Critical care management of acute ischemic stroke – An overview of current concepts

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ABSTRACT

Acute ischemic stroke is a major cause of morbidity and mortality globally. Early recognition and prompt revascularisation are the cornerstones of treatment. Advances in the management of stroke, notably with the endovascular interventions has led to improved functional outcomes. Identification of stroke subtype, timely decision making, institution of specific therapy and periprocedural care in an intensive care unit make the difference between a favourable and an unfavourable outcome. To this effect, dedicated stroke centres, multidisciplinary teams with trained experts and critical care management play an important role. Improvements in the understanding of the disease process, ever expanding literature and development of promising novel therapeutic strategies, notwithstanding, stroke is still a leading cause of acquired long term disability and mortality worldwide. End of life care and associated decision making precariousness, pose a significant prognostication challenge to the critical care team. The aim of this review is to discuss the current evidence regarding diagnosis, revascularisation modalities and optimal critical care management strategies.

Keywords: acute ischemic stroke, critical care, mechanical thrombectomy, thrombolysis.
INTRODUCTION

Stroke is an important global health concern comprising of acute ischemic stroke (AIS), intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). AIS can be further subdivided into lacunar (23%) and non-lacunar (77%) stroke. Lacunar stroke is mostly attributed to small vessel disease while, non-lacunar stroke can be cardioembolic, cryptogenic, large vessel related and others. Posterior circulation is affected in around 20% of strokes due to basilar artery occlusion, and is associated with significantly higher (80%) mortality and morbidity. A significant number of individuals experience transient ischemic attack (TIA) every year which adds on to the disease burden worldwide. The National Institutes of Health Stroke Scale (NIHSS) is the most widely used tool to objectively quantify the deficit caused by stroke.

A wake-up stroke is clinically defined as an ischemic stroke that is associated with neurological symptoms on awakening, with last known normal corresponding to the onset of sleep before presentation, which is in contrast to the daytime strokes or witnessed strokes. Stroke mimics are disorders which mimic the clinical signs of stroke and may lead to false or delayed diagnosis and inappropriate treatment. Examples of stroke mimics include brain tumors, metabolic disorders, psychological disorders or demyelinating disorders.

The management of AIS has taken massive strides in recent years, especially therapy for large vessel disease via endovascular route, which has resulted in improved functional outcomes. Patients who develop ICH following stroke have significant 30 day mortality (46%) despite surgical intervention and medical management. Critical care management after stroke is of vital importance to reduce mortality and morbidity and improving the overall functional outcomes. Majority of stroke can be prevented through a combination of blood pressure control, healthy diet, regular physical activity and smoking cessation. Aspirin, statins, antihypertensives and life style modification have additive benefits for secondary prevention.

DIAGNOSIS

Early recognition of stroke is of utmost importance. Prehospital care incorporates prompt recognition of stroke symptoms, activation of emergency medical services (EMS), accurate recognition of stroke by the EMS personnel, in field treatment and ongoing stabilisation, rapid transport of the patient to the hospital, preferably a stroke centre, and early mobilisation of resources once the patient arrives in the emergency department. The signs and symptoms of an acute stroke can be identified by BEFAST (Table 1). A significant limitation, especially in developing countries is failure to recognize stroke signs and symptoms by the victim, family and even heath care workers. This prehospital time delay is influenced by geographical, demographical , educational , socioeconomic and organisational factors.

The emergency physician should complete assessment within 10 minutes of receiving the patient in emergency department (ED) as per the recommendation of National Institute of Neurological Disorders and Stroke (NINDS). NIHSS (Neurological Institutes of Health Stroke Scale) is helpful in evaluation and objective documentation of neurological status, plan appropriate treatment and enables better prognostication in acute stroke patients as it is a predictor of both long and short term outcomes. The NIHSS comprises of 11 items, each item has a minimum score of 0 indicating normal function and a maximum score of 4 indicating deficit (Table 2). Posterior circulation stroke presents with a myriad of non-specific signs and symptoms such as abnormal cough, dysphagia and ataxia and have a fluctuating clinical course which are underrepresented in NIHSS. To circumvent this issue, the posterior NIHSS (POST-NIHSS) score was developed by BATMAN (Basilar Artery Treatment and Management) collaborators. POST-NIHSS is compiled by adding 3 points for gait/truncal ataxia, 4 points for dysphagia and 5 points for abnormal cough to the baseline NIHSS and is shown to have a higher prognostic accuracy than NIHSS in identifying posterior circulation stroke. The use of a stroke severity rating scale, like NIHSS is recommended.

