Great North Children's Hospital/Regional Paediatric Arterial Ischaemic Stroke Acute Management Guidelines

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Overview

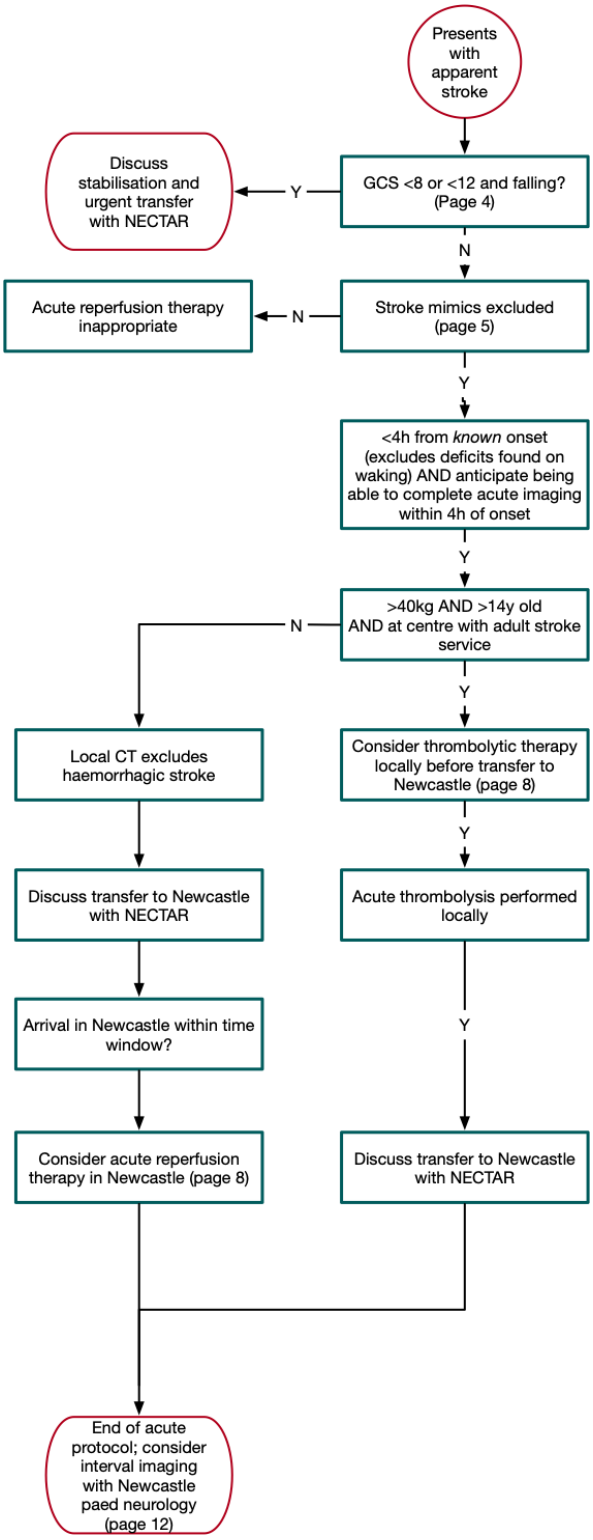


Figure 1. Simplified overview Figure (refer to indicated pages for more information and more detail)

Regional Paediatric Arterial Ischaemic Stroke Acute Management Guidelines

Introduction

In adults with proven, large vessel Arterial Ischaemic Stroke (AIS), confirmation of the benefits of hyperacute reperfusion therapies (thrombolysis and/or thrombectomy) has led to the development of well-established acute stroke teams and pathways and there is an understandable desire to not exclude appropriate children and young people from such potential advances in treatment.

The narrow window of opportunity for such treatments places a premium on the rapid identification of the very small number of young people who might benefit in the absence of bespoke paediatric stroke services. It will require flexibility of approach from a range of disciplines and what is possible will to considerable extent depend on both when (e.g. in/out of office hours) and to which hospital the young person has presented.

Paediatric arterial ischaemic stroke (AIS) is rare. Excluding perinatal stroke (which is the largest group) there will perhaps be ~5 cases in the northern region per year with marked heterogeneity even in this group. There is something of a bimodal distribution with small vessel disease (e.g. as a complication of varicella) responsible for much AIS in preschoolers; and then a growing incidence of large vessel disease in later childhood and adolescence through into adulthood.

Thrombolytic therapy will only be applicable to children with radiologically demonstrable arterial occlusion. This is thus a subgroup of an already small group: perhaps one or two cases at most per year across the Northern region.

