatric patients. Level of Evidence (CBR, IV). References (289).
Practice Statement
The timing of decompressive craniectomy after symptom onset remains controversial. Adult trials largely recommend surgical intervention within 48 hours. The limited paediatric data suggests the time window may be extended due to different aetiologies and the sometimes-stuttering symptom onset.
Strong Recommendation
Elevation of the head of the bed to 30 to 45 degrees is recommended after decompressive craniectomy. Level of Evidence (Adult, I). References (292).

12 STROKE AND CONGENITAL HEART DISEASE

Congenital heart disease is the most common congenital disorder in newborns (295), affecting about 1 in 100 births. With births totalling over 300,000 in 2015 (296), this equates to approximately 3,000 Australian babies that were born with some form of cardiac malformation that year. More than half of these children will require some form of treatment (297) including cardiac surgical, interventional catheter procedures or medical management alone. Children with complex heart disease often require multiple surgical procedures. In 2015, 2,831 cardiac surgical procedures were performed across Australia and New Zealand (298). Recent surgery in an important consideration as strokes are more likely to occur around the time of a cardiac procedure (91). Over the last few decades, advancements in surgical techniques and patient management have dramatically increased survival rates with more than 85% of children with congenital heart disease now reaching adulthood (299). As a result, congenital heart disease is now considered a life-long disease and clinical guidelines and national registries have been developed to facilitate the continuum of life-long care (300, 301).

Neurological outcomes

Long-term neurodevelopmental outcomes are of concern for children with congenital heart disease with some studies suggesting more than 50% of the population suffer poor neurodevelopmental outcomes (91, 302-304), with seizures cognitive impairment, delays in speech, language and learning disabilities commonly reported (reviewed in (305)).

Historically, poor neurological outcomes have largely been attributed to brain injury occurring during surgery, and this has driven research into maximising organ protection during cardiopulmonary bypass. As a result of more recent studies, despite being born at term 40-50% (93, 306-308) of infants with congenital heart disease have asymptomatic preoperative brain abnormalities, including markers of dysmaturation (309), decreased brain volume (310, 311), abnormal white matter integrity and an increased incidence of stroke (312).

Neuroimaging in the setting of congenital heart disease

MRI is the accepted gold standard for detecting stroke in infants and children. Using MRI, the nature and frequencies of brain abnormalities have been documented across a variety of congenital heart diseases postnatally, and more recently, in the prenatal period. Postnatally, a meta-analysis of 13 studies and 425 cases of congenital heart disease (313), and a separate meta-analysis of eight studies (314) consistently found that congenital heart disease is associated with an increased prevalence of brain lesions on pre-operative neuroimaging. Furthermore, postoperative and follow-up neuroimaging show that small injuries sustained from surgery commonly resolved over time (314, 315). These analyses and individual cohort studies suggest that pre-operative brain abnormalities are of antenatal origin (93, 307, 308, 316).

MRI studies of fetuses with congenital heart disease have demonstrated a deceleration in volumetric brain growth and metabolism, reduced cortical and subcortical matter, and delays in cortical maturation in the third trimester of development (311, 316, 317). At this late stage in development, in the healthy fetus, there is a surge in brain synapse formation, increased demand for oxygen and metabolic substrates to maintain sodium potassium ATPase gradients, and cerebral myelination. This increase in brain activity is thought to place increased demands on the circulation which may not be met in certain cardiac conditions (318, 319). The role of fetal MR imaging in predicting patients at increased risk of postnatal brain injury, in particular those at risk of stroke, also remains unclear. In a cohort of 103 infants with congenital heart disease that underwent fetal and postnatal MR imaging, fetal MR imaging detected brain abnormalities in only nine of the 33 that displayed pre-operative abnormalities (320). The same authors have also been unable to associate fetal MRI abnormalities with cardiac phenotype (321). As such, the predictive value of fetal MRI for pre-operative brain injury remains to be determined.

