Emergency Neurological Life Support: Acute Ischemic Stroke

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Abstract

Acute ischemic stroke (AIS) is a neurological emergency that can be treated with time-sensitive interventions, including intravenous thrombolysis and endovascular approaches for thrombus removal.

Numerous studies have demonstrated that rapid, protocolized assessment and treatment is essential to improving neurological outcomes.

For this reason, management of AIS was chosen as an Emergency Neurological Life Support (ENLS) protocol.

The protocol focuses on the early identification and initial management, within the first hour(s) following acute onset of a neurological deficit.

The highlights of this module include identification of AIS using prehospital stroke scales, prehospital triage and transportation of a suspected stroke patient, an algorithm for emergent evaluation of AIS with target benchmarks, updated inclusion and exclusion criteria for intravenous thrombolytic use, selection criteria for endovascular therapy, and early management of patients with AIS and transient ischemic attack (TIA) who are not candidates for intravenous thrombolysis or endovascular therapy.

Key words: Ischemic stroke, Endovascular therapy, Transient ischemic attack, Alteplase

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1 Introduction

According to the World Health Organization statistics, cerebrovascular disease is the second leading cause of death worldwide, and one of the leading causes of disability[1]. In the United States, approximately 795,000 strokes occur annually, of which nearly 25% are recurrent strokes[2]. Stroke is the 5th most common cause of death and the leading cause of disability in the United States. Although there have been many new advances in the treatment of stroke, it is crucial that proper diagnosis and management occur as soon as possible, since delays in therapy are associated with worse neurological recovery[3].

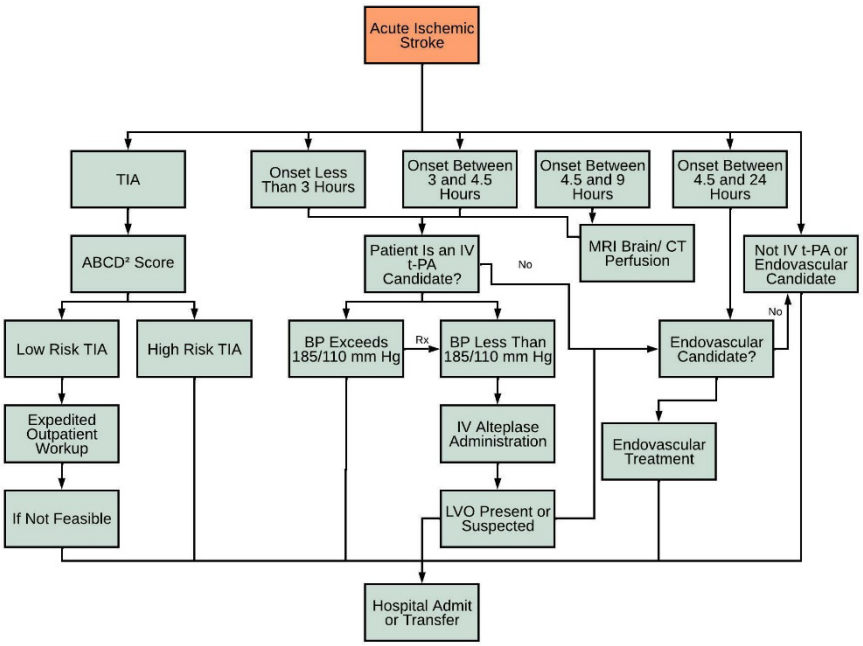

FIGURE 1
ENLS Acute Ischemic Stroke protocol The Acute Ischemic Stroke (AIS) algorithm is a broad overview of the initial evaluation of an acute stroke patient and is a quick reference for the major treatment options.

2 Management Protocol

The ENLS algorithm for initial management of acute ischemic stroke (AIS) is shown in Figure 1. Suggested items to complete within the first hour of evaluating a patient with AIS are shown in Table 1.

The most important information that guides therapy is the last known well (LKW) time or time of symptom onset. All patients with LKW time <24 hours should be emergently evaluated for an AIS.

Thrombolytics should be administered to all patients with LKW time <4.5 hours that meet the inclusion and exclusion criteria and should be considered for patients who present between 4.5 to 9 hours, many of these could be wake up strokes.

All patients < 24 hours of symptom onset who have an NIHSS ≥6 should be evaluated with CT angiogram / CT perfusion (CTA/CTP) or multimodal MRI including diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI) with intracranial vessel imaging for the presence of a large vessel occlusion (LVO).

If the patient has an LVO and favorable perfusion studies, they should be emergently taken for endovascular intervention or transferred to a facility for this. In patients with complete resolution of symptoms upon evaluation, expedited work up for a TIA should be initiated.

TABLE 1
Acute ischemic stroke checklist for the first hour

Acute ischemic stroke checklist for the first hour
☐ Activate stroke code system (if available)
☐ Vital Signs
☐ Supplemental oxygen to maintain saturation ≥ 94%
☐ Determine time of onset / last known well (LKW)
☐ Determine NIHSS score
☐ CT, CTA with CTP (0 – 24 hours of LKW) or MRI DWI with MR perfusion (4.5 – 9 hours of LKW and ineligible for thrombectomy)
☐ Medication list*
☐ IV access - 18g peripheral IV
☐ Labs: Fingerstick glucose, CBC with platelets, PT/ INR, PTT, and beta-HCG for women of child-bearing age
☐ EKG

** When asking about medications, be sure to ask specifically about anticoagulants and when medication was last taken/administered.*

3 Prehospital Considerations

The prehospital providers play a key role in the multidisciplinary effort in assessing, transporting and providing timely acute care for an AIS patient. Providers should always err on the side of caution in triaging patients to stroke receiving facilities, utilizing emergent ground and air transport and resources. Stroke-receiving facilities should be active in working with local emergency medical services (EMS), regulatory agencies and providers to ensure continuity of care and best practices across all levels of care for the AIS patient.

3.1 Clinical Suspicion of Stroke and Prehospital Transportation

Acute stroke is suspected when a patient exhibits a sudden onset of focal neurological deficit (e.g., facial droop, arm/leg weakness, ataxia, sudden onset vertigo or dizziness,

aphasia, dysarthria, vision disturbances, gaze preference, sensory disturbances, neglect, or other focal findings).

In the absence of an observed seizure, the deficit can most likely be attributed to stroke or TIA. The time from symptom onset to arrival at an emergency department (ED) is the greatest source of delay and a frequent cause of ineligibility for reperfusion therapies.

In countries that treat stroke as an emergency, prehospital personnel are typically the first to evaluate these patients at their homes or at a scene (Figure 2). Patients with suspected acute stroke should be triaged with the same priority as serious trauma or acute myocardial infarction, regardless of the severity of deficit.

The "Implementation of Strategies for Emergency Medical Services Within Stroke Systems of Care" policy statement outlines specific parameters for the Emergency Medical Services Systems (EMSS)[4]:

- Stroke patients are dispatched at the highest level of care available in the shortest time possible.
- Time between the receipt of the call and dispatch of the EMSS team is < 90 seconds.
- EMSS response time is < 8 minutes (time elapsed from the call receipt to arrival on the scene by the equipped and staffed ambulance).
- The on-scene time is <15 minutes (barring extenuating circumstances such as extrication difficulties).
- Travel time expectation is equivalent to trauma or acute myocardial infarction calls.

Standard treatments for EMSS are to perform routine airway, breathing, and circulation (ABC) assessments; administer supplemental oxygen as needed; check blood/capillary glucose and treat hypoglycemia (glucose <60 mg/dl); and perform a validated stroke severity scale examination eg: Field Assessment Stroke Triage – (Emergency Destination (FAST-ED)[5], Rapid Artery Occlusion Evaluation (RACE)[6], Los Angeles Motor Scale (LAMS)[7], Cincinnati Prehospital Stroke Scale (CPSS)[8]).

Rapid IV access (ideally 18 g placed) should be obtained to facilitate contrast imaging.

The last known well time or symptom onset plays a critical component in the evaluation of a patient suspected to have an AIS, and every effort should be made to establish this while balancing the on-scene time guidelines and without delaying transport time.

Thus, a strong consideration should be made to either bring a witness in the ambulance, or have their contact information available for the ED staff. Prehospital systems should call ahead to the receiving hospital, and patients should preferentially be transported to the appropriate certified stroke center (Table 2) [4].

In patients that are ineligible for thrombolytics and suspected to have an LVO, direct transport to a thrombectomy capable center is recommended [3].

Patients may have a stroke while in the hospital, at rehabilitation centers, or nursing homes, or may present directly to an ED triage.

Nurses or Advanced Practice Providers (APPs) may be the first health care providers to have contact with the patient in these circumstances; therefore, it is important for them to recognize and respond quickly and appropriately.

In cases of uncertainty, with respect to whether a patient is having a stroke and stroke team activation is necessary, the simple mantra "If in doubt, call it out" is best.

TABLE 2
Prehospital Standard Assessment and Treatment

Prehospital Standard Assessment and Treatment
☐ Perform history and physical exam
☐ Determine time patient was last known well (LKW)
☐ ABCs (routine airway, breathing, and circulation assessments)
☐ Administer supplemental oxygen as needed
☐ Check blood/capillary glucose
☐ Perform a stroke severity scale examination (FAST-ED, RACE, LAMS, CPSS)
☐ Obtain intravenous (IV) access
☐ Obtain blood tubes vials for evaluation at the receiving stroke center (optional)
☐ Transport the patient to the closest certified stroke center
☐ Rapid transport of patients that are ineligible for IV thrombolysis that have a high probability of LVO should be performed
☐ Activate pre-hospital notification
☐ To decrease door to imaging time, strongly consider a brief doorway assessment on arrival to the ED and take the patient to brain imaging on the EMS gurney

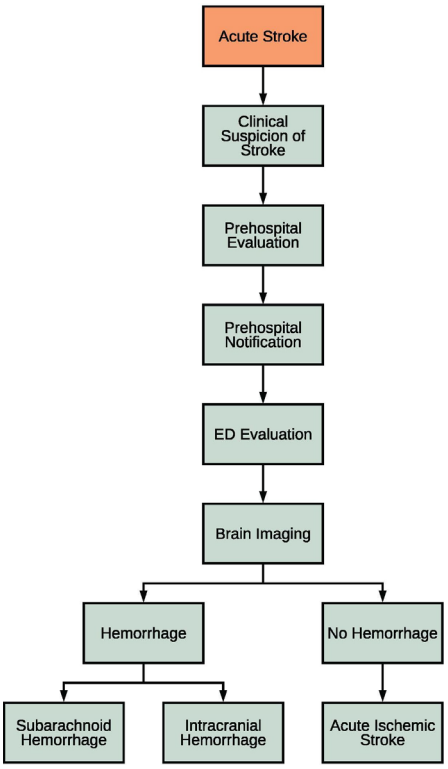

FIGURE 2

Clinical suspicion of stroke algorithm: This algorithm assumes the patient is outside of the hospital when stroke occurs. Based on the results of brain imaging, the patient can be triaged to one of the three ENLS protocols (bottom): **Subarachnoid Hemorrhage**, **Intracranial Hemorrhage**, or **Acute Ischemic Stroke**.