### Table 1. Signs and Symptoms of Acute ischemic stroke – BEFAST:

<table>
<thead>
<tr>
<th>Balance</th>
<th>Acute or sudden onset of loss of balance or coordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Blurred or unclear vision, double vision and gaze preference</td>
</tr>
<tr>
<td>Facial</td>
<td>Facial weakness or asymmetry</td>
</tr>
<tr>
<td>Arm</td>
<td>Arm and/or leg weakness</td>
</tr>
<tr>
<td>Speech</td>
<td>Difficulty/slurring of speech</td>
</tr>
<tr>
<td>Time</td>
<td>Time is brain</td>
</tr>
</tbody>
</table>

### Table 2. NIHSS based stroke severity:

<table>
<thead>
<tr>
<th>Score</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stroke</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to severe stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe stroke</td>
</tr>
</tbody>
</table>

Other diagnostic laboratory tests include assessment of blood glucose (must before initiation of IV alteplase), coagulation profile if there is suspicion of coagulopathy and baseline troponin. A baseline 12 lead electrocardiogram and chest radiograph can be done in hyperacute stroke, though none should delay the initiation of IV alteplase.
NEUROIMAGING

A non-contrast computerised tomography (NCCT) scan is effective to exclude ICH or SAH. The Alberta Stroke Program Early CT Score (ASPECTS) is a topographic scoring system to determine middle cerebral artery (MCA) infarct severity using a 10-point scale. Magnetic resonance (MR) - ASPECTS score can be used for the early detection of ischemic signs and is more sensitive than CT, but CT is faster and more accessible than MRI and, therefore, is the neuroimaging modality of choice. For basilar artery occlusion, a posterior circulation ASPECTS (pc-ASPECTS) has been developed and validated. The pc-ASPECTS is a 10-point scale as well with points deducted for every region involved. Thalami, occipital lobes and cerebellar hemispheres (1 point each) and midbrain and pons (2 points each). 16

Mechanical thrombectomy (MT) is recommended with ASPECTS ≥6 at presentation. A lower ASPECTS score or early signs of infarction on NCCT are associated with poor prognosis and higher risk of haemorrhagic conversion. CT-angiography (CTA) is useful in detecting large vessel occlusion (LVO) and delineating cerebral vascular anatomy, while, CT-perfusion (CTP) imaging assesses cerebral blood flow (CBF) and can provide core (CBF <30%) to penumbra (tissue at risk) ratio. A core: penumbra ratio of >1.8 may indicate eligibility for endovascular therapy. CTA with CTP or magnetic resonance angiography (MRA) with diffusion weighted magnetic resonance imaging (DW-MRI) with or without MR perfusion is useful for selecting candidates for mechanical thrombectomy between 6 and 24 hours after last known well. 18,20 In patients eligible for IV alteplase, treatment should not be delayed for additional neuroimaging such as CTP or MRI perfusion imaging. 14

A door to imaging time of ≤20 minutes is recommended to help reduce the time to treatment initiation as studies have shown that odds of favourable outcomes declined with longer time from symptom onset to arterial puncture. In case of wake-up strokes, a combination of multimodal CT and MRI are preferred as imaging modalities. 21

REVASCULARIZATION

The mainstay of treatment is revascularisation by intravenous (IV) thrombolysis and/ or mechanical thrombectomy (MT) and thereby, limiting the secondary neuronal injury. Intraarterial thrombolysis has a potential role as an adjunct to MT in treating patients with large vessel occlusion

Intra-arterial Thrombolysis

In patients with large vessel occlusion, intra-arterial thrombolysis using urokinase, tPA or glycoprotein IIb/IIa inhibitors like tirofiban combined with MT has been reported to have achieved better functional outcomes with lower mortality rate and was not associated with increased risk of symptomatic intracranial haemorrhage compared to MT alone in one meta-analysis. Ongoing clinical trials and their results will be crucial in providing further evidence. 24

