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MANAGEMENT OF ACUTE ISCHEMIC STROKE IN PEDIATRIC PATIENTS: CLINICAL METHODS AND OUTCOMES

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ABSTRACT

Background: Acute ischemic stroke (AIS) in the pediatric population is a rare condition. Despite its severe outcomes—including long-term neurological deficits and mortality— diagnosis of pediatric AIS is often delayed. In contrast to adult AIS, evidence-based guidelines for the pediatric population are limited, primarily due to the absence of data from multicenter randomized clinical trials.
Aim: This review aims to present a comprehensive overview of the treatment methods of AIS in children, focusing on thrombolysis, mechanical thrombectomy and supportive neuroprotective strategies.
Material and Methods: An in-depth literature review was performed using PubMed, ScienceDirect and Google Scholar including keywords such as: "pediatric acute ischemic stroke", "PAIS", "acute ischemic stroke in children", "acute ischemic stroke management", "tenecteplase", "thrombolysis in children"
Results: Intravenous thrombolysis with alteplase (0.9 mg/kg) may be considered in children ≥2 years of age within 4.5 hours of symptom onset, although data are still limited due to poor patient enrollment in the Thrombolysis in Pediatric Stroke Study (TIPS). Mechanical thrombectomy may be effective, even beyond the 6-hour window, particularly in cases involving large-vessel occlusion. Neuroprotective measures—such as glucose, temperature and blood pressure control—may contribute to improved outcomes. For secondary prevention, antiplatelet or anticoagulant therapy is recommended.
Conclusions: Management of AIS in children still relies on extrapolated adult data. There is an urgent need for pediatric-specific clinical trials to establish evidence-based treatment protocols and guidelines. In the meantime, early diagnosis, reperfusion strategies and supportive neuroprotective measures appears to be critical.

KEYWORDS

Acute Ischemic Stroke, Mechanical Thrombectomy, Thrombolysis, Pediatric Acute Ischemic Stroke, PAIS

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1. Introduction

Acute ischemic stroke (AIS) is a rare diagnosis in the pediatric population. It affects 3 to 13 in 100,000 children each year, with incidence peaks observed in newborns, younger children (<5 years) and in adolescence (Mastrangelo et al., 2021; Ferriero et al., 2019; Pilarska et al., 2023). Children with AIS are often misdiagnosed or experience delayed diagnoses, which can lead to lifelong disabilities (Tsze and Valente, 2011; Yock-Corrales et al., 2011). 70% of paediatric strokes result in long-term neurological deficits, 20% in recurrent strokes, and 10% in death (Ganesan et al., 2003; Fullerton et al., 2002; Krishnamurthi et al., 2015).

There are numerous recommendations for the management of AIS in adults, derived from multiple large randomized controlled trials, which cover specific time frames, medications, dosages, comorbidities, exceptions, etc. However, there is a lack of clear corresponding pediatric guidelines.

This review will focus on treatment methods of AIS in the pediatric population.

2. Materials and Methods

A comprehensive literature review was conducted in March 2025 using PubMed, ScienceDirect and Google Scholar. The authors searched databases using keywords "pediatric acute ischemic stroke", "PAIS", "acute ischemic stroke in children", "acute ischemic stroke management", "tenecteplase", "thrombolysis in children". Suitable articles in English were selected after an assessment of their titles, abstracts and full-texts. The review included original articles, review articles and case reports that focus on acute ischemic strokes in children and their management. It excluded studies that did not concentrate on pediatric population or were published in languages other than English, Polish, German, French or Spanish.

3. Discussion

The main goal of AIS therapy is early reperfusion of an affected area of the brain, minimizing brain damage, preserving neurological function and improving patient outcomes. This is typically achieved through recanalisation strategies:

- thrombolysis with intravenous or intra-arterial tPA
- mechanical thrombectomy

Thrombolysis:

There are some differences between fibrinolytic system of a pediatric patient comparing to adults (Parmar et al., 2006):

- decreased plasma concentrations of plasminogen and endogenous tPA
- decrease plasmin generation and general fibrinolytic activity
- increased plasma concentrations of PAI-1 (plasminogen activator inhibitor 1)