A specific aim of this guidance is to address the scenario of a larger, older teenager (14+) presenting to a hospital with an adult stroke team; and specifically, to encourage involvement of that team to consider thrombolytic therapy locally *prior* to any transfer into Newcastle. This is a scenario that will only be seen in any given centre once every several years, but clinician flexibility and willingness to act outside usual areas of practice may make a huge difference for this small number of young people.

This guidance is intentionally narrow in scope. It only addresses the first few hours, beginning at the moment of first presentation of a child or young person with suspected stroke to an Emergency Department (ED) or other service in the region, until the window for any acute intervention has closed. Paediatricians in the presenting centre may still be playing a key role in care during this phase.

This guidance does not cover matters of post-acute investigation of stroke aetiology or consideration of measures aimed at reducing risk of occurrence. These aspects (and any need for rehabilitation) are typically managed by the GNCH paediatric neurology service and are covered in standard texts.

Although children with cardiac disease are at high risk of stroke this guidance explicitly excludes children on Left Ventricular Assist Devices (LVADs) on the cardiac PICU at Freeman Hospital* although it does include all other “cardiac” children known to Freeman services.

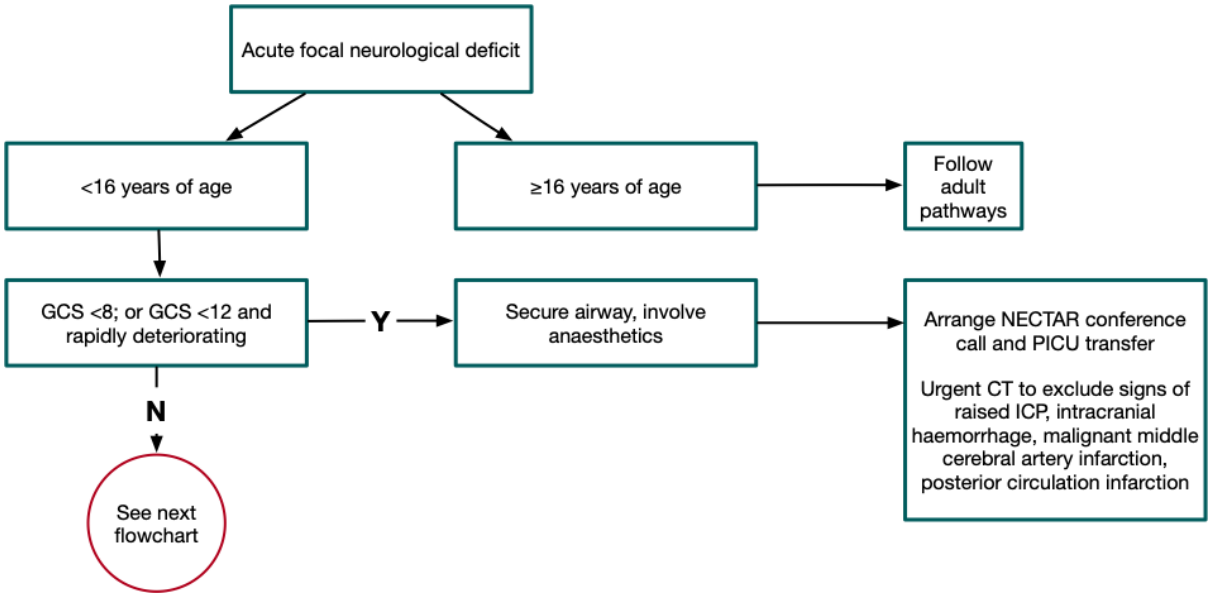
NEXT: STABILISATION

* Although LVADs are a potent cause of AIS this current exclusion is justified on three grounds: (i) AIS in children on LVADs is often subclinical meaning that they cannot be precisely timed and it is not uncommon at the time of identifying a clinically symptomatic stroke to find that previous subclinical AIS events have already occurred; (ii) full and necessarily ongoing anticoagulation, and physical tethering to LVADs preclude interventional neuroadiological procedures; (iii) the risk of AIS is ongoing whilst on LVAD and *repeated* thrombolysis is untested.

Stabilisation

It should be stressed again that acute thrombolysis and/or thrombectomy are appropriate for only a proportion of young people *even with confirmed AIS* (those with demonstrated vessel occlusion) and such considerations should not detract from the first priority of triage, stabilisation and liaison with NECTAR where necessary for the planning of transfer to PICU or HDU.

Figure 2



Acute management

i. ABC: maintain 100% saturation.
ii. Treat hypoglycaemia.
iii. Measure BP.
iv. If GCS <8 needs anaesthetics and NECTAR/PICU input: may need neurosurgical intervention (e.g. evacuation of haematoma) to manage ↑ICP. Consider urgent CT to identify surgically amenable lesions.
v. Treat seizures.