Intravenous Thrombolysis

Intravenous (IV) tissue plasminogen activator (tPA) administration window currently stands at 4.5 hours as recommended by AHA (American Heart Association) based on ECASS-3 study. 25,26 It is given in a dose of 0.9 mg/kg (maximum dose 90 mg) with 10% dose as an IV bolus over one min, followed by rest of the drug as continuous infusion over 60 mins. EXTEND trial reported that IV-tPA can be administered effectively and safely up to 9 hours when CTP imaging was used to assess the eligibility for IV-tPA. 27 The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) suggested that when MRI criteria is utilised, almost 50% of wake-up strokes and daytime strokes of unknown onset are IV-tPA candidates. 28 Tenecteplase in a dose of 0.25 mg/kg with maximum up to 25 mg is being used as an alternative drug with an advantage of being administered as a single bolus and being cost effective while having similar recanalization rate as Alteplase. In the Tenecteplase (TNK) versus Alteplase before Thrombectomy for Ischemic Stroke (EXTENT- IA-TNK) trial, Tenecteplase was associated with a higher reperfusion rate and improved functional outcome. 29,30 In the systematic review comparing the efficacy of TNK with alteplase with regards to rate of symptomatic ICH, functional outcome at 90 days and reperfusion grade after thrombectomy, TNK when compared to alteplase yielded better results. 31 A retrospective multicentre study reported that TNK for AIS was associated with a lower mortality rate, favourable safety profile (reduced ICH) and cost effectiveness. In the alteplase compared to TNK (ACT) trial, published in 2022, authors found the outcome measures to be comparable while TNK was reported to be superior in a subgroup analysis in patients with large vessel occlusion. 32 Recently published TASTE-A trial (Tenecteplase versus alteplase for stroke thrombolysis evaluation in the Ambulance – Mobile Stroke Unit) in Australia reported a superior safety profile and early rate of reperfusion with TNK compared to alteplase when administered in mobile stroke unit. 33 Currently, AHA gives a grade II B recommendation for 0.25 mg/kg TNK over alteplase based on EXTEND-IA-TNK trial. 14 European guidelines 2021 give a weak recommendation for TNK citing low quality evidence while Canadian guidelines do not give any recommendation. 34,35 Australian guidelines, on the other hand, strongly recommend the use of either TNK or alteplase in patients with LVO stroke. 36 Multiple trials are ongoing like ATTEST-2, TIMELESS and ETERNAL trial, the results of which will shed further light on the TNK vs alteplase debate in various clinical AIS scenarios. 37 Contraindications for IV-tPA administration have been mentioned in Table 3.
Table 3. Contraindications for IV-tPA:

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or prior history of intracranial haemorrhage</td>
</tr>
<tr>
<td>History of ischemic stroke within 3 months</td>
</tr>
<tr>
<td>Uncontrolled blood pressure (&gt;185/110)</td>
</tr>
<tr>
<td>Severe head trauma within 3 months</td>
</tr>
<tr>
<td>Intracranial/ intraspinal surgery within 3 months</td>
</tr>
<tr>
<td>Gastrointestinal malignancy or bleeding within 21 days</td>
</tr>
<tr>
<td>Bleeding diathesis</td>
</tr>
<tr>
<td>Aortic arch dissection</td>
</tr>
<tr>
<td>Intraparenchymal intracranial neoplasm</td>
</tr>
</tbody>
</table>