Furthermore, the increased volume of distribution and faster hepatic clearance indicate that children will eliminate tPA from their system more rapidly (Vinayan et al., 2022). These arguments imply that a higher proportional dose of tPA may be needed for thrombolysis in children compared to adults (Vinayan et al., 2022). However, research on the structure of fibrin clots in pediatric populations revealed that their pore size is significantly larger compared to adults, indicating a clot that is more susceptible to fibrinolysis (Ignjatovic et al., 2015). The aim of promising prospective TIPS study (Thrombolysis in Pediatric Stroke) was to determine safety, best dose, pharmacokinetics and possibility of treatment with i.v. tPA of children in age of 2 - 18 years old who presented with AIS (Rivkin et al., 2015). Unfortunately the study was closed due to poor patient enrollment. Thus, because of insufficient clinical trial data, it is suggested to use IV tPA (alteplase), within 4.5 hours of onset, at the same dose of 0.9 mg/kg (maximum dose of 90 mg) to pediatric patients (age 2-17 years) as in adults (Rivkin et al., 2015). 10% of the total dose should be given as an IV bolus over 5 minutes, with the remaining 90% administered through infusion over 60 minutes (Rivkin et al., 2015). Inclusion and exclusion criteria with relative contraindication (Rivkin et al., 2015) are illustrated in tab. 1 and 2.

Table 1. Inclusion Criteria for thrombolysis (Rivkin et al., 2015)

Tab. 1. Inclusion Criteria for thrombolysis
symptoms onset in <4,5 hours
patient's age ≥2 years old
PedNIHSS ≥ 4 and ≤ 24 points and sudden onset of neurological deficit

Alteplase vs tenecteplase

In some adult stroke centers, tenecteplase is becoming the preferred fibrinolytic agent over alteplase for the acute management of ischemic stroke, owing to its practical and pharmacokinetic advantages, while providing similar outcomes (Wang et al., 2024). Experience with tenecteplase in children is extremely limited for any indication and crucially, there is a lack of data on its safety, dosing, and efficacy for treating childhood stroke (Sun et al., 2023). Although studies of the adult population with AIS cannot be directly extrapolated to children, they might indicate tenecteplase as a prospective agent for pediatric patients with AIS.

Mechanical thrombectomy (MT)

Inclusion criteria for MT are as follows (Mastrangelo et al., 2021):

1. symptoms onset <6 hours

It was assumed, based on the adult data, that the **6-hour time window** for MT in AIS can be extrapolated on the pediatric population. However, there are case reports of successful MTs performed even after 24 hours from symptom onset (Sporns et al., 2023). In secondary analysis of the Save ChildS Study, the mismatch between neurological deficit and infarct was used as a selection criterion for extended-time-window (24 hours) MT (Sporns et al., 2021). Given these recent reports, a **24-hour time window** is certainly worth considering for the future.

2. patient's age ≥2 years old

One of the major concerns of endovascular thrombectomy is the potential risk of damaging the cerebral vasculature, which could lead to arterial dissection or thrombosis (Sporns et al., 2020; Chabrier et al., 2021; Sporns et al., 2021). Children's vessels are also more susceptible to vasospasms. There is rapid growth in the diameter of cervicocerebral vessels during the first 5 years of life, at which point their diameter reaches about 94% of the adult vessel size (compared to 59% in newborns) (He et al., 2016). As a result, thrombectomy devices designed for adults can be used in patients **older than 5 years**, however it may still be possible to use the same devices on younger children - criteria for MT included an **age ≥2 years old** (He et al., 2016). Another consideration is the diameter of the femoral artery, which serves as the access point for mechanical thrombectomy (MT). Some studies suggest that a patient's height is the best predictor of femoral artery diameter (López Álvarez et al., 2017) and, consequently, the safety of procedures like MT. G. Pero and F. Ruggieri concluded that a **height greater than 110 cm** significantly reduces the risk of femoral complications (Pero et al., 2023).