Brain dysmaturation

Newborns with congenital heart disease have immature brains relative to their gestational age (307, 316), corresponding to a delay of one month in structural brain development. Using quantitative MRI measures of diffusion tensor imaging and tracking, and MR spectroscopy a cohort 68 of mixed congenital heart disease infants undergoing surgery were given brain maturity scores pre- and post-operatively (309). Immaturity was determined by grading myelination, cortical infolding, involution of the germinal matrix, and the presence of bands of migrating glial cells. Brain abnormalities were noted in 75% of infants and immaturity scores were associated with injuries both pre- and post-operatively (309).

Congenital heart disease as a risk factor for stroke

Preoperative brain injury, particularly stroke and white matter injury, is common in neonates with congenital heart disease. Infants with congenital heart disease make up to 25% of the total paediatric stroke population (121). In mixed congenital heart disease cohort studies between 10 to 40% of infants have been diagnosed with pre-operative stroke (93, 312, 322). There are ongoing studies into neuroprotective measures during surgery (e.g. surgical strategies, bypass strategies, anaesthetic agents, therapeutic hypothermia and the use of erythropoietin and regenerative treatments). Whilst these trials are important, focus should also be given to our poor understanding of the

mechanisms underpinning brain injury in addition to the multitude of factors contributing to brain injury during development in the setting of congenital heart disease.

Preoperative brain imaging

Performing cerebral and renal ultrasounds for neonates is common practice in preparation for cardiac surgery. While ultrasound is a simple non-invasive and easily accessible investigation, it is relatively insensitive in detecting brain injury. In a study by Rios et al, 167 asymptomatic term infants with congenital heart disease underwent preoperative cranial ultrasound scans and MRIs (323). Whilst the MRI scans were typically performed about four days after the ultrasound, brain injury was detected on only five ultrasound scans compared with 44 of the MRI scans. The majority of the lesions on MRI were white matter injury (n=32), infarct (n=16) and haemorrhage (n=5). Of the 5 abnormal ultrasound scans, four showed intraventricular haemorrhage which was not seen on the subsequent MRI scans.

Postoperatively, new brain injury, mainly new white matter injury has been reported in between 35 to 44% of studied cohorts (324, 325). In a study of 37 neonates with hypoplastic left heart syndrome a longer time to surgery was associated with new postoperative white matter injury (326). Injuries identified preoperatively, including stroke, have a low risk of progression with surgery (93).

Table 35. Neuroimaging recommendations for children with congenital heart disease and stroke

Strong Recommendation
In all children with congenital heart disease magnetic resonance imaging should be performed as the diagnostic imaging modality of choice to diagnose stroke. Level of Evidence (II-III). References (93, 312, 322, 323, 327, 328).
Strong Recommendation
Where clinically feasible pre-operative cerebral MRI should be considered for all children with congenital heart disease. Level of Evidence (I-III). References (93, 98, 307-309, 312, 314-316, 322, 324, 329-333).
Weak Recommendation
There is growing evidence supporting the association between poorer neurodevelopmental outcomes and pre-operative brain injury or markers of cerebral dysmaturation, independent of type and timing of surgical intervention. Level of Evidence (II-III). References (98, 302, 313, 314, 324, 332, 334).
Weak Recommendation
In children/infants with congenital heart disease and a pre-operative MRI diagnosis of stroke, the timing of surgical intervention may not necessarily result in injury expansion and should not dictate timing of surgery, however evidence is limited. Level of evidence (III). References (93, 323, 325, 326).
Weak Recommendation **Against**
Routine fetal magnetic resonance imaging is not currently recommended to detect increased risk of postnatal stroke in the setting of congenital heart disease. Level of Evidence (I-III). References (306, 311, 320, 321, 335, 336).
Strong Recommendation
All infants with congenital heart disease diagnosed with stroke should be considered for structured neurodevelopmental surveillance and follow-up. Level of Evidence (III). References (302, 310, 324, 334).
Strong Recommendation
In infants/children with congenital heart disease undergoing MRI a minimum initial imaging protocol (i) axial DWI/ADC, (ii) axial gradient echo (such as SWI) for detection of haemorrhage, (iii) axial fast spin echo (FSE) or turbo spin (TSE) T2 iv) consideration of fluid-attenuated inversion recovery (FLAIR) if greater than 1 year of age, v) axial T1 and vi) time of flight (TOF) MRA, to diagnose stroke. Level of Evidence (III-IV). References (63, 69).
Weak Recommendation
Measures of brain maturation, in addition to standard sequences to detect structural lesions, can be considered for all children with congenital heart disease undergoing MRI. Level of Evidence (II-III). References (307, 310, 314, 316).
Practice Statement
Where measures of brain maturation are being evaluated, the following imaging parameters may be considered (i) brain volume (ii) N-acetylaspartate/choline ratio (iii) Average diffusivity (iv) Fractional anisotropy. Level of Evidence (I-III). References (309, 313).