IV-tPA is fraught with complications, most notably ICH (2.4% - 6.4%), systemic haemorrhage (1.6%) and orolingual angioedema (1.3-5.1%). Tenecteplase has similar adverse effects including bleeding and anaphylaxis. ICH post thrombolysis is associated with significant morbidity and mortality. Risk factors include early ischemic changes in >1/3 of MCA territory, elevated blood glucose, history of diabetes mellitus, high systolic blood pressure, low platelets and elderly age group. There is paucity of standardised guidelines regarding management of post thrombolysis ICH and treatment is mostly institution based. Patient must be monitored in an intensive care unit and one must suspect ICH if there are signs of clinical deterioration, altered mental status, new onset headache, nausea, hypertension and emesis. Other causes of neurological deterioration should be ruled out like seizures, hemodynamic instability or infection. If ICH is suspected, IV tPA infusion should be immediately discontinued, and an emergent NCCT should be done. Sample should be sent for coagulation profile, platelet count, fibrinogen levels and thromboelastogram. Prompt correction of fibrinolytic state is warranted and can be achieved by transfusion of cryoprecipitate to maintain fibrinogen levels >150 mg/dL followed by platelets. Periodic assessment of coagulation profile and fibrinogen levels must be done. Neurosurgeon should be informed regarding the ICH and possibility of emergent evacuation. Airway, breathing and circulation must be managed accordingly with intracranial pressure management protocols. A repeat NCCT should be done to assess the ICH growth. There is limited evidence pertaining to the role of other agents like tranexamic acid, prothrombin complex concentrate (PCC), fibrinogen, fresh frozen plasma (FFP), and recombinant factor VII in post thrombolysis ICH management. There is lack of data for blood pressure management in patients with post thrombolysis ICH. It is prudent to follow the current recommendations for spontaneous ICH which suggest a modest reduction in blood pressure to a mean arterial pressure (MAP) of 110 mm HG or a target blood pressure (BP) of 160/90 mm Hg with blood pressure monitoring every 15 minutes and maintaining cerebral perfusion pressure of >60 mm HG, if SBP >180 or MAP > 130 mm Hg. The decision of surgical evacuation is complex and must be considered only after adequate reversal of fibrinolytic effects of tPA.39

**Mechanical Thrombectomy**

In patients presenting beyond the therapeutic window of IV-tPA administration, mechanical thrombectomy has been the cornerstone for the management of AIS caused by occlusion of a large vessel. Eligibility for MT in patients with AIS caused by a LVO, include presentation within 6 hours of stroke onset, NIHSS ≥6, baseline modified Rankin score of 0-2 and ASPECTS ≥5. The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke) trials established the effectiveness of mechanical thrombectomy in management of proximal anterior circulation AIS (Table 4).39 Mechanical thrombectomy has shown benefits in patients who have received IV-tPA administration, in elderly (>80 years) age group patients and in patients up to 24 hours post symptom onset.20

Table 4. Summary of trials on MT for anterior circulation stroke:

<table>
<thead>
<tr>
<th>Study</th>
<th>MR CLEAN</th>
<th>REVASCAT</th>
<th>ESCAPE</th>
<th>SWIFT-PRIME</th>
<th>EXTEND-IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Centres</td>
<td>16</td>
<td>4</td>
<td>22</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Duration in years</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Sample size</td>
<td>500</td>
<td>206</td>
<td>316</td>
<td>196</td>
<td>70</td>
</tr>
<tr>
<td>Symptom onset in hours</td>
<td>0-6</td>
<td>0-8</td>
<td>0-12</td>
<td>0-6</td>
<td>0-6</td>
</tr>
<tr>
<td>Pre stroke modified Rankin Score</td>
<td>Not used</td>
<td>≤1</td>
<td>Barthel index used</td>
<td>≤1</td>
<td>≤2</td>
</tr>
<tr>
<td>NIHSS cut off point</td>
<td>≥2</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>8-30</td>
<td>Nil</td>
</tr>
<tr>
<td>Median ASPECTS</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Successful recanalization TICI 2b or 3(%)</td>
<td>75.4</td>
<td>66</td>
<td>72.4</td>
<td>88</td>
<td>86.2</td>
</tr>
<tr>
<td>90 day mRS 0-2 (best medical treatment) %</td>
<td>19.1</td>
<td>28.2</td>
<td>29.3</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>90 day mRS 0-2 (MT) %</td>
<td>32.6</td>
<td>43.7</td>
<td>53 (P&lt;0.001)</td>
<td>60 (P&lt;0.001)</td>
<td>71 (P&lt;0.001)</td>
</tr>
<tr>
<td>Rate of symptomatic ICH (%)</td>
<td>7.7</td>
<td>1.9</td>
<td>3.6</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mortality (%) (best medical treatment)</td>
<td>18.4</td>
<td>15.5</td>
<td>19</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Mortality (%) MT</td>
<td>18.9</td>
<td>18.4</td>
<td>10.4</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Mortality difference between MT and best medical treatment</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
NIHSS- National Institute of Health Stroke Scale; ASPECTS- Alberta stroke programme early computed tomography score; MT- Mechanical thrombectomy; mRS- Modified Rankin Score; TICI- Thrombolysis in cerebral infarction.