Consult RVI Paediatric Haematology urgently if known sickle cell disease. (Out of hours contact GNCH Paediatric Oncology and/or RVI Adult Haematology who provide on call paediatric haematology advice)

NEXT: CONSIDERATION OF STROKE MIMICS

Consideration of Differential Diagnoses

Stroke presentations in children include acute onset focal neurological deficit (typically hemiparesis ± visual field defect) with or without headache or neck pain.

Important clues in the history include

- Associated otitis media, mastoiditis or tonsillitis (these are more likely to cause *venous sinus thrombosis* rather than arterial ischaemic stroke)
- Varicella infection in the preceding few months typically in a preschool age child. This is an important cause of small perforator artery AIS due to an inflammatory focal arteritis. These children typically show associated large artery *stenosis* but not usually actual occlusion. They typically make good motor recoveries without thrombolysis). The role for high dose steroids in this situation is the subject of an ongoing international RCT.
- Sickle cell disease (these children sustain strokes through the development of large vessel stenosis and compensatory moya-moya: they are not candidates for thrombolysis).
- Abrupt onset (favours haemorrhage or embolus) versus 'stuttering' onset (favours thrombosis).
- History/family history of stroke.

Clinical contexts where there is a higher likelihood of large vessel AIS and thus a potential role for thrombolysis/thrombectomy include:

- Recent flexion/rotation injuries involving the neck (which can be quite trivial: including 'awkward' falls off bicycles, gymnastics accidents etc) causing carotid artery dissection and embolic stroke (a Horner syndrome on side opposite hemiplegia would be strongly suggestive).
- Known left-heart cardiac disease (or right-heart disease with right-to-left shunt).

Unlike in adult medicine **AIS is not the commonest cause of unilateral apparent paralysis in paediatrics**. Although they should not really be confused, the low prior likelihood of true AIS means these differentials ("stroke mimics") should be actively considered and excluded:

Migraine with focal neurological signs

Hemiplegia and other focal neurological signs (e.g. dysphasia) can be a feature of so-called "complicated" migraine. Onset is often gradual (over tens of minutes) and clearly associated with severe headache and prominent autonomic symptoms. It is much easier to be confident of this diagnosis with a past history of similar episodes: in first presentation it is something of a diagnosis of exclusion and may require MRI.

Functional symptoms

Functional ("non-organic") neurological signs may take many forms including apparent hemiplegia. The hallmark of functional symptoms is their attention-dependent severity.

Lower motor neurone facial nerve (Bell's) palsy

Bell's palsy will cause unilateral facial weakness although upper and lower motor neurone facial palsy should not really be confused: weakness of ipsilateral eyelid closure confirms *lower* motor neurone involvement.

Post-ictal (Todd's) paresis

A period of 20-30 minutes weakness in a limb involved in an immediately preceding focal motor seizure.

Others

Tumours, infection, demyelination/inflammation. Onset of the focal signs is usually progressive over time rather than abrupt.

Being well in the week before presentation, GCS ≤ 12, inability to talk or walk, face and arm weakness are associated with ↑odds of AIS.

NEXT: ACUTE NEURORADIOLOGY

Acute Neuroradiology

Diffusion Weighted Imaging (DWI) MRI sequences give the earliest indications of ischaemia and all children presenting with possible stroke will require MRI at some point, however in practice urgent access to MRI from paediatric ED is often limited, particularly outside office hours.

Thrombolysis/thrombectomy is only recommended if it can be delivered within a few hours of *known* onset. Current paediatric guidelines suggest this window to be 4 to 4.5 hours, although adult practice is increasingly extending this timeframe. **This excludes situations where a child has woken with a stroke**.

Although MRI+MRA is the imaging modality of choice, if still within a ~4 hour window and if there is **any barrier to immediate MRI**, CT with CT angiography (CT+CTA) is the optimum initial modality for rapidly identifying situations of Large Vessel Occlusion (LVO) without haemorrhage, and thus the potential for acute reperfusion therapy.