13 PATIENT AND FAMILY CONSIDERATIONS

Childhood stroke survivors and their families can face a future of uncertain and complex challenges. An investigation into the key issues for Australia parents and families should also be a research priority.

For Australian adults who suffer stroke high quality standardised information exists for family members and carers. This information supports the transition from hospital to home, even addressing the support children need should an adult family member suffer a stroke (enableme.org.au). No such resource currently exists for children or their carers whom suffer stroke.

A set of interviews conducted with French families who had a child affected by stroke identified six main narrative themes or key issues. The brutality of diagnosis, a lack of information, a feeling of abandonment after discharge, a focus on functional recovery, a late awareness of cognitive deficits and the need for family psychological support to adapt to life changes, were all common issues for families experiencing the diagnosis of childhood stroke (134). Many themes are consistent with the 2004 UK Childhood Stroke Guidelines that identified lack of information, family support, disjointed communication between health care professionals and access to therapy as key issues in a workshop that was held for children affected by stroke and the families (120). A subsequent Delphi consensus survey of 26 parents identified that parents want research to focus on children's motor, cognitive and communication abilities with the ongoing need to determine aetiology and risk of recurrence (133). These themes are not new to childhood stroke. In 2005 the Royal Children's Hospital in Melbourne held a consumer forum engaging parents of children affected by stroke. Key issues raised by the 40 families in attendance included lack of awareness amongst community and local doctors, lack of understanding about the causes, delayed recognition by emergency services and physicians, limited evidence around treatment options, access to family centre rehabilitation and lack of family support services.

There is a critical need to initiate community-wide campaigns to educate parents and carers on the signs and symptoms of childhood stroke, with the goal of reducing pre-hospital delays in diagnosis and provide better family support to deal with the 'shock' of diagnosis. Furthermore, elucidating the key issues for Australian parents and children following diagnosis will be important and then to use this to develop appropriate information at all stages of care.

Table 36. Recommendations for the management of patient and family factors

Strong Recommendation
Parents/carers and children should be provided with the appropriate level of stroke literature. Level of Evidence (IV). References (133, 134).
Practice Statement
A key worker (ideally a stroke nurse/coordinator) should be appointed as contact point for family, to assist on provision of family education and for continuity of care between the multidisciplinary team.

14 RESEARCH RECOMMENDATIONS

The development of this guideline has identified the need for high-quality multi-centre research across many areas of childhood stroke beginning with;

- Development of a national paediatric registry with common data elements to elucidate incidence, standardise reporting, measure implementation of the guidelines, and facilitate multi-centre research.
- A comprehensive economic analysis of lifetime cost of paediatric stroke and quality adjusted life years for decreasing time to diagnosis in Australia.
- Determine the accuracy of diagnosing arterial ischaemic and haemorrhagic stroke using rapid neuroimaging sequences compared to standard stroke neuroimaging protocols.
- Development and implementation of a paediatric stroke code protocols within Australia's tertiary paediatric centres.
- Development of evidence-based information for families/ carers and children to improve knowledge and aid transition from hospital to home care.
- Ongoing assessment of implementation across Australian tertiary paediatric centres.