4 Emergency Department

4.1 Diagnosis

Immediately on arrival to an ED, patients should be screened for stability, undergo rapid clinical stroke assessment ("at the door"), then be taken directly for rapid imaging, with non-contrast computed tomography (CT). Non-invasive CTA of head and neck should be obtained as quickly as possible to expedite the identification of an LVO. These are often completed in succession, but should not delay the administration of thrombolytics for eligible patients [9, 10]. Some centers use limited MRI, MRA and MR perfusion studies instead of CT.

In the United States, the Joint Commission (TJC) has recommended benchmark metrics for acute evaluation and treatment of the acute stroke patient. Similarly, ENLS recommends targeting goals based on the metrics outlined by the respective local or national organizations.

Interval	Target
Door-to-Provider	10 minutes
Access to neurological expertise	15 minutes
Door-to-CT completion	20 minutes (in at least 50% of patients)
Door-to-CT interpretation	45 minutes
Door-to-IV thrombolytics	60 minutes (primary objective) 45 minutes (secondary objective)
Door-to-Puncture time for endovascular intervention	90 minutes
Door-to-Recanalization	120 minutes
Admission to stroke unit or ICU	3 hours

Utilization of "telestroke" networks (hub-and-spoke model) is helping to solve the shortage of neurologists in rural areas and has demonstrated high rates of safe administration of thrombolytics while decreasing time to initiate thrombolytics[11, 12].

Hemorrhage, mortality rates, and functional outcomes are comparable to randomized trials of patients treated live at study sites.

Many regional arrangements have been made for "telestroke" consultation in order to expedite the administration of thrombolytic therapy in the "drip-and-ship" model followed by transfer to a higher-level certified stroke center if necessary or possible.

If patients are eligible for thrombolysis, it should be administered prior to transport. Transport of patients from spoke to hub (originating to destination site) may involve air medical transport.

Mobile Stroke Units are slowly emerging across the country and provide availability of CT scanner and IV thrombolytic therapy when patients are in the ambulance, thus helping to cut down the time of thrombolytic administration in certain cases.

Currently there are no recommendations from the American Heart Association/American Stroke Association (AHA/ASA) on the time for evaluation of patients and transfer from an outside hospital to the receiving hospital for endovascular therapy.

Interhospital transfer of AIS patients is associated with delay in Endovascular Therapy (EVT) and worse clinical outcomes[13].

Direct transfer from the outside hospital or the emergency department to the thrombectomy suite prior to hospital admission in patients who meet the criteria have reduced the door to groin times[14].

Delays in evaluating, treating, and transferring an AIS patient to an accepting hospital should be minimized.

One method to accomplish this is for primary stroke centers to establish ongoing transfer agreements with nearby comprehensive or endovascular-ready hospitals.

Protocols for prehospital triage and interhospital transfer of patients should be established and approved beforehand so that efficient patient transfers can be accomplished at all hours of the day and night[4].

As shown in Figure 2, imaging is essential to confirm the correct diagnosis and exclude intracranial hemorrhage. If the non-contrast head CT is negative for hemorrhage, an AIS or TIA must be considered for acute onset of neurological symptoms.

When confronted with a patient whose focal neurological symptoms have begun within the preceding few hours, it should be assumed that the patient would eventually be diagnosed with stroke.

Most TIAs are brief, typically lasting less than 20 minutes before completely resolving. Therefore, if the patient is still manifesting physical signs of a stroke in the ED, those signs must be managed as if the patient is having a stroke.

In some centers, patients may be screened for clinical stability immediately upon arrival (“at the door”) and taken directly to CT based on clinical symptoms suspicious for acute stroke.

However, there are a number of stroke mimics including seizure, hypoglycemia, sepsis, fever, migraine , and Bell’s palsy. Given that treatment of AIS is time-sensitive, it is not uncommon for patients with stroke mimics to be treated with thrombolysis.

Stroke mimics should be ruled out as best as possible; however, if mimics are inadvertently treated with thrombolytics, there seems to be minimal risk of adverse effects associated with their utilization[15, 16].

Ultimately, if the patient is manifesting physical signs of a stroke in the ED and falls within AHA/ASA recommendations, then thrombolytics should be offered and administered[2, 3, 17].

Each of the following elements should be addressed in rapid protocolled succession.

4.2 Time of Symptom Onset

One of the chief criteria used to select patients for acute stroke interventions is the patient’s time of stroke onset defined as LKW time or alternatively the time of symptom onset (if witnessed).

Acute stroke treatment therapies such as thrombolysis are time sensitive, and delays can lead to a lower likelihood of a good outcome and an increased risk of intracranial hemorrhage[18].

The LKW time without neurological deficits must be established from the patient or a bystander. If the patient went to bed and awoke with the stroke symptoms, the LKW time is considered to be when the patient went to bed.

It is always worthwhile to ask the patient or family member about getting up during the night to go to the bathroom as the information may allow changing the LKW time to a more recent time, which may place the patient back into a treatable time window for thrombolysis.

In patients with AIS with unknown last known well time who are ineligible for thrombectomy, intravenous altelpase in patients with MRI showing diffusion positive and FLAIR negative lesions (WAKE – UP trial) has resulted in significant improvement in functional outcome at 3 months[3, 19, 20].

The results of endovascular therapy in patients with perfusion mismatch on imaging with LVO have also clearly benefited this subset of patients from the DAWN and DEFUSE-3 studies[20-22].

Recent data from Chinese patients with AIS has shown that endovascular thrombectomy alone was noninferior with regard to functional outcome when compared to thrombectomy with intravenous alteplase in patients with LVO[23].

However, until more data is available, intravenous thrombolysis must be recommended in all eligible patients.

4.3 Vital Signs

Pulse oximetry should guide whether the patient needs supplemental oxygen to achieve an oxygen saturation ≥ 94%.

Hyperoxia may be detrimental in stroke, so there is no need for high flow oxygen for patients with adequate oxygenation [3, 4].

Blood pressure (BP) measurements are vital and must be obtained frequently, especially in the early management of AIS.

Hypotension is uncommon in AIS and may indicate recrudescence of symptoms of a previous stroke due to poor perfusion of previously injured tissue.

It is recommended that hypotension should be corrected to maintain systemic perfusion to support organ function[15].

Blood pressure in excess of 220/120 mmHg should be lowered, regardless of the ultimate diagnosis; however, allowing permissive hypertension (i.e. allowing BP to rise naturally) up to 220/120 mmHg for AIS patients deemed not to be candidates for thrombolysis, including those who have failed attempts to lower BP to allow eligibility, has been suggested[9].

If the patient is a potential thrombolysis candidate, interventions to control BP should be initiated immediately.

In this manuscript, the term intravenous thrombolysis is used to discuss both IV-tissue plasminogen activator (tPA)/alteplase and Tenecteplase (where applicable).

Target BP goals for patients eligible for IV alteplase is < 185/110 mmHg, and once it is initiated, BP must be maintained below 180/105 mmHg for 24 hours after administration of IV alteplase to limit the risk of intracranial hemorrhage.

A strategy for careful BP lowering should be employed while ensuring large fluctuations in BP once at goal are limited.

Short-acting intravenous agents such as labetalol, nicardipine, clevidipine, urapidil, or hydralazine are preferred (see Table 3) to achieve a BP < 180/105 mmHg.

Intravenous clonidine is sometimes used, but this is not available in the United States. Hypertension is common in the setting of AIS.

Titratable IV antihypertensive agents like , nicardipine, clevidipine, and labetalol infusions are preferred, although urapidil and hydralazine can also be used for treatment of hypertension in the acute setting[3].

There is variability in the specific agent used for BP lowering across the world in the acute setting.

TABLE 3

Intravenous Antihypertensive Agents Used to Lower Blood Pressure to Attain Alteplase Eligibility

Labetalol

• Start with 10 to 20 mg IV bolus over 1 to 2 minutes; may repeat every 10 minutes.

Onset of action 2 – 5 minutes, peak effect 5-15 minutes and duration of action 16-18 hours and is dose dependent (e.g. longer effect with multiple doses).

• Consider doubling dose (i.e., 20 mg, 40 mg, 80 mg) to a maximum total dose of 300 mg, followed by a maintenance infusion (0.5-10 mg/min).

The importance of the maintenance infusion should not be underestimated or dismissed.

If a bolus was required to lower the blood pressure, then the BP should be assumed to climb again as soon as the bolus wears off, potentially placing the patient in danger of ICH due to the uncontrolled BP.

Start an infusion if labetalol boluses successfully lower the BP.

Accumulation of labetalol after multiple doses may lead to prolonged hypotension.

If the patient is no longer deemed a candidate for alteplase and permissive hypertension is being planned, then the infusion may be discontinued, provided the BP does not rise above 220/120 mmHg.

Hydralazine

• 10 to 20 mg IV every 4 – 6 hours.

• In hypertensive crisis 5 – 10 mg IV/IM initially, then 5 – 10 mg every 0-30 min PRN or 0.5 – 10 mg/hour IV infusion.

Dose is increased and decreased by 2 mg/hour every 10 minutes

• Onset of action 5 – 20 minutes, duration 2 – 12 hours and half-life 2 – 8 hours

Nicardipine

• Begin with 5 mg/hour IV infusion.

• Titrate by 2.5 mg/hour at 5 – 15 minute intervals to a maximum total dose of 15 mg/hour to achieve goal BP.

Be prepared to lower the dose once target BP has been reached.

Continued on next page

Table 3 continued

- Onset within minutes, half-life 2 hours and duration of action 0.5 – 3 hours.