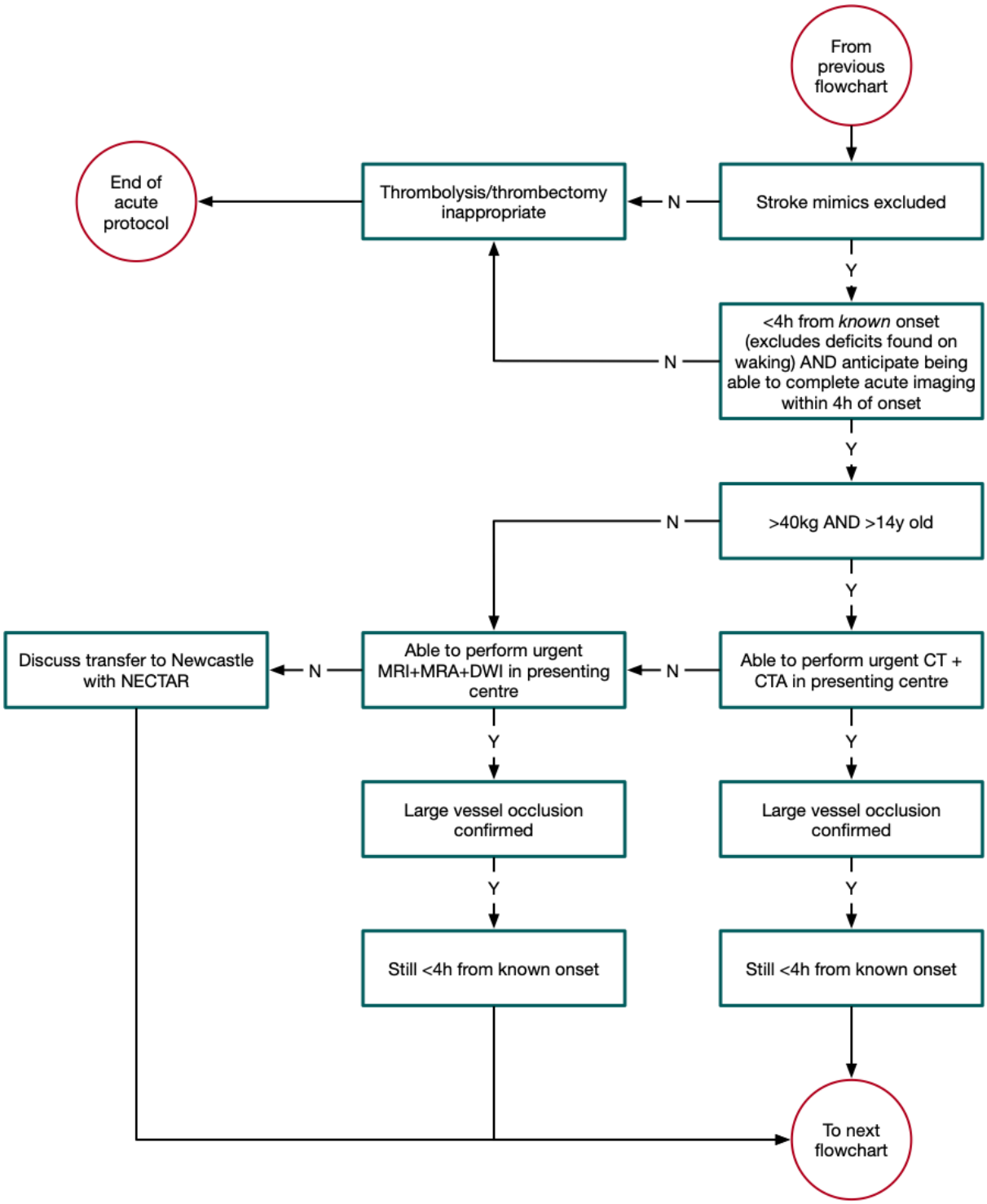
Radiologists more used to suspected stroke in adults will be familiar with using acute CT to exclude haemorrhage (which would contraindicate thrombolysis). *Stronger prior evidence of AIS* is required in children, given the lower prior likelihood of this causing acute focal neurological deficit in comparison to migraine and other mimics, so CT *with CTA* rather than CT alone is required. Although parenchymal changes of ischaemia/infarction are slow to develop on CT (and may be relatively normal in the first few hours post onset), CTA will confirm large vessel occlusion if present and exclude haemorrhage.

CTA requires rapid infusion of contrast which in adults is done using an infusion pump (“Miller protocol”). This is feasible in young people >40kg but requires a large (pink or green) cannula in a large vein to accommodate the flowrate.

- In smaller (<40kg) children, CTA requires hand injection of contrast which in practice will require transfer to Newcastle.
- Although all centres in the Region have access to commercial “AI” automated software (currently Brainomix) for the automated interpretation of CTA however it is only validated for adults and should not be used for paediatric decision-making. Although these systems provide a remote image-sharing and reviewing platform, in practice we suggest using standard PACS transfers.