Table 2. Exclusion criteria and relative contraindications for thrombolysis (Rivkin et al., 2015)

Exclusion Criteria	Relative Contraindications
Unknown time of symptom onset	Major surgery or biopsy within 10 days
Pregnancy	Bleeding from gastrointestinal tract or urinary tract within 21 days
Clinical symptoms suggesting a subarachnoid haemorrhage even with normal CT imaging	Arterial puncture in a place inaccessible to pressure or lumbar puncture within 7 days
Patients in whom consent has not been obtained for a potential blood transfusion	Active neoplastic disease or within 1 month after treatment was finished
History of intracranial haemorrhage	History of significant bleeding disorder (patients with mild platelet dysfunction, mild von Willebrand's disease, or other mild coagulation deficits are not excluded)
History of arteriovenous malformation, aneurysm, or brain tumor	PedNIHSS < 4 or PedNIHSS > 24 points
Systolic blood pressure in lying or sitting position > 15% higher than 95th percentile for age	Stroke in course of bacterial endocarditis, moya moya disease, sickle cell anaemia, meningitis, myeloid, air or fat embolism
Blood glucose < 50 mg/dL (2.78 mmol/L) or > 400 mg/dL (22.22 mmol/L)	History of primary central nervous system vasculitis (PACNS) or secondary central nervous system vasculitis
Platelet count < 100,000, PT > 15 sec, INR > 1.4, PTT > laboratory norm	Intracranial haemorrhage demonstrated by MRI or CT
Symptoms of myocardial infarction or pericarditis requiring cardiac evaluation	Dissection of intracranial arteries (distal to ophthalmic artery)
Stroke, major head trauma, or intracranial surgery within ≤3 months	Volume of infarct on MRI covering > 1/3 of MCA supply area
	Known allergy to recombinant plasminogen activator
	INR > 1.4
	APTT in laboratory standard for heparin treatment up to 4 hours
	LMWH in the previous 24 hours (aPTT and INR do not reflect LMWH effect)

3. **large vessel occlusion (radiologically confirmed)**
4. **PedNIHSS≥6** (Ichord et al., 2011)

The recent Save ChildS Pro prospective study involving children between 28 days and 18 years old presenting with AIS concluded that MT was associated with better functional outcomes in paediatric patients with large-vessel or medium-vessel occlusions, compared to those receiving the best medical treatment (thrombolysis) (Sporns et al., 2024). Although publications on MT in younger children have reported good outcomes (Sporns et al., 2023), some data suggest that MT may be less beneficial for children <6 years old (Sporns et al., 2023). Complication rates and neurological outcomes in children were similar to those observed in randomized controlled trials involving adults, suggesting that MT has a similar safety profile in both pediatric and adult populations (Sporns et al., 2021).

Other:

Several neuroprotective measures can be implemented, regardless of recanalisation strategies, that can potentially reduce further neurological damage and improve outcomes of pediatric patients with AIS (Ferriero et al., 2019):

- ***Bed positioning -*** if there are no signs of elevated ICP, AHA recommends keeping the head of the bed flat for the first 24 hours (Amlie-Lefond and Wainwright, 2019). However, the impact of head of bed position on AIS outcome is still debatable (Alexandrov et al., 2018).
- ***Oxygenation -*** both **hypoxia** and **hyperoxia** may exacerbate ischemic neuronal injury. Thus, oxygen is not routinely administered unless the child is hypoxemic. Exceptions include patients with sickle cell anemia, in which oxygen may be used initially to reduce complications (Hirtz and Kirkham, 2019). It is strongly advised to maintain oxygen saturation of ≥94% (Amlie-Lefond and Wainwright, 2019).
- ***Hyperglycemia*** - studies of both animal and human models suggest that in cerebral vasculature hyperglycemia promotes (Martini and Kent, 2007):

1. inflammation - by reduction in the availability of NADPH, an essential cofactor involved in cellular antioxidant defense mechanisms
2. constriction - by causing eNOS dysfunction
3. thrombosis - by increasing levels of PAI-1

Additionally, high glucose levels increase likelihood of hemorrhagic complications of thrombolytic therapies. It is highlighted that patients without a history of diabetes appear to be more affected by high glucose levels (Capes et al., 2001). Meta - analysis suggests that non-diabetic hyperglycemics face over 3-fold greater risk of 30-day mortality compared to 2-fold greater risk in case of diabetic patients who are hyperglycemic on admission (Capes et al., 2001). Thus, in patients with AIS the goal is to maintain glucose levels between 140-180 mg/dL (Ferriero et al., 2019).