For posterior circulation strokes, a meta-analysis of BASICS, BEST, ATTENTION AND BAOCHE trials, have reported significantly better outcomes (modified Rankin score 0-3, p=0.03)), functional independence (modified Rankin score 0-2, p=0.03) and lower mortality (p<0.001) associated with MT compared to medical treatment alone (Table 5).40-43 MT entails removal of thrombus endovascularly under fluoroscopic guidance using a stent retriever and/or direct aspiration technique.

Table 5. Summary of trials on MT for posterior circulation stroke:

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>BASICS</th>
<th>BEST</th>
<th>ATTENTION</th>
<th>BAOCHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Centres</td>
<td>2021</td>
<td>2020</td>
<td>2022</td>
<td>2022</td>
</tr>
<tr>
<td>Duration in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>300</td>
<td>131</td>
<td>507</td>
<td>217</td>
</tr>
<tr>
<td>Symptom onset in hours</td>
<td>0-6</td>
<td>0-8</td>
<td>0-12</td>
<td>6-24</td>
</tr>
<tr>
<td>Pre stroke mRS</td>
<td>≤2</td>
<td>≥6</td>
<td>≥2</td>
<td>≤1</td>
</tr>
<tr>
<td>NIHSS cut off point</td>
<td>≥10</td>
<td>≥6</td>
<td>≥10</td>
<td>≥10</td>
</tr>
<tr>
<td>Pc-ASPECTS</td>
<td>Not used</td>
<td>≥6</td>
<td>≥6</td>
<td>≥6</td>
</tr>
<tr>
<td>Successful recanalization TICI 2b or 3 (%)</td>
<td>72</td>
<td>71</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>90 day mRS 0-2 (best medical treatment) %</td>
<td>30</td>
<td>28</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>90 day mRS 0-2 (MT) %</td>
<td>35</td>
<td>33</td>
<td>33</td>
<td>39</td>
</tr>
</tbody>
</table>

NIHSS- National Institute of Health Stroke Scale; ASPECTS- Alberta stroke programme early computed tomography score; MT- Mechanical thrombectomy; mRS- Modified Rankin Score; TICI- Thrombolysis in cerebral infarction

The Thrombolysis in Cerebral Infarction (TICI) scale is used to assess the success of mechanical thrombectomy with TICI scores of 2B and 3 considered as achievement of successful reperfusion. First pass effect is the achievement of complete recanalization on the first pass of a thrombectomy device and is associated with good clinical outcome.44 MT can be performed, either under general anaesthesia (GA) or conscious sedation. GA offers the benefit of airway control and complete immobilisation, while, conscious sedation allows early and continuous neurological examination and faster door to groin puncture times. Available evidence is not adequate to establish the superiority of one technique over the other and must be tailored according to the patient.4 Blood pressure fluctuations in the peri-procedural period is associated with poor functional outcomes.52 Post IV t-PA, it is recommended to keep the systolic BP <185 mmHg and Diastolic BP < 110 mmHg to reduce the risk of haemorrhagic transformation.46 Further studies are warranted to assess the efficacy of mechanical thrombectomy in patients with minor strokes (NIHSS < 5).

Mechanical thrombectomy is associated with intra and post procedural complications (4% to 29%) and device related complications like vessel perforation or dissection leading to SAH or ICH, contrast induced nephropathy, injury to arterial access site and development of pseudoaneurysm.47

INTENSIVE CARE UNIT MANAGEMENT

Airway, breathing and oxygenation

All stroke patients must be kept nil orally as endotracheal intubation may be required in cases of reduced level of consciousness, neurological deterioration or in patient at risk of aspiration because of impaired oropharyngeal function due to large interhemispheric stroke or stroke involving brainstem resulting in bulbar dysfunction.48 Prompt control of airway prevents secondary neuronal injury due to hypoxia, hypercapnia and aspiration.48 It is recommended to provide supplemental oxygen to maintain oxygen saturation >94%.49