All sites should have local provision for urgent reporting. RVI diagnostic neuroradiology may be asked to review studies transferred via PACS from other centres where large vessel occlusion is suspected but only where GNCH paediatrics teams are already involved and at their request.

Figure 3



NEXT: THROMBOLYSIS AND THROMBECTOMY

Thrombolysis and thrombectomy

The role of emergency interventions to try to remove clot and restore perfusion in paediatric AIS is the subject of active ongoing research. The evidence base is much poorer than for adult AIS. Some key messages from~~of~~ the paediatric literature are summarised in Table 3 (page 16).

Options include:

- Thrombolysis: infusing fibrinolytic agents (e.g. alteplase or, increasingly, tenecteplase) either intravenously or (less commonly) via endovascular intra-arterial infusion.
- Thrombectomy: mechanical retrieval of clot using endovascular devices.

The potential benefit of arterial recanalization has to be balanced against the risks of adverse effects (particularly major cerebral haemorrhage from thrombolysis). This risk is low (see Table 3 page 16) but more favourable the earlier the intervention can be delivered.

Standard paediatric practice currently is to recommend consideration of thrombolysis within 4 – 4½ hours of *known* ictus (~~i.e.~~ excluding stroke discovered on waking). There is a growing trend in *adult* stroke medicine to consider wider windows of opportunity (up to several hours) in particular situations but paediatric advice does not currently reflect this.

Criteria for consideration of thrombolysis or thrombectomy

Use of tissue plasminogen activator (alteplase, tenecteplase) in children can be considered in children with confirmed AIS where:

Table 1. Inclusion and exclusion criteria for thrombolysis/thrombectomy

Inclusion criteria (all must be met)	Exclusion criteria for thrombolysis (none must apply)	Criteria for thrombectomy
Acute focal neurological deficit consistent with arterial ischaemia	No CNS surgery, trauma, or haemorrhage in the previous 30 days.	No absolute contraindications to interventional neuro-radiology techniques although suspected dissection (due to recent craniocervical trauma or flexion/extension) is a RELATIVE CONTRAINDICATION Normal clotting The therapeutic window for INR may be longer than for thrombolysis (see Post acute imaging on page 13). The feasibility of thrombectomy in smaller children will depend on the availability of catheters of appropriate size and the paediatric experience of the on-call interventional neuroradiologist.
Treatment can be delivered within 4.5 hours of known onset of symptoms (this excludes stroke discovered on waking)	No systemic bleeding in previous several weeks.	
Intracranial haemorrhage has been excluded on CT	No general surgery in the last 7–10 days.	
Paediatric National Institute of Health Stroke Scale (PedNIHSS) score (consult Table 2, page 14) > 4 and < 24	No diagnosis of CNS tumour; uncorrectable thrombocytopenia or coagulopathy; pregnancy; or severe liver disease	
CTA demonstrates partial or complete occlusion of the intracranial artery corresponding to the clinical or radiological deficit and normal brain parenchyma or minimal early ischaemic change with no haemorrhage OR MRI/MRA shows evidence of acute ischaemia on diffusion weighted imaging plus partial or complete occlusion of the intracranial artery corresponding to clinical or radiological deficit.	No cardiopulmonary resuscitation or lumbar puncture in the last 7 days.	

	NOTE: Thrombolysis is not recommended below 2 years of age.	

Practicalities of delivery of thrombolysis or thrombectomy

Refer to Figure 4

Intravenous *thrombolysis* is delivered *to adults* by adult acute stroke teams available in:

- RVI Newcastle
- Cramlington (NSECH)
- UHND Durham
- North Tees
- Sunderland
- Carlisle
- James Cook Middlesborough.

For adolescents >40kg and >14 years of age meeting the criteria of Table 1 who have presented to one of these centres, local delivery of thrombolysis is to be preferred and in the first instance the duty adult stroke physician/advanced nurse practitioner should be contacted via hospital switchboard for advice.

- All these adult stroke services have expressed willingness to *advise* in care of young people over 14. Willingness to *accept clinical responsibility* between the ages of 16 and 18 varies between centres. Willingness (or otherwise) to advise and become involved must be respected
- Unless the adult service is willing to accept clinical responsibility, clinical and prescribing responsibility remain with the paediatric team.
- Similarly it is recognised that paediatricians' willingness to prescribe tPA off licence is a matter of individual choice that must be respected.
- It is recommended that formal consent is obtained from parents documenting the discussion of potential risks and benefits. Useful summary evidence and current guidance on this issue is summarised in Table 3 on Page 16.
- The recommended paediatric dose of IV alteplase is 0.9 mg/kg to a maximum dose of 90 mg. Ten percent of the total dose is given as a bolus over 1 minute and the remaining 90% of the dose infused over the next 60 minutes.
- The recommended paediatric dose of IV tenecteplase is 0.25mg/kg as a bolus.