Clevidipine

- Begin with 1 – 2 mg/hour IV infusion.
- Double the dose every 90 seconds until BP goal is neared, then increase in smaller increments until desired BP goal is reached. Maximum dose is 32 mg/hr.
- Onset 2 minutes, half-life 1 minute and duration of action 5 – 15 minutes.

Urapidil

- Bolus of 12.5 – 25 mg followed by continuous infusion at a rate of 5 – 40 mg/hour.
- Onset in 3 – 5 minutes and duration of action 4 – 6 minute

Clonidine

- Initial oral dose of 0.1 – 0.2 mg followed by hourly doses of 0.05 – 0.1 mg until goal blood pressure is achieved
- Total dose of 0.3 mg
- *Clonidine** Begin with 75 mcg bolus followed by intravenous infusion of 0.2 mcg/kg/min and not to exceed 0.5 mcg/kg/min. Not to exceed 0.15 mg per infusion or >0.9 mg/day * parenteral formulation in US only for epidural administration

Sodium Nitroprusside

- 0.3 – 0.5 mcg/kg/min initially, increase by 0.5 mcg/kg/min every few minutes to achieve desired effect, maximum 10 mcg/kg/min, but recommend maintaining < 3 mcg/kg/min to avoid toxicity
- Onset in < 2 minutes, duration 1 – 2 minutes and half-life 2 min.

If the patient's BP proves refractory to the above medications, the patient is considered to be high risk for intracerebral hemorrhage (ICH) and should not be treated with thrombolysis.

However, efforts to reduce BP below 220/120 mmHg should be continued. Permissive hypertension up to 220/120 mmHg is allowed for TIA, as it is for patients who did not receive thrombolytics.

This elevated blood pressure may be gradually lowered over the next 24 – 48 hours[15].

4.4 Laboratory Examination

A complete laboratory examination for AIS includes capillary blood glucose (CBG), complete blood count (CBC) with platelets, chemistries, prothrombin time/partial thromboplastin time (PT/PTT), international normalized ratio (INR), and beta-human chorionic gonadotropin (HCG) for women of childbearing age. The only required lab prior to administration of IV thrombolysis is CPG (fingerstick glucose) since it can be completed quickly to rule out hypoglycemia as a stroke mimic[9].

The safety of thrombolytic use in patients taking direct thrombin inhibitors or direct factor Xa inhibitors is not firmly established. It may be prudent to check a thrombin time (TT), and/or Ecarin clotting time (ECT), or chromogenic anti-Xa activity assays, respectively. While accurate cut-off points of these labs have not yet been determined, negative results may assist in identifying the patient who is non-compliant with this class of medications, and therefore eligible for thrombolysis. Many hospitals may not have these laboratory tests/results available quickly within the thrombolysis window. Currently, the AHA does not provide recommendations on reversing oral anticoagulants with their antidotes in order to give thrombolysis[3]. However, this may be considered on selected patients based on the preliminary observational data[24]. If a patient is deemed a candidate for thrombolysis and there is no reason to suspect abnormal laboratory test results, thrombolytics should be administered without waiting for these laboratory values to prevent further delay. If the patient's coagulation and platelet count results are abnormal (INR >1.7 or PT is abnormally elevated, platelet count <100,000 mm3) then thrombolytics should be discontinued[9].

4.5 Imaging

With EMS prehospital notification of a potential stroke patient, a doorway assessment by the clinician and simultaneous patient registration can facilitate rapid patient transport to imaging. There should be a goal of completing a head CT scan and/or MRI within 20 minutes of the patient's arrival in at least 50% of patients who are candidates for thrombolysis and/or mechanical thrombectomy[3]. CTA of the head and neck and CT Perfusion should be completed, when possible, with this initial CT. These multimodal imaging studies should not delay administration of thrombolytics[3]. Chest x-ray is no longer routinely recommended during the acute phase of the workup[9].

4.6 Activate Stroke Team

If available, the stroke code system should be activated prior to arrival. The acute stroke team should evaluate the patient <15 minutes of the patient entering the ED[9]. The composition of the stroke team will vary between centers but usually consists of one or more of the following: neurologist, ED physician, resident or APP, rapid response nurse who is specifically trained in recognition and acute management of AIS, and pharmacist. Again, prehospital notification by EMS and paging the stroke team can expedite patient assessment on arrival and in CT, thereby decreasing time to determine thrombolytic candidacy.

4.7 NIHSS

The National Institutes of Health Stroke Scale (NIHSS) is the preferred stroke severity rating scale recommended as a standardized method for examiners to reproducibly and quantifiably assess a patient's stroke symptoms[25]. Scores range from 0 (no deficit) to 42 (Table 4).

TABLE 4
NIHSS

Category	Scale Definition	Score
1a. Level of consciousness	0 = Alert	
	1 = Not alert, arousable by minor stimulation	
	2 = Not alert, requires repeated stimulation	
	3 = Unresponsive, responds only with reflex	
1b. Level of consciousness questions	0 = Answers both questions correctly	
	1 = Answers one question correctly	
	2 = Answers neither question correctly	
1c. Level of consciousness commands	0 = Performs both tasks correctly	
	1 = Performs one task correctly	
	2 = Performs neither tasks correctly	
2. Best gaze	0 = Normal	
	1 = Partial gaze palsy	
	2 = Forced deviation	
3. Visual	0 = No visual loss	
	1 = Partial hemianopia	
	2 = Complete hemianopia	
	3 = Bilateral hemianopia	
4. Facial palsy	0 = Normal	
	1 = Minor paralysis	
	2 = Partial paralysis	
	3 = Complete paralysis of one or both sides	
5. Motor arm	0 = No drift	

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Table 4 continued

5a. Left arm	1 = Drift
5b. Right arm	2 = Some effort against gravity
	3 = No effort against gravity
	4 = No movement
6. Motor leg	0 = No drift
6a. Left leg	1 = Drift
6b. Right leg	2 = Some effort against gravity
	3 = No effort against gravity
	4 = No movement
7. Limb ataxia	0 = Absent
	1 = Present in one limb
	2 = Present in two limbs
8. Sensory	0 = Normal; no sensory loss
	1 = Mild to moderate sensory loss
	2 = Severe to total sensory loss
9. Best Language	0 = No aphasia; normal
	1 = Mild to moderate aphasia
	2 = Severe aphasia
	3 = Mute, global aphasia
10. Dysarthria	0 = Normal
	1 = Mild to moderate dysarthria
	2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality
	1 = Visual, tactile, auditory, spatial or personal inattention

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Table 4 continued

NIHSS Score	Risk of Intracranial Hemorrhage

**Powers WJ, et al. 2019 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019; 49: e344-e418.*

The NIHSS has some limitations especially in scoring brainstem strokes and estimating the severity of a right hemispheric stroke. In the 2007 AHA/ASA guidelines, an NIHSS of 4 was a threshold to treat AIS with thrombolytics, but in the 2019 guidelines, a low score is not an absolute contraindication and potential risks should be weighed against anticipated benefits. While the NIHSS helps to standardize the exam, a better tool to determine whether or not to recommend thrombolysis in patients with a low NIHSS is to determine if the symptoms are disabling to the patient. In mild strokes, asking the patients directly if their symptoms are disabling or hindering them will often make the decision process easy. It is notable that in a large 2011 study of patients deemed "too good to treat," 28% could not be discharged home and another 28% could not walk independently at discharge[26]. Other studies in patients with minor strokes have demonstrated lack of significant difference in outcomes and increased risk of symptomatic hemorrhage from thrombolytic use[27, 28]. Clinicians should carefully consider, and document, the individual patient's relative risks, potential benefit, and premorbid status when evaluating a patient for treatment with thrombolysis.

Health care providers wishing to learn how to perform the NIHSS and receive free certification can find these resources online through the American Stroke Association and the National Stroke Association.

The NIHSS score may also be used as a guideline to predict a relative risk of ICH in patients who are given thrombolytics, as shown in Table 5[29]. However, despite this escalating risk of hemorrhage, the benefits of thrombolytic therapy must continually be weighed against the risk for all eligible AIS patients.

TABLE 5
Risk of Intracranial Hemorrhage with IV Alteplase Treatment

NIHSS Score	Risk of Intracranial Hemorrhage
0–10	2–3%
11–20	4–5%
> 20	17%

Summers D, 2009 [34]

5 Management

5.1 Intravenous Fluids

Patients presenting with AIS are typically hypo- or euvolemic. Hypovolemia should be corrected in the setting of AIS as it can worsen ischemic injury as a result of impaired perfusion to brain tissue.

Hypovolemia may exacerbate ischemic brain edema and increase stress on the myocardium.

Euvolemia is desirable in the acute stroke setting and most stroke patients should receive maintenance isotonic intravenous fluids in the form of sodium chloride 0.9%.

Hypotonic and dextrose containing fluids should be avoided. The utilization of plasma volume expanders has not demonstrated benefit.

5.2 LKW < 3 Hours: IV Thrombolysis

Alteplase is a thrombolytic medication and is the only tissue plasminogen activator approved for treatment of acute stroke in the United States. When patients present <3 hours since their LKW time, then eligibility for IV thrombolytic therapy should be assessed as well as ensuring no contraindications exist (Table 6).

One relative contraindication is "clearing neurological deficit." However, some patients will have symptom resolution without thrombolytics, but others may have some improvement from a severe stroke yet fail to improve further.

If a patient has plateaued or still has significant stroke symptoms without contraindication, treatment with thrombolysis should proceed.

Also, some patients will present with stuttering symptoms.

If symptoms completely resolve, clinicians should reset the clock to start a new thrombolysis candidacy window; if there are still symptoms - however mild - the time of onset remains unchanged.

Patients with stuttering symptoms tend to be high risk for extending their vascular occlusions.

Be aware that some patients will have pressure-dependent lesions and lowering of blood pressure may actually exacerbate their symptoms; conversely, allowing their blood pressure to rise permissively up to accepted thresholds of 220/120 mmHg (when not given thrombolytics) may improve their deficits.

TABLE 6
Eligibility and absolute contraindication for use of IV alteplase (AHA/ASA 2019 Guide- lines)—Abbreviated version

Eligibility

- Ischemic stroke symptoms causing measurable neurological deficit. These range from mild but disabling to severe stroke symptoms.
- Onset less than 3 hours from start of symptoms.
- Patient is ≥ 18 years of age.