15 APPENDICES

15.1 Appendix 1 – Case series of children receiving neuro-interventions for stroke

Table 37. Case series of children treated with neuro-interventions 1994-2016

Author	Year	Age	Sex	Circulation	Territory	Mechanism	mins to treat	Stroke severity	Vessel status	treatment	tPA dose	Recanalisation	outcome	SAE
Amlie-Lefond	2009	7	F	P	Basilar	unknown	1140	NS	NS	IA-tPA	NS	NS	Deceased	none
Amlie-Lefond	2009	15	F	A	ICA	dissection	240	NS	NS	IA-tPA	NS	NS	mild deficit (discharge)	haemorrhage
Amlie-Lefond	2009	15	F	A	MCA	dissection	400	NS	NS	IA-tPA	NS	NS	mod deficit (discharge)	haemorrhage
Amlie-Lefond	2009	15	M	A	MCA	arteriopathy vasculitis	450	NS	NS	IA-tPA	NS	NS	normal (discharge)	none
Amlie-Lefond	2009	5	M	A	ICA	cardioembolism	240	NS	NS	IA-tPA	NS	NS	severe deficit (discharge)	none
Amlie-Lefond	2009	8	F	A	MCA	cardioembolism	228	NS	NS	IA-tPA	NS	NS	severe deficit (discharge)	none
Amlie-Lefond	2009	7	F	A	MCA	dissection	330	NS	NS	IV-tPA	NS	NS	Deceased	none
Amlie-Lefond	2009	13	F	A	ICA, MCA	unknown	234	NS	NS	IV-tPA	NS	NS	unknown	none
Amlie-Lefond	2009	0.2	M	NS	NS	cardioembolism	1200	NS	NS	IV-tPA	NS	NS	mild deficit (discharge)	none
Amlie-Lefond	2009	3	F	NS	NS	arteriopathy moyamoya	3120	NS	NS	IV-tPA	NS	NS	mild deficit (discharge)	none
Amlie-Lefond	2009	4	M	NS	NS	unknown	150	NS	NS	IV-tPA	NS	NS	mild deficit (discharge)	none
Amlie-Lefond	2009	12	F	A	NS	cardioembolism	198	NS	NS	IV-tPA	NS	NS	mild deficit (discharge)	none

Author	Year	Age	Sex	Circulation	Territory	Mechanism	mins to treat	Stroke severity	Vessel status	treatment	tPA dose	Recanalisation	outcome	SAE
Amlie-Lefond	2009	15	M	A	MCA	cardioembolism	180	NS	NS	IV-tPA	NS	NS	mild deficit (discharge)	haemorrhage
Amlie-Lefond	2009	3	M	NS	NS	elevated FVII	210	NS	NS	IV-tPA	NS	NS	mod deficit (discharge)	none
Amlie-Lefond	2009	13	F	A	ICA	arteriopathy, NOS	120	NS	NS	IV-tPA	NS	NS	severe deficit (discharge)	haemorrhage
Arnold	2009	12	M	A	MCA, ACA	unknown	300	22	hyperdense MCA	IA-UK	750,000 IU	partial	Deceased	none
Arnold	2009	9	M	P	Basilar, PCA	infection	720	22	occlusion	IA-UK	NS	partial	mRS 3 (3mths)	none
Baba	2012	11	F	P	PCA	cardioembolism	175	13	normal	IV-tPA	0.6/kg	normal preRx	NIHSS 5 (2hrs)	none
Barnwell	1994	16		P	BA	NS	2880	29	occlusion	IA-UK	300000	partial	NIHSS 2	none
Barnwell	1994	12		A	MCA	cardioembolism	420	24	occlusion	IA-UK	800000	none	NIHSS 9	none
Benedict	2007	2	F	A	MCA	cardioembolism	330	NS	occlusion	IV-tPA	0.53/kg	partial	normal function 2yrs	none
Bhatt	2008	3	F	P	BA	cardioembolism	>1000	NS	occlusion	IA-tPA	3 mg	partial	self-sufficient, spastic dysarthria	none
Bodey	2014	15	M	A	MCA	lymphoma	<360	21	occlusion	MCR		NS	MRS 0 (6 mo)	none
Bodey	2014	6	M	P	BA	unknown	NS	28	occlusion	MCR		partial	MRS 0 (6 mo)	none
Bodey	2014	5	M	P	BA	unknown	240	29	occlusion	MCR		complete	MRS 2 (6 mo)	malignant odema
Bodey	2014	10	M	P	BA	dissection	2160	27	occlusion	MCR		NS	MRS 3 (6 mo)	none
Bourekas	2005	15	M	A	ICA	unknown	405	28	occlusion	IA-UK	560000UIU	complete	NIHSS 8, MRS 3	none
Buompadre	2016	8	F	A	MCA	cardioembolism	300	7	partial occlusion	MCR		complete	NIHSS 4, PSOM 2	none
Byrnes	2012	2	F	A	ICA, MCA	cardioembolism	216	NS	occlusion	IA-tPA, IV-tPA	0.1/kg	partial	mRS 1 (12mths)	none
Cannon	2001	12	F	P	PCA	cardioembolism	150	NS	no image	IV-tPA	0.9/kg	no image	normal function (discharge)	none
Carlson	2000	13	F	A	MCA	dissection	<180	NS	stenosis	IV-tPA	0.9/kg	partial	unknown	none