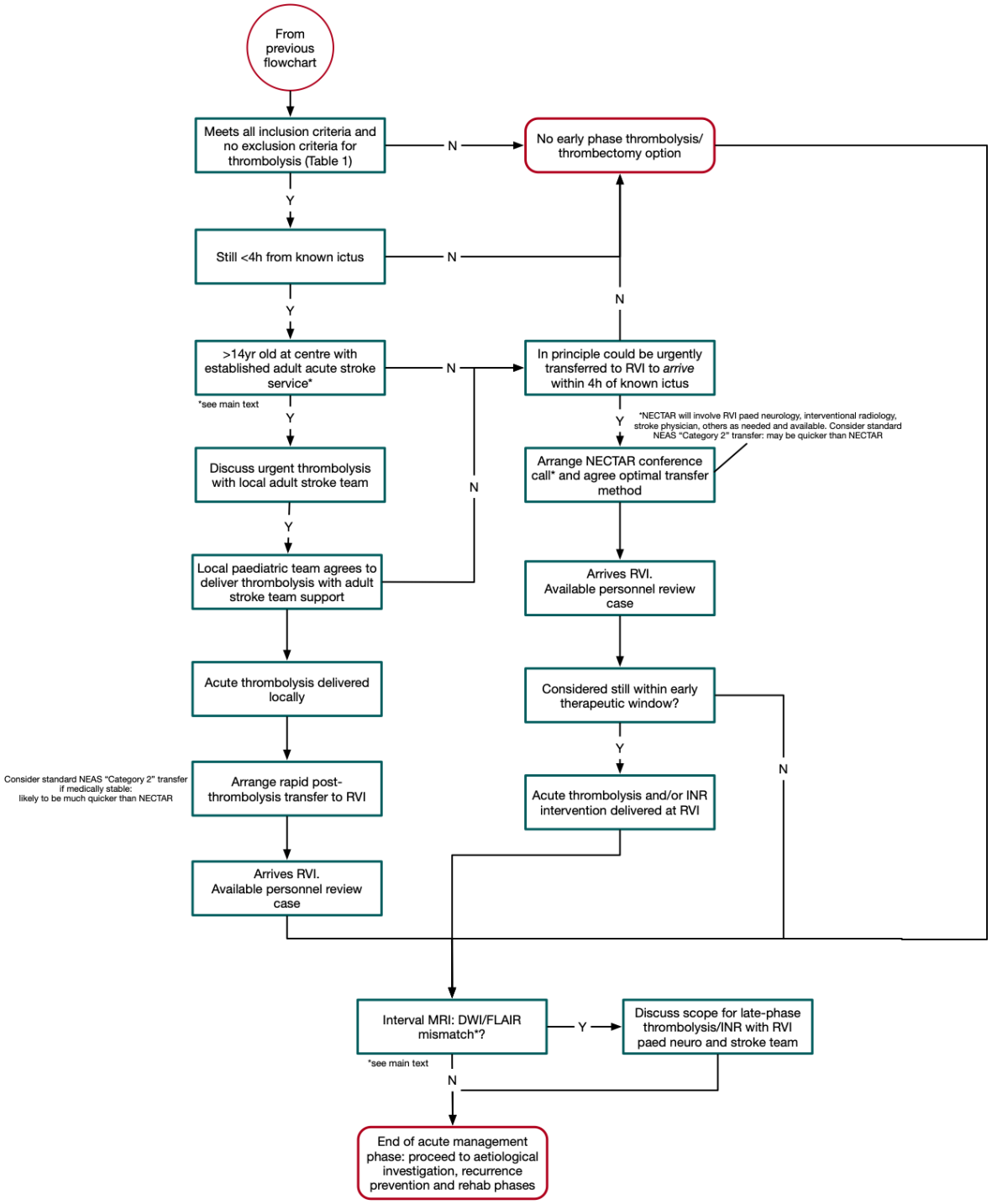
Children ≤14 years of age or <40kg should be discussed urgently with NECTAR (see flowchart in Figure 4) who will convene a conference call with relevant GNCH/RVI teams and agree the most appropriate means of transfer to Newcastle. Acute stroke is recognised by NEAS as a Cat 2 priority and if the child is sufficiently stable, transfer by NEAS should be considered as it may be quicker than a NECTAR retrieval.