Absolute exclusion criteria

- Major head trauma, ischemic stroke, intracranial/spinal surgery in the previous 3 months
- History of intracerebral hemorrhage or intracranial neoplasm
- Signs and symptoms suggestive of subarachnoid hemorrhage, infective endocarditis or aortic arch dissection
- GI malignancy or recent bleeding within 21 days
- Taking direct thrombin inhibitors or direct factor Xa inhibitors unless a PTT, INR, platelet count, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or has not received a dose for >48 hours (with normal renal function)
- Platelets <100,000/mm3, INR >1.7, aPTT >40 seconds, PT >15 seconds
- Currently taking full treatment dose of low molecular weight heparin within previous 24 hours
- Concomitant abciximab or IV aspirin
- CT shows severe hypoattenuation, hypodensity >1/3 of cerebral hemisphere or intracerebral hemorrhage

Additional recommendations

- 3 – 4.5 hours: IV thrombolytics is safe in patients >80 years, patients on warfarin with INR ≤ 1.7, prior stroke with diabetes
- Wake-up and unknown time of onset: IV thrombolytics is safe in patients aged 18 – 80 years, with NIHSS ≤ 80 years, ineligible for thrombectomy with > 4.5 hours of LKW or from baseline state with a DWI-MRI lesion smaller than one-third of MCA and no visible signal on FLAIR.
- IV alteplase is reasonable in patients with early improvement but moderately disabled, seizure at symptom onset if deficits are from stroke, lumbar dural puncture in previous 7 days, major surgery or trauma not involving the head in previous 14 days, extracranial cervical dissections, unruptured intracranial aneurysm, small number (1 – 10) of cerebral microbleeds on MRI, extra-axial intracranial neoplasm, acute or recent MI in the past 3 months, acute pericarditis, diabetic retinopathy, sickle cell disease, angiographic procedural stroke, pregnancy, illicit drug use and stroke mimics.

It is important to recognize that the majority of experience with the administration of thrombolytics over the past 20 years has utilized treatment algorithms consistent with the AHA / ASA guidelines. Some contraindications to thrombolytic use are time (duration from first symptom > 4.5 hours), recent surgery, current bleeding at a non-compressible site, as well as large area of cerebral infarction that is already apparent as low density on the initial brain CT or MRI study (>1/3 of the middle cerebral artery (MCA) territory).

Patients with major neurological deficits have a high risk of poor outcome, regardless of whether or not thrombolysis is administered. In these cases, realistic expectations and risks associated with either choice should be discussed with the patient's family members, and a joint decision should be made. While a glucose level greater than 400 mg/dL / 22.2 mmol/L is not a contraindication, it should be noted that high glucose may be a stroke mimic, can be associated with worse outcome, and may increase the risk of intracranial hemorrhage[30].

Similarly, the presence of fever should prompt a reconsideration of the diagnosis. For example, a urinary tract infection can bring back old, subclinical stroke symptoms and, once corrected, these stroke-like symptoms may resolve.

5.3 LKW Between 3-4.5 Hours: IV thrombolysis

In the United States, the FDA has not yet approved thrombolytic use between 3-4.5 hours, though it has been approved in Europe and Canada. However, thrombolytic use in this timeframe has been endorsed by the AHA/ASA and is widely used in the U.S.[9, 31]. The inclusion criteria are similar to those of onset < 3 hours (discussed above), but are modified as noted in Table 7.

TABLE 7
Additional Inclusions to IV Alteplase Use Between 3 – 4.5 hours

• Meet all criteria of < 3 hours since onset of stroke
• For patients taking warfarin and with an INR ≤ 1.7

(Hacke W, 2008), (Powers, 2019) [3, 31]

5.4 LKW > 4.5 Hours and ineligible for thrombectomy

In patients who wake up with stroke symptoms or unclear LKW time > 4.5 hours but <24 hours who are ineligible for thrombectomy, MRI showing diffusion positive and FLAIR negative lesions can be used to select patients who may benefit from thrombolytics [20] . A s ubset of patients who present between 4.5 hours and 9 hours from LKW may benefit from IV thrombolysis based on CT perfusion mismatch per the EXTEND trial. [32]

5.5 Patient is an IV thrombolysis candidate

Once a patient is deemed a candidate for IV thrombolytics, a minimum of two IVs must be placed. It is imperative to obtain the most accurate dosing weight possible; however, in the event this cannot be done, two experienced health care providers should agree upon a dosing weight to be utilized. Alteplase is dosed at 0.9 mg/kg based on actual body weight and should be mixed by swirling (rather than shaking), with the total dose not to exceed 90 mg. The initial 10% of the total alteplase dose is given by bolus over 1 minute, then the remainder is infused over one hour. As alteplase is dispensed in 100 mg bottles, excess alteplase should be withdrawn from the vial and discarded to avoid accidental infusion of the excess. A 100-ml bag of saline should be administered after the one-hour infusion to flush the IV line to ensure that the entire dose is administered.

This flush should be run at the same rate as the infusion to avoid a terminal alteplase bolus. In the case of patient transfer after initiation of bolus or infusion, conscious efforts should be made to ensure the tubing or flush is complete prior to disconnecting to prevent incomplete dose administration. Use of extension tubing or an IV pump from transporting facility/air or ground-carrier can assist in the timeliness of transfer without losing part of the administered drug. Alternative dosing strategies utilizing lower doses have been evaluated ; however, currently these dosing strategies are not endorsed by the AHA/ASA guidelines and should not be routinely implemented. [3, 33]

During the hospital admission or transfer period, there should be continued observation for complications of thrombolytics including airway obstruction due to angioedema (consider rapid intubation), hemorrhage (stop alteplase), and sudden deterioration in mental status. Guidelines require that the BP and neurological assessment of a patient be checked every 15 minutes for the first 2 hours after starting alteplase, then every 30 minutes for the next 6 hours, then hourly for the next 16 hours. [3,34]

While the half-life of alteplase is approximately 5 minutes, and only 20% of the medication is still present and active at 10 minutes after completion of the infusion, PT and APTT are prolonged and fibrinogen levels are decreased for 24 hours or more. An acute onset of headache, nausea, vomiting, worsening neurological examination during or following alteplase administration may signal an intracranial hemorrhage [35]. Intracranial bleeding following IV alteplase carries a 50% or greater mortality rate. This is often accompanied by a marked rise in blood pressure (BP); however, a marked rise or fall in BP alone may signal an ICH. In these cases, the following steps should be immediately taken.

5.6 Management of Hemorrhage Following Alteplase

For symptomatic intracranial bleeding within 24 hours of IV alteplase:

- Stop alteplase infusion
- Obtain CBC, PT, PTT, INR, fibrinogen level, type and cross-match
- Obtain an emergent non-enhanced head CT scan
- Vital signs every 15 minutes (neurological assessment for signs of increased intracranial pressure). Assess GCS/pupil response. Treat BP and use non-invasive interventions to lower intracranial pressure (ICP) (raise the head of bed, neck midline)[34].
- Supportive therapies, including management of BP, ICP, cerebral perfusion pressure (CPP), mean arterial blood pressure, temperature, and glucose. Cryoprecipitate (contains fibrinogen): 10 units infused over 10 – 30 min (onset in 1 hour, peaks in 12 hours); administer additional dose for fibrinogen level <150 mg/dl. Due to its lack of availability in certain countries, fibrinogen concentrate has been used to replenish the fibrinogen levels[36]. The initial dose is 2 gm of IV fibrinogen followed by further dosing based on fibrinogen levels. In addition, prothrombin complex concentrate (25-50 U/Kg) and fresh frozen plasma (12 ml/kg) may be used as an adjunctive therapy to normalize the INR.

- Antifibrinolytics such as tranexamic acid 1000 mg (10 – 15mg/kg) IV infused over 10 min or ε-aminocaproic acid 4 – 5g IV over 1 hour, followed by 1 g IV until bleeding is controlled (peak onset in 3 hours). These competitively bind to plasminogen and block its conversion to plasmin, thereby inhibiting fibrin degradation. These agents have a theoretical advantage over cryoprecipitate in terms of cost, shorter administration time (as it does not require thawing) or when blood products are contraindicated or declined by patient/family or if cryoprecipitate is unavailable in a timely manner.

- Consult hematology and neurosurgery. If a neurosurgeon is not available, begin the process of transferring the patient to a facility with neurosurgical capability once CT scan results are available

For small, asymptomatic, hemorrhagic conversion, conservative medical management may be considered after weighing the risks and benefits of reversal agents.

5.7 Management of Angioedema Following Alteplase

- Maintain airway. Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips. Edema involving larynx, palate, floor of mouth or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation. Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after thrombolysis. Cricothyroidotomy is rarely required and also problematic after thrombolysis.

- Discontinue IV alteplase infusion and hold ACE inhibitors

- Administer IV Methylprednisolone 125 mg

- Administer IV diphenhydramine 50 mg

- Administer IV ranitidine 50 mg or IV famotidine 20 mg

- If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 ml subcutaneously or by nebulizer 0.5 ml

- Icatibant, a selective bradykinin B2 receptor antagonist, 3 ml (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at 6 hour intervals not to exceed a total of 3 injections in 24 hours; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema.

- Supportive care

5.8 Tenecteplase

Tenecteplase (TNKase) is a thrombolytic agent with high fibrin specificity. In a phase 3, randomized, open-label trial, tenecteplase was not superior to alteplase in ischemic

stroke patients when administered within 4.5 hours of symptom onset[37]. However, administration of tenecteplase (0.25 mg/kg with maximum of 25 mg) within 4.5 hours in patients that underwent thrombectomy was associated with a higher rate of reperfusion and better functional outcome when compared to alteplase[38]. Currently the AHA/ASA has recommended IV bolus of tenecteplase 0.25 mg/kg (maximum 25 mg) over alteplase in patients eligible for thrombolysis who are also eligible for thrombectomy. Tenecteplase 0.4 mg/kg (maximum 40 mg) is listed as an alternative to alteplase in patients with AIS[3]. Tenecteplase (IV thrombolytic) is not FDA-approved for treating AIS in the United States, whereas in some countries, tenecteplase is approved and is the thrombolytic that is more commonly used. ENLS encourages providers to follow their national stroke guidelines for recommendations on tenecteplase use.