Blood pressure

At present, AHA recommends that BP should not be lowered unless it exceeds 220/120 mmHg for the first 24-48 hours to maximise perfusion in ischemic area, if no intervention is planned. Patients with severe comorbidities like acute coronary event, acute heart failure and aortic dissection, emergency reduction of BP by 15% of initial BP is recommended which must be individualised and carefully titrated.50,51 In patients eligible for IV-tPA, since the risk of haemorrhagic transformation is high, a BP of ≤185/110 mmHg prior to the administration of IV-tPA and a BP of ≤180/105 mmHg post administration of IV-tPA is recommended. BP lowering medications include IV labetalol 10-20 mg over 1-2 minutes, IV nicardipine 5 mg/hour, IV clevidipine 1-2 mg/hour, hydralazine and enalaprilat.54 A post-procedure BP of ≤180/105 mmHg is currently recommended by AHA, but this does not take into consideration the degree of reperfusion achieved.11 For TICI 2b and 3, a systolic BP of ≤160 mmHg is reported to be associated with a lesser incidence of ICH and mortality.52 A multitude of studies have shown that high systolic BP in the first 24 hours post procedure are associated with unfavourable outcomes. It is prudent to have an autoregulation based, individually tailored BP target taking into account the degree of recanalization achieved.53
hypertension in acute non-cardioembolic ischemic stroke (SETIN-HYPERTENSION) trial reported that in patients who were ineligible for revascularisation therapy, phenylephrine induced hypertension (to increase SBP up to 200 mm Hg) was safe and was associated with early neurological improvement and functional independence.\textsuperscript{54}

**Monitoring**

Early recognition and prompt management of complications help in reducing the hospital stay and overall costs.\textsuperscript{47} Patients treated with IV-tPA and MT are susceptible to develop secondary brain injury and thus, intensive monitoring and vigilance is essential in ICU.\textsuperscript{55} It is recommended to do vital sign and neurological monitoring post procedure every 15 minutes for 2 hours, every 30 minutes for 6 hours and every hour for 16 hours.\textsuperscript{56}

**Seizures**

Onset of seizure within 7 days of stroke is designated as early, whereas, onset ≥7 days after stroke is termed as late seizure. Risk factors for development of seizures post AIS include stroke severity, anatomical location, younger age group, and haemorrhagic transformation.\textsuperscript{57} Current AHA guidelines recommend treatment of recurrent seizures akin to any other acute neurological condition associated seizure and do not recommend prophylactic use of anti-epileptic medications.\textsuperscript{14} The selection of anti-epileptic medication should be individualised as per the patient characteristics. Recent evidence has shown favourable profile of new generation anti-epileptic medications like lamotrigine, levetiracetam and lacosamide.\textsuperscript{57}

**Glycaemic Control**

Normoglycaemia in the range of 140-180 mg/dL is reasonable to target in ICU.\textsuperscript{11} Both hypoglycaemia and hyperglycaemia were shown to have been associated with poor neurological outcome. As per the results of Stroke Hyperglycaemia Insulin Network Effort (SHINE) trial, intensive IV insulin protocol targeting a systemic glucose range of 80-130 mg/dL as compared to sliding scale regimen, targeting 80-180 mg/dL of systemic glucose was associated with unfavourable outcomes at 90 days.\textsuperscript{58}