- At present the regional paediatric neurology service provides on-call advice 9am – 5pm weekdays and 9am – 1pm weekends only. During these hours they can be contacted via RVI switchboard (0191 233 6161). GNCH general paediatricians covering outside these times will not be able to provide neurology advice.
- *Endovascular* thrombolysis/thrombectomy can only be delivered by interventional neuroradiologists. Interventional neuroradiology (INR) is available at the RVI 9am-6pm seven days per week (and out of hours exceptionally); and at James Cook hospital 9am-5pm weekdays.
- RVI interventional neuroradiologists can be contacted from 7.30am
- The feasibility of interventional radiology intervention will depend on time since ictus and estimated transfer times to an INR centre, the physical size of the patient and the availability of catheters and other equipment of the necessary size.

Discussions with interventional neuroradiology will typically be led by the (adult) stroke physician

NEXT: POST-ACUTE MANAGEMENT

Figure 4


From previous flowchart
Meets all inclusion criteria and no exclusion criteria for thrombolysis (Table 1)
N
No early phase thrombolysis/ thrombectomy option
Y
Still <4h from known ictus
N
Y
N
>14yr old at centre with established adult acute stroke service*
N
In principle could be urgently transferred to RVI to arrive within 4h of known ictus
*see main text
Y
Y
*NECTAR will involve RVI paed neurology, interventional radiology, stroke physician, others as needed and available. Consider standard NEAS "Category 2" transfer: may be quicker than NECTAR
Discuss urgent thrombolysis with local adult stroke team
Arrange NECTAR conference call* and agree optimal transfer method
N
Y
Local paediatric team agrees to deliver thrombolysis with adult stroke team support
Arrives RVI. Available personnel review case
Acute thrombolysis delivered locally
Considered still within early therapeutic window?
Y
N
Consider standard NEAS "Category 2" transfer if medically stable: likely to be much quicker than NECTAR
Arrange rapid post-thrombolysis transfer to RVI
Acute thrombolysis and/or INR intervention delivered at RVI
Arrives RVI. Available personnel review case
Interval MRI: DWI/FLAIR mismatch*?
Y
Discuss scope for late-phase thrombolysis/INR with RVI paed neuro and stroke team
*see main text
N
End of acute management phase: proceed to aetiological investigation, recurrence prevention and rehab phases

Post acute imaging (within 24h)

Whether or not acute thrombolysis was given, there may still be an opportunity for interventional neuroradiological thrombectomy. The “window of opportunity” for thrombectomy may be longer (18-24h post ictus). The key investigation in this regard will be comparison of the extent of the stroked area on FLAIR and DWI sequences can be helpful: brain regions that show restricted diffusion on DWI but *as yet no* FLAIR signal change (“mismatch”) are potentially reversibly ischaemic without established infarction.

The need for post-acute imaging and the scope for further intervention should be discussed with stroke physicians.

Post acute management

Further management of children with AIS, including aetiological investigation, decisions about treatments aimed at recurrence prevention, and rehabilitation, should be led by the paediatric neurology service at the GNCH and will almost certainly entail all children and young people being transferred post-acutely (if not sooner) for this care.

Aspirin therapy

5mg/kg of aspirin (maximum 300mg) once daily should be commenced within 24 h of onset of confirmed AIS in the absence of haemorrhage, however if thrombolysis has been given this should be delayed for 24h.

Aspirin should not be routinely given to young people with sickle cell disease or on anticoagulation, presenting with AIS.

After 14 days reduce dose of aspirin to 1mg/kg (max 75mg) daily.

Duration depends on risk factors identified.

Sickle cell disease

Discuss urgently with GNCH Paediatric Haematology (out of hours, paediatric haematology advice is provided by paediatric oncology and adult haematology). Likely to need urgent transfusion to achieve HbS < 30%, and Hb > 100g/l however this will typically require exchange transfusion. Consider interim transfusion to bring Hb > 100g/l if exchange likely to be delayed by > 6h.

Interval imaging

All children require MRI and MRA within a few days if not achieved acutely. If dissection is suspected (history of trauma, neck pain, headache, posterior circulation stroke ± Horner syndrome implying carotid artery injury) ask for fine basal cuts and fat saturation sequences.

Table 2 Pediatric NIH Stroke Severity Scale (PedNIHSS).