5.9 LKW Between 0-6 hours: Endovascular Treatment

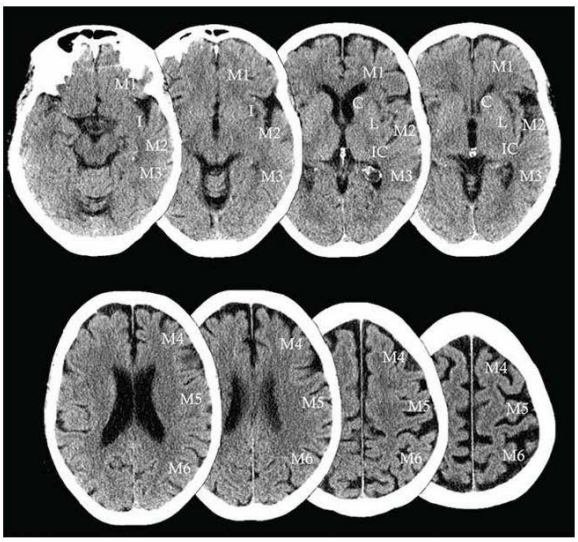
In AIS patients within 6 hours of LKW time and ASPECTS ≥ 6 with an LVO – e.g., proximal (M1) middle cerebral artery (MCA), intracranial internal carotid artery (ICA), basilar or vertebral artery, mechanical thrombectomy treatment should be considered. If the patient is a candidate for IV thrombolytics, it should be administered expeditiously, regardless of endovascular procedure candidacy. Previously, intraarterial (IA) thrombolysis was considered to be an option; however, alteplase has no FDA recommendation for IA use and is no longer recommended as isolated therapy[39, 40]. Several randomized trials of thrombectomy in AIS with LVO stroke have shown marked clinical efficacy and reduction in mortality[41-44]. Patients with distal occlusions e.g., M2, M3, anterior cerebral arteries, posterior cerebral arteries, vertebral or basilar artery have uncertain benefits.

Patients with a high NIHSS will often have an LVO. LVO can be confirmed by seeing a hyper-dense sign (i.e., clot within the vessel) on non-contrast CT, but this sign is insensitive. CTA or MRA are more diagnostic, as is conventional angiography. It is prudent to contact the neurointerventional physician on call, if one is available. If the treating hospital does not have this capability, rapid transfer to a C omprehensive S troke C enter (CSC) is recommended. If the patient is suspected to have an LVO, transfer to a CSC should not be delayed; these patients can deteriorate quickly and a delay in transfer could limit capability of potential endovascular intervention. Some hospitals use CTA and/or CTP or MRI/MRA techniques to select appropriate patients referred for endovascular intervention; there is no standard for these practices in the < 6-hour time window. Sites performing multimodal CT imaging should be able to expeditiously perform a high-quality study and have the capacity to transfer the patient to a CSC.

Exclusions for mechanical thrombectomy include absence of an LVO on CTA or MRA, or large area of infarction already present on the brain imaging study. Many providers use an ASPECTS score of greater than 6 to proceed with intervention[10]. Detailed information on training and scoring of ASPECTS score can be found on www.aspectinstroke.com. Table 8 summarizes the AHA/ASA recommendations for endovascular intervention (Figure 3).

TABLE 8

Recommendations for Endovascular Intervention
• Patients eligible for intravenous alteplase should receive intravenous alteplase even if endovascular treatments are being considered.
• Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria: Prestroke mRS score 0 to 1 Acute ischemic stroke receiving intravenous alteplase within 4.5 hours of onset according to guidelines from professional medical societies Causative occlusion of the internal carotid artery or proximal MCA (M1) Age ≥18 years, (note: there is no upper age limit) NIHSS score of ≥ 6 ASPECTS of ≥ 6 and Treatment can be initiated (groin puncture) within 6 hours of symptom onset based on CTA only Treatment in the 6-24 hour time window is based on presence of target mismatch profile on CTP/ MR perfusion imaging
• As with intravenous alteplase, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous alteplase, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable.
• Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.
• 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 6 hours of symptom onset, but the benefits are not established in this age group.
• Observing patients after intravenous alteplase to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended.
• Endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy.



Subganglionic nuclei:
M1 – Frontal operculum
M2 – Anterior Temporal lobe
M3 – Posterior Temporal lobe

Supraganglionic Nuclei:
M4 – Anterior MCA
M5 – Lateral MCA
M6 – Posterior MCA

Basal Ganglia:
C – Caudate
L – Lentiform Nucleus
I – Insula
IC – Posterior Limb Of Internal Capsule

FIGURE 3

ASPECTS (Alberta Stroke Program Early CT Score) score is a 10-point quan- tiative score used to assess early ischemic changes in anterior circulation strokes on non-contract CT head. Each area of grey white loss constitutes 1 deduction point from a total score of 10.

5.10 LKW Between 6-24 hours: Endovascular Treatment

Based on the results of the DAWN and DEFUSE 3 Trials, it is recommended that AIS patients presenting within 6-24 hours of LKW time who have an LVO in the anterior circulation, obtaining a CTP, DWI – MRI with MR perfusion is recommended to aid in selection of patients for mechanical thrombectomy who meet the eligibility criteria[21, 22]. Both of these trials incorporated CT perfusion or MRI diffusion and perfusion scans that used the RAPID software (iSchemaView), an automated image processing system to calculate the volume of ischemic core (or infarct volume) and penumbral tissue. The size of penumbral tissue was estimated from the volume of tissue for which there was delayed arrival of an injected tracer agent (time to maximum of the residual function) exceeding 6 seconds (Figure 4, 5). Other artificial intelligence modalities, like Viz software (Viz.ai) have been used for rapid detection of LVO and rapid triage for expedited treatment[45].

The DEFUSE 3 trial, randomized patients with signs and symptoms of anterior circulation stroke with LVO, NIHSS ≥ 6 within 6-16 hours from LKW with target diffusion-perfusion mismatch profile to endovascular therapy or medical management[22]. Target mismatch profile was defined as patients with ischemic core volume of < 70 ml, and a mismatch ratio of >1.8 or ≥ 15 ml (ratio of ischemic penumbral tissue volume to infarct volume). This trial showed a benefit in functional outcome at 90 days in favor of endovascular therapy compared with controls (modified Rankin scale 0-2, 44.6% versus 16.7%; RR, 2.67; 95% CI, 1.60-4.48; P<0.0001).

The DAWN trial used clinical imaging mismatch to select patients with anterior cir-

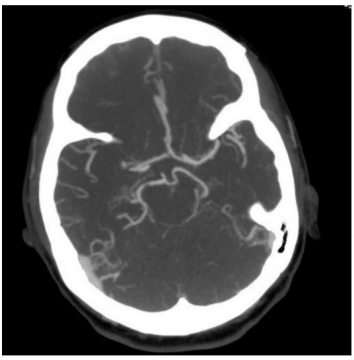


FIGURE 4
Axial view of CTA brain showing Proximal Right M1 occulsion

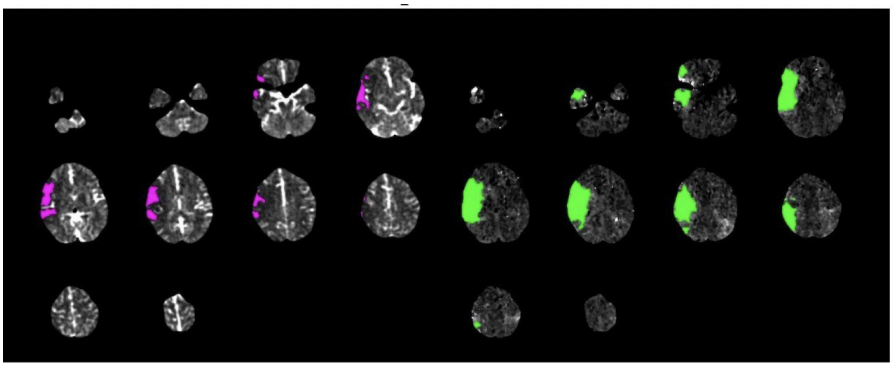


FIGURE 5

CT Perfusion showing a disproportionately large area of hypoperfusion (shown in green) as compared with the size of early infarction - ischemic coreperfusion mismatch

culation strokes due to LVO for mechanical thrombectomy between 6-24 hours of LKW time[21]. It demonstrated an overall benefit in functional outcome at 90 days following endovascular therapy compared to the control group (mRS score 0-2, 49% versus 13%, adjusted difference, 33%, 95% CI, 24-44; with a probability of superiority, >0.999).

An area of intense investigation is trying to determine the ideal destination for patients in the field with suspected LVO. The RACECAT trial, a large randomized trial may provide an answer to the question if direct transfer to a thrombectomy-capable center is associated with better outcome compared to transfer to a comprehensive stroke center based on a pre-hospital rapid arterial, occlusion evaluation scale[46]. Based on patient location, distance , and direction of local Primary Stroke Centers (PSC) and regional CSC, work is being done to try to determine which patients should travel a short distance further to a CSC versus going a shorter distance to a PSC to initiate thrombolytics and then be

transferred out. Unless there are compelling mitigating circumstances, it is recommended by AHA/ASA that EMS not bypass the closest facility to go to the higher-level facility if such a diversion would add 15-20 minutes to the transport time. When there are several PSCs and CSCs with roughly equal distances for transport, AHA/ASA generally recommends transportation to the highest-level facility[4]. Ground versus helicopter transport factors into this as well, especially when the closest PSC is in the opposite direction of the CSC. Prearranged transfer agreements should be established to ensure rapid transfer to the highest level of care when necessary.

5.11 Hospital Admission or Transfer

Assuming there are no complications of alteplase or endovascular therapy, Table 9 lists the orders that should be considered while waiting for the patient to be admitted. Note this sample is based on 2019 AHA/ASA guidelines.

TABLE 9
Sample Acute Stroke Admission Orders

• Neuro checks every 15 minutes for 2 hours, then every 30 minutes for 6 hours, then hourly
• Supplemental oxygen to keep O2 saturation ≥94%
• BP check every 15 min for 2 hours, then every 30 minutes for 6 hours, then every hour for 16 hours (if received alteplase)
• Keep BP after alteplase treatment < 180/105 mmHg (Note: this is lower than pre-treatment values); if no alteplase given, keep BP < 220/120 mm Hg
• Bedside swallow test (30 mL water PO) before anything else PO

Additional admission orders must address glucose, volume status, body temperature, and catheters.