- ***Hyperthermia*** (defined as temperature >37.2°C on axillary recording (Sund-Levander et al., 2002)) - exacerbates neuronal injury by alteration of enzyme activity and damage to cytoskeletal proteins, along with the release of neurotoxic excitatory neurotransmitters and the generation of free radicals (Busto et al., 1994;; Morimoto et al., 1997; Laptook and Corbett, 2002; Castillo et al., 1999; Globus et al., 1995) resulting poor long-term outcomes after ischemic stroke (Saini et al., 2009). Studies emphasize that the prognosis becomes worse as hyperthermia occurs later within the first week after AIS (Saini et al., 2009). Hence, taking proactive steps to prevent and manage hyperthermia could result in better clinical outcomes (Saini et al., 2009). Temperature range of 35.5 - 36 °C during the first few days after AIS is recommended (Amlie-Lefond and Wainwright, 2019).
- ***Blood pressure (BP)*** - transient elevation of blood pressure is usually a compensation to maintain cerebral perfusion and does not require treatment. However, children with significant **hypertension** following an AIS experienced higher 12-month and in-hospital mortality rates and longer hospitalizations (Adil et al., 2016). There are no clear guidelines for high BP management in pediatric patients with AIS, nonetheless Boston Children's Hospital proposed to treat blood pressure greater than 15% above the 95th percentile for sex, age, and height for >1 hour or anytime the blood pressure exceeds 20% above the 95th percentile. For that purpose, they suggest to use labetalol at dose 0,2 mg/kg i.v. or 1 mcg/kg/min drip of nicardipine (Rivkin et al., 2016). AHA aims to lower the blood pressure by ≈25% over the first 24 hours (Amlie-Lefond and Wainwright, 2019). On the other hand **hypotension** in the first 6 hours after AIS also increases mortality. Specific blood pressure goals have not been clearly established yet (Amlie-Lefond and Wainwright, 2019) and there remains a significant knowledge gap.

- ***Seizures*** - can be an initial sign of AIS in children (Tsze and Valente, 2011; Yock-Corrales et al., 2011; Mallick et al., 2014; Wintermark et al., 2017; Chadehumbe et al., 2009; Zimmer et al., 2007; Abend et al., 2011), moreover, the pediatric population is unusually prone to developing epilepsy after a stroke (Fox et al., 2013), therefore seizures should be managed with anticonvulsants eg. levetiracetam or fosphenytoin (Amlie-Lefond and Wainwright, 2019).
- ***Increased intracranial pressure (ICP)*** - extensive strokes eg. MMCAI (malignant middle cerebral artery infarction) cause significant brain swelling that can lead to increased ICP, brain herniation, rapid deterioration of patient's condition and increased mortality (Pilarska et al., 2023; Rivkin et al., 2016). Children (after fontanelle closures) have smaller subarachnoid and cisternal spaces compared to adults. As a result, their ability to tolerate cerebral edema is reduced (Fox et al., 2013). For adult patients with MMCAI decompressive hemicraniectomy (DCH) is recommended. DCH may reduce the fatal spiral of cerebral swelling, elevated ICP and brain ischemia (Fox et al., 2013). Evidence for DCH in pediatric patients is insufficient, however there are case-based presumptions of its safety and efficacy in children with MMCAI (Pilarska et al., 2023; Adil et al., 2016; Carlhan-Ledermann et al., 2023; Medley et al., 2019).
- ***Neuroprotective agents*** - recent studies support an antioxidant and antiinflammatory role of acetyl-L-carnitine in AIS and preliminary suggest that acetyl-L-carnitine administration might be beneficial in adult patients with AIS (Mazdeh et al., 2022). Although corresponding studies for the pediatric population have not been conducted yet, supplementation with intravenous carnitine 50 to 100 mg/kg per day divided 3× times a day during the first 3 days after AIS (Amlie-Lefond and Wainwright, 2019) should be considered.

Summary of neuroprotective measures described above is illustrated in the tab. 3.