Author	Year	Age	Sex	Circulation	Territory	Mechanism	mins to treat	Stroke severity	Vessel status	treatment	tPA dose	Recanalisation	outcome	SAE
Cognard	2000	8	M	P	BA	dissection	2880	NS	occlusion	IA-UK	900,000	partial	normal (3 mo)	none
Cremer	2008	15	F	A	MCA	unknown	150	NS	no image	IV-tPA	0.9/kg	no image	NIHSS 1 (day 10)	none
Dubedout	2013	7	M	P	BA	unknown	480	20	occlusion	MCR		complete	normal	none
Felker	2010	14	M	A	MCA	G2010A mutation	540	NS	stenosis	IA-tPA, MCR	NS	none	poor (3mths)	tPA unsuccessful. MRA wire occluded left M1
Felker	2010	14	M	A	MCA	dissection	540	NS	occlusion	MCR		none	abnormal	haemorrhage
Fink	2012	11	M	P	BA	unknown	240	6	occlusion	IV-tPA, MCR	0.6/kg	complete	normal	none
Gassanov	2011	17	M	A	MCA	cardioembolism	NS	NS	NS	IA-tPA	NS	NS	NS	none
Golomb	2003	17	F	A	MCA	DVT, substance abuse	132	NS	occlusion	IA-tPA	6.25 mg	complete	normal function (discharge)	none
Grigoriadis	2007	6	M	P	BA	unknown	2640	NS	occlusion	IA-UK, MCR	20,000 IU	partial	normal	none
Gruber	2000	6	F	A	MCA	cardioembolism	150	NS	occlusion	IA-tPA	2.5 mg	complete	unknown	none
Grunwald	2010	16	F	A	MCA	unknown	NS	26	occlusion	IV-tPA, MCR		complete	NIHSS 0 (1 mo)	none
Grunwald	2010	16	F	P	BA	unknown	>480	36	occlusion	IV-tPA, MCR	50 mg	complete	NIHSS 23 (1 mo)	none
Grunwald	2010	7	M	A	ICA	cardioembolism	NS	26	occlusion	MCR		partial	NIHSS 0 (1 mo)	none
Heil	2008	16	F	P	BA	G2010A mutation	280	8	hyperdense BA	IV-tPA	0.9/kg	none	NIHSS 0 (1 mth)	none
Hu	2014	9	F	A	MCA	cardioembolism	NS	16	occlusion	IV-tPA, MCR	NS	complete	NIHSS 6 (3mths)	none
Hu	2014	7	M	P/A	MCA, PCA	cardioembolism	NS	17	occlusion	MCR		partial	NIHSS 2 (3mths)	none
Huded	2015	6	M	P	BA	dissection	1560	15	occlusion	MCR		complete	MRS 0 NIHSS 0 (3 mo)	none
Rhee	2014	9	M	A	ICA	cardioembolism	420	6	occlusion	MCR		complete	NS	none
Jain	2008	15	F	A	MCA	cardioembolism	<180	11	hyperdense MCA	IV-tPA	0.9/kg	complete	mRS 5 (discharge)	none
Kirton	2003	15	M	P	BA	unknown	642	NS	occlusion	IA-tPA, MCR	0.1/kg	partial	normal function (discharge)	none
Kitzmuller	1999	2	M	A	ICA	cardioembolism	150	NS	occlusion	IA-tPA	13 mg	partial	hemiparesis	haemorrhage