- Keep glucose 140-180 mg/dL / 7.8-10.0 mmol/L; consider insulin drip if the blood glucose is persistently > 200 mg/dL / 11.1 mmol/L or the patient is known to have insulin-dependent diabetes mellitus. Hyperglycemia is associated with worse outcomes and increased risk of ICH following AIS.

- Administer IV fluids, preferably isotonic saline, at 1.5 ml/kg/hour initially, with a goal of euvolemia.

- Continue telemetry/bedside cardiac monitoring principally to detect paroxysmal atrial fibrillation and should continue for at least 72 hours after admission.

- Treat fever sources with appropriate antibiotics or therapies while preventing fever with antipyretics. While occasionally used in post cardiac arrest situations as a neuroprotective maneuver, hypothermia has not been sufficiently studied to recommend at present. The presence of fever should prompt an investigation of the cause of the fever.

- If thrombolytic was administered, avoid indwelling urinary catheter, nasogastric tubes, and IA catheters for four hours, and do not give anticoagulant/antiplatelet

therapy for 24 hours. Urinary catheters should in general be avoided unless absolutely needed.

- While elevation of the head of the bed is recommended for decreasing the risk of aspiration pneumonia, it was not found to make any difference in disability outcome of the stroke injury[47].
- Patients should be NPO until evaluated for swallowing difficulties by a bedside nurse or a speech therapist.

6 Nursing Considerations

Stroke patients presenting to triage often present with varying symptoms and sudden onset of symptoms which should trigger stroke protocol activations. Using pre-approved assessment tools can help with organizing vital time stamps, key neurological assessments, and goals of care during the acute phase of AIS management. Frontline nursing education is vital to ensure key time-stamp goals are achieved by intimate knowledge of alert protocols and team roles.

While timely administration of IV thrombolytics is crucial, a timeout within the 15 minutes prior to administration of medication is considered best practice. A timeout is beneficial to ensure patient safety, establish clear goals of care within the stroke team, and identify key personnel if issues should arise. Once IV thrombolytics administration has been initiated, nursing should ensure accurate administration time including time of the start of the bolus, infusion start time, and when the infusion ended.

In the first 24 hours of care, a nursing handoff during transitions of care (ER to ICU, ER to endovascular suite, endovascular suite to ICU, etc.) should include a bedside report with both nurses completing the neurological assessment on the patient together. Any differences in scoring should be identified if it is a true change, and if a true change has occurred, clinician notification should occur for additional orders. Any decline in neurological assessment should prompt an expedited CT to rule out hemorrhagic transformation.

For those patients who do not receive thrombolytics but underwent mechanical thrombectomy, frequent neurological status checks should be done to quickly identify changes from potential re-occlusion, hemorrhagic transformation and other causes. The site of catheterization should also be monitored for bleeding.

Nursing Pearls

If patient has acute neurological deficit, check fingerstick glucose, activate the stroke team.
CT scan of head should not be delayed for lab work.
Obtain the actual weight of the patient, consider use of a bed scale.
Obtain an 18-gauge IV access for perfusion imaging, obtain 2nd IV if the patient will be receiving thrombolytics or going to interventional radiology for thrombectomy.
IV alteplase is mixed with swirling not shaking.
IV alteplase dose should be double checked with 2nd clinician (RN, PharmD, APP, MD) & BP and neurological status checked within 15 minutes prior to administration.
Bolus dose, infusion dose, wasted IV alteplase, and follow-up flush post IV-alteplase should be documented.
BP goals prior to IV alteplase administration is < 185/110 mm Hg, and after IV alteplase administration is < 180/105 mm Hg for 24 hours.
Patients not receiving IV thrombolytics may be allowed to have permissively higher blood pressure up to 220/110 mm Hg.
Notify the provider immediately with sudden decline in neurological status and/or acute hypertension or angioedema.

7 Pediatric Stroke

While not as common as in older adults, pediatric stroke is an important cause of long-term disability[48-51]. Incidence of childhood AIS is 0.9- 1.7 /100,000 children/year, while neonatal AIS is 4-13 per 1,000 live births[52]. Associated mortality rates are as high as 12 % but causes for mortality are most often attributable to associated conditions (e.g. congenital heart disease)[53-55]. Stroke specific mortality is significantly lower and estimated to be closer to 4-5%[49, 51]. Pediatric stroke is traditionally divided into neona- tal and childhood stroke and these subtypes are treated with distinction in the literature.

Risk factors for pediatric AIS are distinct from adult risk factors. Neonates (birth to < 28 days) are the age group most highly affected by pediatric AIS. Risk factors for this subtype include birth and cardiac disease[56]. Childhood stroke has more varied risk factors including vasculopathy, congenital heart disease, infection and acute head and neck disorders. Prothrombotic conditions are also identified in ~13% but are rarely the only risk factor identified[57]. Slightly less than 10 percent will have no identified risk factor[58].

7.1 Presentation and Differential diagnosis

Diagnostic challenges in pediatric stroke are well established. Neonatal strokes are most commonly identified through neonatal seizures (~95%)[52], and less commonly through encephalopathy or diffuse abnormalities in tone. Unique to this population, a significant number of strokes are asymptomatic in the acute period, even when large territories are infarcted. These patients are collectively diagnosed with the subtype "presumed perinatal infarct"[59].

Pediatric stroke often presents with seizures, hemiparesis and/or speech disturbance[60]. Stroke mimics are common[61, 62].

Pediatric Stroke Mimics		
Hemiplegic migraine	Todd's paralysis	Spinal cord disease (e.g., acute flaccid myelitis (AFM))
Conversion disorder	Bell's palsy	Acute disseminated encephalomyelitis (ADEM)
CNS neoplasm	CNS infection	Posterior Reversible Encephalopathy Syndrome (PRES)
Methotrexate toxicity	Musculoskeletal disorders	Intracranial hemorrhage

Many of the stroke mimics occur at a higher incidence than pediatric stroke. For this reason, pediatric stroke should never be diagnosed in a child presenting with an acute neurologic change without radiographic confirmation[50, 63].

High risk populations and conditions	
Neonates	Connective tissue disorder (e.g. Marfan's syndrome)
Sickle cell disease (SCD)	Moyamoya
Congenital heart disease	Recent head or neck trauma
Endocarditis	Bacterial meningitis
ECMO/VAD support	Systemic lupus erythematosus (SLE)

7.2 Diagnostic Studies

The 2019 AHA "Management of Stroke in Neonates and Children" guideline provides a detailed table with recommendations for a targeted evaluation[64].

Suggested Basic Evaluation of a Child With AIS for Common Causes

Category	Common Causes	Examination
Stroke confirmation	Ischemia Ischemia mimickers (eg.,migraine)	Brain MRI with DWI, FLAIR, GRE or SWI, T1, and T2 (optional: T1 after gadolinium, DTI, pCASL)
Cardiac*	PFO (controversial role as a stroke cause in childhood) Congenital cardiac anomaly Acquired cardiac anomaly Arrhythmia	TTE with bubble study ECG and inpatient telemetry Consideration of 4-extremity Doppler ultrasound in cryptogenic stroke with positive bubble study
Arteriopathy	Extracranial dissection FCA-inflammation FCA-dissection Moyamoya Takayasu arteritis	Brain MRA 3-D TOF and MRA of the neck with/without gadolinium (optional VWI)144 or CTA of the head and neck (not preferred given exposure to radiation and intravenous contrast)
Thrombophilia*	Inherited thrombophilia Acquired thrombophilia	CBC FVL mutation Prothrombin G20210A mutation Protein C Protein S Antithrombin mutation Lupus anticoagulant Anticardiolipin antibody (IgG/IgM) Anti-β2 glycoprotein antibody (IgG/IgM)
Inflammatory*	Lupus	ESR, CRP, ANA

3-D indicates 3-dimensional; AIS, arterial ischemic stroke; ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; CTA, computed tomography angiography; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; ESR, erythrocyte sedimentation rate; FCA-d, focal cerebral arteriopathy dissection type; FCA-i, focal cerebral arteriopathy inflammation type; FLAIR, fluid-attenuated inversion recovery; FVL, factor V Leiden; GRE, gradient recalled echo; Ig, immunoglobulin; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; pCASL, pseudo-continuous arterial spin labeling; PFO, patent foramen ovale; SWI, susceptibility-weighted imaging; TOF, time of flight; TTE, transthoracic echocardiogram; and VWI, vessel wall imaging.

*May not be clinically indicated if an alternative cause is identified.

MRI brain is the preferred imaging modality to diagnose pediatric AIS though re-

source constraints can limit the feasibility of obtaining an MRI. Increasingly, MRIs with limited sequences are utilized in large centers where there is expertise in getting children through a brief study without sedation. Similar to adult AIS evaluations, a combination of DWI and perfusion-weighted sequences can be used to understand the extent of the penumbra[65, 66].

7.3 Treatment

Similar to adult stroke management, establishing the last known well time is critical to determining the acute care plan. If a child presents within 24 hours of onset of symptoms, admission to a hospital with pediatric stroke care services is generally recommended. The severity of the presenting deficits should be established using the Pediatric NIHSS (PedNIHSS)[67] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065389/bin/NIHMS268930-supplement-1.pdf . This validated scale, similar to the adult NIHSS, uses age-appropriate assessments for quantifying neurologic deficits in pediatric stroke[68-70].

Given the nuances of treating pediatric stroke, development of a pediatric stroke team is encouraged to provide the safest and most comprehensive care to this high-risk population[71]. Algorithms can also be used to facilitate appropriate care in an efficient manner (see ENLS AIS algorithm and ENLS Figure 5).