Table 3. Neuroprotective measures implemented in AIS

Aspect	Recommendation
Bed Positioning	Head of the bed flat for the first 24 hours (if no signs of elevated ICP)
Oxygenation	Oxygen is not routinely administered unless child is hypoxemic; maintain oxygen saturation ≥94%
Hyperglycemia	Maintain glucose levels between 140-180 mg/dL
Hyperthermia	Keep temperature between 35.5-36°C during the first few days after AIS
Blood Pressure (BP)	Treat BP >15% above 95th percentile for sex, age, height for >1 hour or >20% above 95th percentile. Aim for ≈25% reduction over the first 24 hours
Seizures	Manage with anticonvulsants (e.g., levetiracetam, fosphenytoin)
Increased Intracranial Pressure (ICP)	Decompressive hemicraniectomy (DCH) may be needed in severe cases (e.g., MMCAI)
Neuroprotective Agents	Consider intravenous acetyl-L-carnitine 50-100 mg/kg/day (3× daily) during the first 3 days after AIS

Anticoagulants and antiplatelets as treatment and prevention of AIS in children

If a patient receives thrombolytic treatment, antiplatelets or anticoagulants can be administered after >24 h (Pilarska et al., 2023; Medley et al., 2019) . If a patient does not qualify for thrombolytic therapy, they should immediately receive antiplatelets, as long as there is no CNS bleeding. (or other contraindications). For that purpose it is recommended to use ASA at a dose of 5 mg/kg (up to 300 mg daily) (Pilarska et al., 2023) for 5-7 days (while investigating the cause of AIS).

More than 10% of pediatric patients will have another stroke within a year (Fullerton et al., 2016). Arteriopathies have the highest recurrence risk - over 30%. Additionally, children who have a posterior circulation stroke tend to have a higher recurrence rate compared to those with an anterior circulation stroke (Uohara et al., 2017). Although clinical trials have not yet determined whether antiplatelet or anticoagulant therapy is superior (Ferriero et al., 2019), it is a fact that the absence of antithrombotic therapy increases the risk of AIS recurrence by 1,5 to 2-fold (Rivkin et al., 2016).

Long-term anticoagulant therapy for children is implemented after the exclusion of hemorrhage and typically involves vitamin K antagonists (**VKA**s) administered orally, such as warfarin or acenocoumarol. Alternatively, **LMWH** may be used via subcutaneous injection (Pilarska et al., 2023). Patients predisposed to thrombosis (PTS - prothrombotic states) or with AIS of cardiac origin should be treated with anticoagulation (LMWH/UFH/VKA) for ≥3-6 months or ≥6 weeks (in the case of arteries dissection) (Pilarska et al., 2023; Medley et al., 2019). Usually, in other patients maintenance therapy involves 1 mg/kg/d (up to 75 mg) of **ASA** for 2 years, because the majority of recurrent strokes occur during the first 2 years after the incident (Fullerton et al., 2016). However the duration of therapy is determined by the underlying condition and other risk factors.

4. Conclusions

Acute ischemic stroke in children, though rare, carries significant morbidity and mortality. Its diagnosis is often delayed due to age-specific symptoms variability and lack of awareness, resulting poor outcomes.

Currently, the treatment of pediatric AIS is mostly extrapolated from adult protocols and guidelines due to the lack of corresponding data in the pediatric population. Thrombolysis with intravenous alteplase and mechanical thrombectomy have shown promising outcomes in pediatric patients, although their use remains guided by expert consensus, case series, and limited observational studies. Moreover, some emerging data suggest that tenecteplase may be a better alternative to alteplase. Neuroprotective strategies and supportive care play a vital role in minimizing secondary brain injury and antithrombotic therapy with anticoagulants and antiplatelets remains essential in both acute and preventive treatment. Although clinical trials have not yet determined whether anticoagulants or antiplatelets are superior, it is well-established that the absence of antithrombotic treatment increases the risk of recurrent AIS.

Future efforts should prioritize the development of clinical trials and guidelines specifically for the pediatric population, especially in order to determine appropriate dosing, safety profiles and timing of reperfusion therapies. Until such data are available, clinicians should make individualized decisions carefully balancing efficacy, safety and potential benefits in this complex population.

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