Domain	Operationalisation	Score	
1a. Level of Consciousness:		0	Alert; keenly responsive
		1	Not alert, but arousable by minor stimulation
		2	Requires repeated stimulation to attend, or strong or painful stimulation to make non-stereotyped movements
		3	Responds only with reflex motor or autonomic effects or totally unresponsive
1b. Level of consciousness questions:	"Where is [familiar family member present in room]?" and "How old are you?" (> 2 years)	0	Answers both questions correctly
		1	Answers one question correctly
		2	Answers neither question correctly
1c. Level of consciousness Commands:	Open / close your eyes', 'Touch your nose' (> 2 years)	0	Performs both tasks correctly
		1	Performs one task correctly
		2	Performs neither task correctly
2. Best Gaze:	Assess horizontal eye movements	0	Normal
		1	Partial gaze palsy
		2	Forced deviation / complete gaze palsy
3. Visual:	Visual threat (2–6 years); confrontation, finger counting (> 6 years)	0	No visual loss
		1	Partial hemianopia
		2	Complete hemianopia
		3	Bilateral hemianopia (including cortical blindness)
4. Facial Palsy:	Show teeth/raise eyebrows /close eyes	0	Normal symmetrical movement
		1	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
		2	Total or near total paralysis of lower face
		3	Complete paralysis of one or both sides
5a Motor Left Arm 5b Motor Right Arm	Extend arm 90° (if sitting) or 45° (if supine)	0	No drift for full 10 seconds
		1	Drift ≤ 10 seconds
		2	Some effort against gravity
		3	No effort against gravity
		4	No movement
		5	Amputation
6a Motor Left Leg 6b Motor Right Leg	Extend leg 30°	0	No drift for full 5 seconds
		1	Drift ≤ 5 seconds
		2	Some effort against gravity
		3	No effort against gravity
		4	No movement
		5	Amputation
7. Limb Ataxia:	Reach for/kick a toy (< 5 years); finger-nose/heel-shin (> 5 years)	0	Absent
		1	Present in one limb
		2	Present in two limbs
8. Sensory:	Behavioural response to pin prick	0	Normal
		1	No sensory loss
		2	Mild to moderate sensory loss
		3	Severe to total sensory loss
9. Best Language:	Spontaneous speech and comprehension (2–6 years); describe a picture (> 6 years)	0	Normal
		1	Mild to moderate aphasia
		2	Severe aphasia
		3	Mute, global aphasia

Add the 13 subdomain scores to give a total score between 0 and 43. A score <4 or >24 excludes consideration of thrombolysis.

Table 3 Brief summary of paediatric AIS literature with reference to acute thrombolytic and thrombectomy interventions

The following are some extracts and conclusions of recent reviews and practice guidelines for the benefit of paediatricians and adult stroke physicians unfamiliar with the paediatric literature. There is no class I evidence to support the use of acute thrombolytic or endovascular therapy in paediatric AIS (an RCT closed early because of poor recruitment) nevertheless there is a consensus that these therapies should be considered

- 2019 American Heart Association and American Stoke Association "Scientific Statement" [1]:
  - "In the absence of clinical trial data, a consensus opinion has suggested that when intra-venous tPA is considered in children, the adult [alteplase] dose of 0.9 mg/kg be used, which would likely be a conservative dose because developmental differences in plasminogen levels may actually make the effective dose for children higher"[1].
  - "Mechanical thrombectomy may be considered for acute ischemic stroke due to large vessel occlusion (ICA terminus, M1, basilar artery) in patients aged 1–18 years (Level C evidence; Class IIb recommendation)"[2]
- 2017 Royal College of Paediatrics and Child Health guidance (emphases added):
  - "The off-label use of tissue plasminogen activator (tPA) **could** be considered in children presenting with AIS who are more than eight years of age and **may** be considered for children aged between two and eight years of age on a case-by-case basis when [the criteria in Table 1] have been met" [3]
- Risk of intracerebral haemorrhage in children receiving thrombolysis is increased over controls not receiving thrombolysis (RR 3.48, CI 1.7-7.3) [4] but remains lower than in adults (2.1% vs 6.4%) when given within 4.5h of ictus[5].
- Younger children have lower levels of endogenous tPA and higher levels of plasminogen activator inhibitor-1 (PAI-1) compared with older children and adults: thus doses extrapolated from adult experience may be relatively low, with consequently lower likelihoods of both wanted and unwanted effects.

References

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2. Bhatia K, Kortman H, Blair C et al. Mechanical thrombectomy in pediatric stroke: systematic review, individual patient data meta-analysis, and case series. J Neurosurg Pediatr. 2019;24:558-571.

3. Royal College of Paediatrics and Child Health. Stroke in childhood: Clinical guideline for diagnosis, management and rehabilitation [section 6.2.1]. 2017

4. Pacheco JT, Siepmann T, Barlinn J et al. Safety and efficacy of recanalization therapy in pediatric stroke: A systematic review and meta-analysis. Eur J Paediatr Neurol. 2018;22:1035-1041.

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