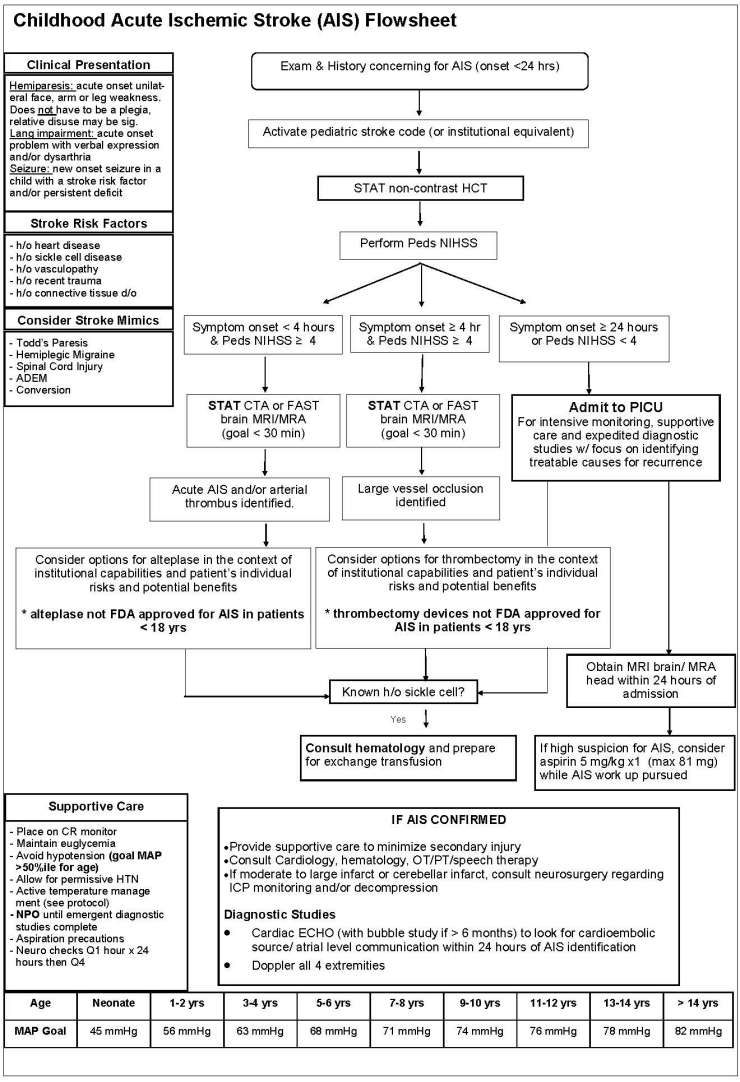


FIGURE 6

7.4 Childhood acute ischemic stroke protocol.

7.4.1 Hyperacute therapies

Thrombolytic medications Despite its lack of approval for children under 18 years of age, there are several case reports of alteplase use in pediatric AIS in the literature. A recent multi-center trial to examine safety and efficacy of alteplase in children 2-18 years

old was closed early due to insufficient enrollment[72]. While this study highlights the challenge of confirming a diagnosis of stroke in children within 4.5 hours of symptom onset, analysis of data from the Kids Inpatient Database from 1998-2009 demonstrated an increase in the number of pediatric patients treated with alteplase, particularly among the adolescent population[73]. While individual physicians may continue to offer thrombolysis therapy with appropriate parental informed consent, one should be careful to apply similar strict inclusion and exclusion safety criteria as used in adults[64]. Regardless of age or antithrombotic treatment, similar neuroprotective strategies should be employed for pediatric stroke as described above for adult stroke.

Endovascular therapies There are several case reports and series of children <18 years old that underwent endovascular treatment for LVO documenting high rates of recanalization and favorable outcomes; however, there are no randomized trials[74-76].

7.4.2 Sickle Cell Patients and Exchange Transfusion

Current standard therapy for sickle cell patients with acute stroke includes optimal hydration, blood exchange transfusion (maintaining Hgb ≤10 g/dL/ 6.21 mmol/L to avoid hyperviscosity syndrome), and correction of hypoxia and hypotension. Chronic transfusion therapy significantly decreases the risk of stroke recurrence and thus should be recommended for any SCD patient with a symptomatic infarct[77].

Safety and efficacy of intravenous alteplase and endovascular interventions in this population is not established. However, a case control retrospective analysis from the Get With the Guidelines-Stroke Registry of adults with SCD compared with a NIHSS and BP matched control population demonstrated no difference in symptomatic ICH or outcome measures after treatment with alteplase[78]. There are currently no guidelines recommendations regarding use of alteplase in pediatric patients with stroke due to SCD[64].

7.4.3 Supportive care

Supportive care is critical to minimizing expansion of the penumbra, secondary injury and stroke recurrence. Supportive care strategies include active temperature management and maintaining normoglycemia, euvolemia and adequate BP (50-90%tile for age and height)[79, 80].

7.5 Secondary Prevention

A comprehensive evaluation to identify stroke risk factors is recommended for all patients presenting with a pediatric stroke. Multiple studies have documented a large percentage of patients have a number of stroke risk factors[48, 58]. There is a wide range of recurrence rates reported (7-66 % at 5 years) based on the population studied[81, 82]. Risk for recurrence depends on risk factors present and the number of coexisting risk factors. Recurrence is highest in patients with vasculopathy and/or cardiac disease[83,84].

8 Pregnancy

Pregnant and postpartum women have a 3 times higher risk of stroke compared to other young adults with an incidence rate of 30 per 100,000 pregnancies[85]. The incidence of pregnancy- related strokes have increased over time that is concurrent with increased rates of hypertension, heart disease, obesity, smoking, and migraine[86, 87]. The most common causes of ischemic stroke in pregnancy are cardioembolism, coagulopathy, preeclampsia/eclampsia, and carotid and vertebral artery dissection[85]. Risk factors that are specific to pregnancy include peripartum cardiomyopathy, choriocarcinoma, and rarely amniotic fluid embolism. Management of stroke in pregnant women should occur in collaboration with the obstetric team and the gestational age should be established as soon as possible to assist in risk/benefit decisions. Acute stroke imaging is crucial for all treatment decisions in pregnant women. Noncontrast CT is an acceptable initial imaging modality for acute stroke in pregnant women. Brain MRI without gadolinium up to 3.0 tesla is the imaging of choice in pregnant women and is not associated with increased harmful effects on the fetus. MR angiogram time of flight and arterial spin labeling modalities can provide sufficient information of vascular status for emergent decision-making. Gadolinium exposure in the first trimester may be associated with increased adverse events[88]. In emergent situations or when MRI is not readily available, CT angiogram and perfusion of the head and neck with iodinated contrast to confirm large vessel occlusion is acceptable as the amount of radiation and negative effects on the fetus is low89. Duplex ultrasonography can be performed to evaluate the carotids for dissection or atherosclerosis.

There is a lack of large randomized controlled trials in the management of ischemic stroke in pregnant women. Intravenous thrombolysis should be considered in pregnant women with moderate to severe stroke, where the benefits outweigh the anticipated risk of uterine bleeding[15, 90]. Besides intracranial hemorrhage, uterine hemorrhage and placental abruption can occur , such that the decision to administer thrombolysis should be based on case-to-case basis after discussion with the mother[90, 91]. Alteplase and tenecteplase are large molecules and do not cross the placenta, therefore intracranial and systemic bleeding of the fetus does not occur[92]. Thrombolytics administered in the early postpartum period especially within 48 hours of delivery is associated with increased risk of bleeding especially following cesarean section compared to vaginal delivery[93]. Endovascular thrombectomy for all eligible women with large vessel occlusion should be considered without delay. In cases with large vessel occlusion, those that are eligible for intravenous thrombolysis and have rapid access to endovascular thrombectomy, proceeding to thrombectomy without administration of thrombolytics may be considered on case-to-case basis to minimize the risk of maternal bleeding[90]. All efforts to avoid or reduce the risk of fetal injury such as abdominal shielding and judicious use of x-rays are reasonable. In case of hemorrhagic transformation, the focus is on management of blood pressure and reversal of coagulopathy. Several factors play a role in secondary stroke prevention that includes the etiology of stroke, gestational age, and risk of bleeding from hemorrhagic transformation. If antiplatelets are indicated, low dose aspirin is preferred. Contrary to the initial reports of adverse events, recent data has shown no significant increase in congenital anomalies from its use in the first trimester[94]. There is insufficient

evidence to support the safety of other antiplatelet agents like clopidogrel, ticagrelor, aspirin with dipyridamole and should be considered on a case-by-case basis by an interdisciplinary approach[95]. When anticoagulation is considered, low molecular weight heparin (LMWH) is preferred throughout pregnancy[95]. Low dose LMWH should be stopped at least 12 hours prior to administration of regional anesthesia and full dose LMWH should be stopped at least 24 hours in advance of regional anesthesia or planned induction of labor or cesarean section[96]. Intravenous heparin could be considered in hospitalized women instead of LMWH if there is concern about urgent delivery, surgery, or invasive procedures and in patients with glomerular filtration rate less than 30 ml/min. Warfarin is potentially teratogenic and is avoided between 6 – 12 weeks of gestational age[95]. If this is strongly indicated, this may be resumed after the twelfth week of pregnancy until closer to delivery. There is insufficient evidence on the safety of direct oral anticoagulants in pregnancy. Interpretation of lipid levels is unreliable in pregnancy and should not be used to guide therapy. Healthy diet and exercise are the first line management of dyslipidemia in pregnancy. There is insufficient evidence of safety of statins in pregnancy and lactation and it is reasonable to hold statin therapy during pregnancy[95].

9 TIA

The diagnosis of TIA is based on the new onset of focal neurological symptoms and signs that are explainable by a vascular disease (e.g., arterial occlusion of a single or group of arteries adequately explain the patient's signs and symptoms), and the resolution of these signs and symptoms within 24 hours (most TIAs resolve in a much shorter period of time).

However, up to one-third of TIAs have demonstrable injury on MRI[97]. These cases are now classified as stroke. Despite evidence of tissue injury, it is unlikely that emergency reperfusion therapy should be attempted, since all symptoms have resolved.

TIAs present a conundrum as there clearly was an event and the patient is at some risk for a recurrence. There are several tools that may help provide guidance assessing the risk of recurrence or outright stroke at different time intervals and each has its limitations. One must assess the patient's compliance and available resources in one's practice environment and make a decision with the patient and family for the best disposition and follow-up plan. The ABCD2 score is commonly used and is presented below (Table 10).

9.1 ABCD^2 Score

The ABCD^2 score is an ordinal scale that provides risk prediction of subsequent stroke following a TIA[98, 99]. While limitations exist it is useful at stratifying risk of stroke to some degree[100-102]. Table 10, 11 demonstrates how to calculate this score.

TABLE 10
ABCD^2 Score for TIA [64, 65].