**Cerebral Oedema and elevated ICP management**

Cytotoxic cellular injury secondary to ischemia leads to the development of cerebral oedema. The most concerning sequelae is the development of malignant oedema which has an incidence of 2-8% and associated mortality of 40-80%.\textsuperscript{59} Various predictors of malignant cerebral oedema include involvement of ≥50% territory of MCA, an infarct volume of >82 cm\textsuperscript{3} within 6 hours of symptom onset and patients with large hemispheric infarcts.\textsuperscript{60,61} Raised ICP aggravates secondary brain injury by worsening cerebral ischemia and cerebral oedema via an interplay of excitatory neurotransmitters, free radicals and increased intracellular influx of calcium. Medical management for raised ICP include facilitation of cerebral venous drainage by head end elevation by 30 degrees, midline head positioning, usage of minimum PEEP in ventilated patients, avoidance of hypo-osmolar fluids, adequate sedation and analgesia to avoid coughing and bucking, fever control.\textsuperscript{62} There is insufficient evidence regarding the efficacy of hyperosmolar therapy using 20% mannitol or hypertonic saline in treating malignant cerebral oedema associated with AIS and their use should be individualised and tailored according to the patient profile.\textsuperscript{63,64} ICP monitoring may be incorporated as a part of multimodal monitoring strategy in AIS patients management in ICU, but at present there is limited evidence to support their routine use in AIS patients.\textsuperscript{48} Novel therapies, like glyburide, have been proposed for the management of cerebral oedema. The GAMES-RP (Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction) clinical trial showed that intravenous glyburide was well tolerated in patients with large anterior interhemispheric infarction with cerebral oedema, though no difference in the primary outcome was noted.\textsuperscript{65} Sulphonylurea drug like Glibenclamide, is a potent inhibitor of SUR1-TRPM4 channels that play an important role in cerebral oedema formation.\textsuperscript{56} CHARM clinical trial is ongoing to evaluate the efficacy and safety of intravenous BIB093 (Glibenclamide) for severe cerebral oedema following large hemispheric infarction (ClinicalTrials.gov: NCT02864995). Patient with large hemispheric infarcts with significant cerebral oedema are prone to raised intracranial pressure and cerebral herniation. Surgical management for raised ICP includes external venous drainage and decompressive hemicraniectomy. Decompressive hemicraniectomy in patients with or at risk of malignant cerebral oedema, was shown to be associated with reduced mortality by 50% and improved functional outcome.\textsuperscript{67,68} In the hemicraniectomy after MCA infarction with life threatening oedema trial (HAMLET), authors found that surgical decompression reduced the case fatality and poor outcome when treated within 48 hours of stroke onset, but no benefits were observed when it was delayed for up to 96 hours after stroke onset.\textsuperscript{69}

The Decompressive Surgery for the treatment of malignant infarction of the MCA (DESTINY-II) clinical trial demonstrated that decompressive hemicraniectomy in patients older than 60 years increased the survival probability, but with significant disabilities.\textsuperscript{70} The Hemicraniectomy and durotomy upon deterioration from infarction-related swelling trial (HeADFIRST) compared a standardised medical treatment approach consisting of normoglycemia (glucose <200mg/dL), permissive hypernatremia (sodium <155 mEq/dL), and hyperosmolar therapy with decompressive hemicraniectomy in patients with large supratentorial cerebral hemispheric infarction and found no morbidity or mortality benefit with decompressive hemicraniectomy in these subset of patients.\textsuperscript{71}
Further studies are required to shed more light on the optimal management strategy in patients with large hemispheric infarction, with regards to the trial of a standardised medical management initially, ideal timing of decompressive hemicraniectomy and a clearer definition of a favourable outcome with respect to the degree of disability it entails for adequate prognostication.

**Haemorrhagic transformation after AIS**

Haemorrhagic transformation after AIS is an interplay between multiple pathological processes. Oxidative stress and reperfusion injury lead to an increase in reactive oxygen species and matrix metalloproteinases, coagulopathy and destruction of basal lamina which in turn results in an increase in vascular permeability, disruption of blood brain barrier and ultimately extravasation of blood in the brain parenchyma. Haemorrhagic transformation is associated with poor outcome and increased mortality.72 Infarct size is a more reliable predictor of post stroke haemorrhagic transformation compared to level of matrixmetalloproteinase-9,73,74

As per the European Cooperative Acute Stroke Study (ECASS) criteria, post stroke haemorrhagic conversion is classified as haemorrhagic infarction type 1 (small petechiae) and 2 (more confluent), and parenchymal hematoma type 1 (<30% of the infarct territory with mild mas effect) and type 2 (>30% of the infarct territory with significant mass effect). Management strategies can be medical or surgical evacuation of hematoma. Medical management comprises of reversal of coagulopathy, blood pressure regulation, temperature control and therapy focussed on maintenance of blood brain barrier integrity.88