Author	Year	Age	Sex	Circulation	Territory	Mechanism	mins to treat	Stroke severity	Vessel status	treatment	tPA dose	Recanalisation	outcome	SAE
Lai	2009	12	F	A	ICA, MCA	dissection	>480	6	occlusion	IA-UK, MCR	NS	complete	NIHSS 2 (discharge)	none
Larner	1998	18	F	P	BA	unknown	720	NS	occlusion	IA-SK	2400000 IU	none	Bartel 15 (18 mo)	haemorrhage
Losurdo	2006	4	M	A	MCA	arteriopathy post varicella	NS	NS	stenosis	IV-tPA	0.1/kg	NS	unknown	none
Mittal	2015	17	M	A	MCA	cardioembolism	NS	12	occlusion	IV-tPA, MCR		complete	NIHSS 4 (discharge)	none
Muniz	2012	15	M	A	MCA	cardioembolism	103	7	stenosis	IV-tPA	0.9/kg	NS	NIHSS 2 (33min)	none
Noser	2001	16	F	A	MCA	unknown	168	NS	no image	IV-tPA	0.9/kg	no image	unknown	none
Ortiz	2007	8	F	A	MCA	unknown	120	22	no image	IV-tPA	0.9/kg	no image	mRS 3 (discharge)	none
RenerPrimec	2013	0.8	M	A	MCA	cardioembolism	170	NS	NS	IV-tPA	0.9/kg	no image	mRS 1 (2mths)	none
Rosman	2003	18	F	P	BA	cardioembolism	NS	NS	occlusion	IV-tPA	NS	partial	hemiparesis	none
Sainz de la Maza	2014	12	F	A	ICA	unknown	480	18	occlusion	MCR	NA	complete	NIHSS 1, MRS 1	haemorrhage
Sampaio	2011	14	M	A	MCA	cardioembolism	120	14	hyperdense MCA	IV-tPA	0.9/kg	NS	NIHSS 2 (day 9)	none
Savastano	2016	1.8	M	P	BA	unknown	16	NS	occlusion	MCR	NA	partial	normal (6 mo)	vasospasm
Shuayto	2006	16	M	A	MCA	cardioembolism	160	NS	NS	IV-tPA	0.9/kg	no image	4+/5 strength, norm speech (8hrs)	none
Sousa	2012	13	F	P	BA	unknown	NS	NS	occlusion	IV-tPA	0.9/kg	complete	full permeabilisation	none
Stidd	2014	2	M	A	MCA	cardioembolism	420	4 (mRS)	occlusion	MCR	NA	partial	MRS 1 (1 mo)	none
Sunagarian	2003	9	M	P	BA	dissection	<360	NS	thrombosis	IA-UK	750000 IU	partial	NS	none
Sunagarian	2003	10	F	P	BA	arteriopathy pseudoaneuryms	290	NS	occlusion	IA-UK	1000000 IU	NS	UMN signs/ normal gait	none
Tan	2009	12	F	A	ICA, MCA	cardioembolism	360	18	occlusion	IA-tPA	0.16/kg	partial	NS	none
Tanaka	2012	12	M	A	MCA	cardioembolism	179	15	hyperdense MCA	IV-tPA	0.6/kg	NS	NIHSS 7	none