ABCD^2 Score	Points
Age > 60 years	1
BP ≥ 140/90 mmHg at initial evaluation	1
Clinical Features of the TIA:	1
Speech disturbance without weakness	2
Unilateral weakness	
Duration of Symptoms:	1
10–59 minutes	2
> 60 minutes	
Diabetes Mellitus in Patient's History	1

Add all of the points for the total ABCD^2 score (0–7).

TABLE 11
Percent risk of stroke following TIA with various ABCD2 scores [98, 99].

Total Risk	Score	2 Day	7 Day	90 Day
Low	0–3	1.0	1.2	3.1
Moderate	4–5	4.1	5.9	9.8
High	6–7	8.1	12	18

9.2 Low-Risk TIA

For low-risk patients (ABCD2 scores 0-3), an outpatient workup in 1-2 days following score calculation may be most appropriate. Alternatively , observation or admission may be an option. In either case, stroke risk can be decreased by rapid implementation of the following regimen[104]:

- Begin an antithrombotic agent (aspirin (ASA) 81-325 mg/day, clopidogrel 75 mg/day, or ASA 25 mg/extended release dipyridamole 200 mg twice daily)[105, 106]
- Perform carotid imaging: Carotid ultrasound, CTA, or MRA.
- Consider transthoracic echocardiography; if bilateral infarcts are present on CT or there is high suspicion of cardiac embolic source, and transthoracic echo is normal, obtain transesophageal echocardiogram (TEE).
- Consider 30-day ambulatory cardiac monitor to detect intermittent atrial fibrillation (cryptogenic Afib). This should be strongly considered if the workup shows no other etiology for cause of stroke or TIA.

- Encourage smoking cessation.
- Initiate high-intensity statin (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg or equivalent). Consider moderate intensity statins (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg) in patients > 75 years old[107].

If ECG or rhythm strip shows atrial fibrillation, consider starting anticoagulation (oral anticoagulant or low molecular weight heparin) or ASA; calculate CHADS2 or CHA2DS2-VASc, and HAS-BLED, scores to help guide long term therapy[108, 109]. In these cases, referral to a vascular neurologist or cardiologist is appropriate.

9.3 High-Risk TIA

For patients with higher risk TIAs (ABCD2 scores > 3), hospital admission is advisable. Permissive hypertension is encouraged (not to exceed 220/120 mmHg), and BP should be gradually lowered over 24-48 hours. In a high-risk TIA (ABCD2 score ≥ 4) the CHANCE trial demonstrated that dual antiplatelet therapy using a combination of clopidogrel (initial dose of 300 mg followed by 75 mg/day) and aspirin 81 mg/day for 21 days followed by clopidogrel 75 mg/day for 90 days was superior to aspirin alone in reducing the risk of stroke in Chinese patients[105]. Similarly, the multi-center POINT trial showed that combined use of clopidogrel at a loading dose of 600 mg once followed by 75 mg/day for 90 days plus aspirin 50-325 mg/day for first 21 days was superior to aspirin 50-325 mg/day for 90 days[106]. The SAMMPRIS trial showed that in patients with TIA from stenosis of a major intracranial artery (70% to 99%), medical management with aspirin 325 mg/day and clopidogrel 75 mg/day with aggressive medical management of primary risk factors was superior to combined medical therapy and intracranial stenting group[110].

9.4 Carotid Disease

As part of emergent evaluation of patients with TIA or ischemic stroke, gathering information of extracranial and intracranial vasculature using non-invasive imaging like CTA or MRA of the head and neck is typically performed as part of the standard acute stroke work-up[3]. Patients with ischemic stroke or TIA from extracranial carotid or vertebral artery dissection, administration of antiplatelet or anticoagulation medication within 24-48 hours is recommended. Recent data has demonstrated lack of significant difference between antiplatelet and anticoagulation in patients with extracranial carotid and vertebral artery dissection[111]. For patients with ischemic stroke or TIA from extracranial carotid or vertebral artery dissection who have recurrent ischemic events despite medical therapy, endovascular therapy or surgical treatment may be considered[112].

Revascularization for secondary prevention in patients with minor, non-disabling stroke and symptomatic carotid stenosis > 70% is performed between 48 hours and 7 days of the event if there is no contraindication for early revascularization[3]. The usefulness of emergent or urgent carotid endarterectomy (CEA) or carotid artery stenting (CAS) in patients with small core and large territory at risk due to inadequate flow from critical

carotid stenosis or occlusion in acute stroke is not well established[3]. Recent data has demonstrated safety of emergent CAS of extracranial carotid stenosis and CEA in patients with tandem lesions, but this will need to be confirmed by randomized trials[113, 114].

9.4.1 Medical-Legal Considerations

Administration of thrombolysis carries inherent risk of bleeding complications, which can be lethal. Therefore, patients must be properly screened for inclusion and exclusion criteria. Patients and families must be counseled quickly, but properly about the risks and benefits, and alternatives of thrombolytic therapy. The following points should be kept in mind:

- Far more lawsuits have been filed for failure to offer thrombolytic treatment, than for bleeding complications arising from thrombolytic treatment[115, 116].
- For acute stroke patients meeting guidelines for thrombolytic therapy who are unable to consent for themselves and have no family to consent for them, the treating physician should not delay treatment to find a surrogate to give permission for treatment.
- Written/signed consent for administering thrombolytics is not necessary. The consenting conversation, however, should be documented in the medical record.
- If a patient is not being offered thrombolytic therapy, there should be clear communication with the patient/family why thrombolysis is contraindicated. This conversation should be documented in the medical record.

10 Communication

When communicating to an accepting or referring physician about this patient, consider including the key elements listed in Table 12.

TABLE 12
Ischemic stroke communication regarding assessment and referral

Communication
☐ Age
☐ Airway status
☐ Last known well time (LKW)
☐ NIHSS
☐ Coagulation parameters – PT, PTT, INR
☐ CT – Dense MCA sign, MCA dot sign, Dense basilar sign, ASPECT score, Early ischemic changes
☐ CTA/MRA – Large vessel occlusion (ICA, M1, M2, Basilar, PCA)
☐ CTP – Volume of core and penumbra, matched or mismatched perfusion
☐ Thrombolytic administration – Yes (Initiation, completion time); No (Reason)
☐ Endovascular intervention (Time to groin puncture, recanalization, TICI score)
☐ Target BP
Sample Sign-Off Narrative
Prehospital to ER: "I am signing out a 62 yo male with known hypertension and atrial fibrillation who is not on anticoagulation". "He was found down on the floor at 7:10 am by his wife. He was last seen normal at 10 pm last night. He is aphasic with right-sided weakness, GCS of 11, HR of 130/minute and BP of 200/110 mm Hg. IV Metoprolol 5 mg given and his follow up HR was 94/minute and BP was 182/90 mm Hg" ER to ICU: "Upon arrival to the ER at 9:10 am his NIHSS was 21 - global aphasia, left gaze preference, right hemiplegia and neglect." "CT completed at 9:26 am showed a left dense MCA sign. CTA showed a left M1 occlusion. CTP showed a core of 38 ml, penumbra of 140 ml, mismatch volume 102 ml, mismatch ratio 3.7." "He was out of the IV tPA window. Endovascular team was notified at 9:38 am". "He was taken to the cath lab at 9:50 am. His HR was 106/minute and BP was 190/106 mm Hg. Groin puncture was attained at 10:06 am. TICI3 revascularization was achieved. He had started moving his right arm and leg few minutes after the procedure". "His target post procedural BP should be <140/80 mm Hg". MRI brain is pending"

Clinical Pearls
In patients with symptoms upon awakening the LKW time is the time they went to bed.
In case of fluctuating symptoms determine if the patient was back to baseline. Q In cases of stuttering symptoms, the clock is reset only if the patient is back to baseline.
With patients on direct oral anticoagulants, determine the last time they took their medication.
IV thrombolytics can be offered in several scenarios after weighing the risk and benefit.
Low NIHSS is not a contraindication to thrombolysis
In patients with hypoglycemia, correct the blood glucose and determine if the symptoms have resolved. If these are persistent, IV thrombolytics could be administered.
Administer IV thrombolysis as quickly and safely as possible. Many facilities administer IV thrombolysis during the wait time between CT and CTA/CTP.
Observing patients after thrombolysis to assess for clinical response in patients with LVO and mismatch profile is not required.
Endovascular therapy 0-6 hours = NIHSS ≥ 6, CTA/MRA with LVO and ASPECT 6.
Endovascular therapy 6-24 hours = NIHSS ≥ 6, CTA/ MRA with LVO and CTP / MR Perfusion with mismatch profile using DAWN or DEFUSE trial criteria in anterior circulation strokes.
Consider short-term dual antiplatelet therapy in patients with TIA and ischemic stroke.

11 Starred References:

** Landmark paper

* Important paper

*3 (Powers WJ, et al 2019.): This is the most recent update for early management of acute ischemic stroke from the AHA.

*10 (Demaerschalk BM, et al): This paper elaborates the scientific evidence and rationale for the various inclusion and exclusion criteria for alteplase and forms the basis for the updated 2018 AHA guidelines.

**19 (Nogueira RG, et al.): This is the DAWN study for delayed thrombectomy between 6-24 hours from last well known demonstrating improved outcomes in anterior circulation strokes with mismatch profile undergoing thrombectomy with standard of care.

**20 (Albers GW, et al.): This is the DEFUSE-3 study for delayed thrombectomy between 6-16 hours from last well known demonstrating improved outcomes in anterior circulation strokes with mismatch profile undergoing thrombectomy with standard of care.

**28 (Hacke W, et al.): This is the ECASS study expanding the time window of intravenous alteplase to 4.5 hours.

**37 (Berkhemer OA, et al.): MR CLEAN Trial. This was the first published RCT for patients with acute ischemic stroke and proximal vessel occlusion demonstrating the superiority of endovascular thrombectomy within 6 hours of stroke onset.

*64 (Johnston SC, et al.): ABCD2 score for stratifying TIA.

*71 (Yang W, et al.): This is the CHANCE study of dual antiplatelet use for TIA and minor stroke demonstrating recurrent stroke reduction at 90 days.

*72 (Johnston SC, et al.): This is the POINT study of dual antiplatelet use for TIA and minor stroke demonstrating recurrent stroke reduction at 90 days.

*76 (Chimowitz MI, et al.): This is the SAMMPRIS trial that demonstrated superiority of aggressive medical therapy in patients with intracranial stenosis compared to stenting.

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