**Surgical clot evacuation**

Surgical evacuation of clot did not demonstrate a significant benefit compared with medical management and to date was considered as a life saving measure in cases with large supratentorial hematomas.75 No significant difference was found in good outcomes between early surgery and medical management arms, both in STICH (The International Surgical Trial in Intracerebral Haemorrhage) trial and STICH2 trial, however, the study results were limited by high rate of crossover from the medical arm to surgical arm.76,77 Conventional surgical evacuation of hematoma was riddled with concerns regarding craniotomy related secondary brain injury due to mechanical manipulations of brain tissue and use of electrocautery. In view of this, minimally invasive surgery plus alteplase for intracerebral haemorrhage evacuation (MISTIE) III trial was conducted, where, stereotactic evacuation of hematoma was done followed by lysis of residual clot with alteplase. The trial showed no improvement in functional outcome, but did demonstrate a reduction in mortality compared to medical treatment.78 Multiple Randomised controlled trials are underway evaluating the optimal management of ICH by utilising minimally invasive neuroendoscopic procedures for removal of clot, like the Early Minimally-invasive Removal of IntraCerebral Haemorrhage (ENRICH) trial and the Minimally Invasive Endoscopic Surgical Treatment with Apollo vs. Medical Management for Supratentorial ICH (INVEST) trial.79,80

**Venous Thromboembolism Prophylaxis**

Venous thromboembolism (VTE) is a relatively common complication post AIS, especially in elderly patients with hemiparesis, and is associated with high morbidity and mortality.81,82 It is recommended to initiate measures for VTE prophylaxis as early as clinically feasible in patients with AIS.83,84 Non pharmacological measures include intermittent pneumatic compression and early mobilisation, while pharmacological measures include administration of unfractionated heparin or low molecular weight heparin, if no haemorrhagic complication is present.85 AHA recommends initiation of oral anticoagulants within 4-14 days after AIS if there is no associated haemorrhagic transformation.14 European Society of Cardiology and European Heart Rhythm Association recommend starting anticoagulants within 1 day of transient ischemic attack, after 3 days in patients with minor stroke (NIHSS <8), after 6 days in mild stroke (NIHSS 8-15) and after 12 days in severe stroke (NIHSS >15).86

**Fever Management and Therapeutic Hypothermia**

Various studies have reported the association of fever with poor functional outcome post AIS and, thus, it is prudent to treat fever in such patients.87,88 INTREPID trial (Impact of Fever Prevention in Brain Injured Patients) is underway and results of it will shed more light on the association between treating fever and targeting normothermia in ICU with achievement of better functional outcomes.89 Therapeutic hypothermia, on the other hand, has failed to show any outcome benefit and is not recommended.90

**Tracheostomy**

In the Early Tracheostomy in Ventilated Stroke Patients 2 (SETPOINT-2) trial, authors reported that among patients with severe stroke receiving mechanical ventilation, early tracheostomy (< 5 days) was statistically not significant in improving the survival rate without severe disability at six months but clinically relevant benefit from early tracheostomy strategy cannot be excluded.91

**Rehabilitation**

Early rehabilitation post AIS is associated with better functional recovery and outcome.92 AVERT trial (A Very Early Rehabilitation Trial after stroke) results demonstrated that short and frequent mobilisation sessions were associated with improved functional outcome as opposed to very early mobilisation (<24hours) and spells of prolonged rehabilitation in post stroke patients.93 At present there is paucity of evidence as regards to optimal rehabilitation session duration and timing of mobilisation and further studies are warranted. Rehabilitation post discharge from hospital is of significant
improvement and requires developing an innovative, patient-oriented, culturally sensitive multidisciplinary approach to cater to the rehabilitation needs of stroke survivors.

**Nutrition**

Early (within 48 hours) enteral nutrition is recommended in all critically ill patients to avoid malnutrition. Malnutrition, stemming from dysphagia post stroke, has a high prevalence (up to 62%) reported in literature and is associated with poor outcome. It is recommended that all patients with ALS are subjected to a swallowing screen before any oral intake is commenced. If a difficulty in swallowing is detected in the initial screen, it is imperative that a complete dysphagia assessment must be done by speech and language specialist within 72 hours of admission.

**CONCLUSION**

Acute ischemic stroke is a significant global health burden. With the advancements in imaging technology, development of dedicated stroke centres, availability of trained multidisciplinary teams, improvements in the understanding of disease evolution and ever updated guidelines, it is feasible to have an early detection and management of stroke with markedly improved functional outcomes. Several critical care decisions like tracheostomy, artificial nutrition, speech and language therapy, long-term ICU care and rehabilitation strategies mandate clear communication and proper prognostication. Increasing the awareness about stroke amongst the general population and development of optimal evidence-based management strategies are the need of the hour.

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