Author	Year	Age	Sex	Circulation	Territory	Mechanism	mins to treat	Stroke severity	Vessel status	treatment	tPA dose	Recanalisation	outcome	SAE
Taneja	2011	14	F	P	BA	unknown	480	NS	occlusion	MCR	NA	complete	normal	vasospasm
Tatum	2013		NS	P	BA	arteriopathy, NOS	1200	5	occlusion	MCR	NA	complete	MRS 0 (3 mo)	none
Tatum	2013		NS	P	BA	cardioembolism	555	2	occlusion	MCR	NA	complete	MRS 0 (3 mo)	none
Tatum	2013	17	NS	A	MCA	arteriopathy, NOS, artery to artery	450	12	occlusion	MCR	NA	complete	MRS 1 (3 mo)	none
Tatum	2013	4	NS	P/A	BA, ICA	cardioembolism	240	17	occlusion	MCR	NA	partial	MRS 3 (3 mo)	haemorrhage
Thirumalai	2000	16	F	A	MCA	unknown	105	NS	no image	IV-tPA	0.9/kg	no image	normal function (discharge)	none
Tsivgoulis	2008	6	M	A	ICA	cardioembolism	205	17	occlusion	IA-tPA, MCR	1.1 IU	partial	NIHSS 2, mRS 1 (3 months)	tPA unsuccessful/ MCR advanced clot
Vega	2015	11	M	A	MCA	cardioembolism		16	occlusion	MCR	NA	partial	MRS 1 (discharge)	none
Viaro	2015	15	M	A	ICA, MCA	unknown	120	18	occlusion	IV-PA	NS	complete	NIHSS 2 (discharge)	none
Weiner	2016	15	M	A	MCA	cardioembolism	480	9	thrombosis	MCR	NA	complete	Normal(6 weeks)	none
Zaidat	2005	16	M	P	BA	unknown	NS	5 (mRS)	occlusion	MCR	NA	partial	MRS 2 (3 mo)	none

M, male; F, female; P, posterior; A, anterior; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; NS, not stated; MCR, mechanical clot retrieval; IV-tPA, intra-venous tissue plasminogen activator; IA-tPA, intra-arterial tissue plasminogen activator; mRS, modified rankin scale; NIHSS, ped NIH stroke severity score; NA, not applicable. References: (188, 190-208, 220-241, 337-349) .

15.2 **Appendix 2 – PICO questions**

Topic	Question
Emergency assessment & management	In children with neurological symptoms relevant for stroke, do clinical assessment tools in emergency departments improve a) diagnostic accuracy and b) diagnostic reliability?
	In children with suspected or confirmed stroke does care within a stroke unit improve a) functional outcome b) recurrent stroke or c) all-cause mortality?
	In children with suspected stroke dose stabilisation of blood pressure, glucose levels, seizure, fever and hydration status, and/or the use of supplemental oxygenation improve functional outcome or all-cause mortality?
Imaging	In children with suspected stroke which imaging modalities and sequences are most sensitive and specific for detection of ischaemic and haemorrhagic stroke?
Post diagnosis investigations	In children with confirmed stroke what additional investigations associated with known risk factors elucidate aetiology and risk of recurrence?
Treatment	In children with acute ischemic stroke does anticoagulation or aspirin compared with each other or no therapy a) improve functional outcome, b) reduce early or late recurrent stroke, c) reduce all-cause mortality, d) result in adverse bleeding events?
	In children with acute ischemic stroke is tPA treatment or endovascular therapy associated with a) functional outcome, b) recurrent stroke, c) all-cause mortality, d) adverse bleeding events?
	In children with acute ischemic stroke following exclusion of cardio embolic or dissection as a source does treatment with aspirin and steroids, versus aspirin only; a) prevent recurrent stroke, and b) improve overall outcome?
	In paediatric patients with raised intracranial pressure and acute stroke which, if any interventions improve functional outcome and reduce mortality?
Cardiac patients	In paediatric patients with congenital heart disease which imaging modality most accurately detects brain injury around time of surgery?
	In paediatric patients with congenital heart disease that suffer stroke, what period of recovery prior to subsequent cardiac surgery reduces recurrence or expansion of stroke?

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