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REVIEW

Acute ischaemic stroke: challenges for the intensivist

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Abstract

Purpose: To provide an update about the rapidly developing changes in the critical care management of acute ischaemic stroke patients.

Methods: A narrative review was conducted in five general areas of acute ischaemic stroke management: reperfusion strategies, anesthesia for endovascular thrombectomy, intensive care unit management, intracranial complications, and ethical considerations.

Results: The introduction of effective reperfusion strategies, including IV thrombolysis and endovascular thrombectomy, has revolutionized the management of acute ischaemic stroke and transformed outcomes for patients. Acute therapeutic efforts are targeted to restoring blood flow to the ischaemic penumbra before irreversible tissue injury has occurred. To optimize patient outcomes, secondary insults, such as hypotension, hyperthermia, or hyperglycaemia, that can extend the penumbral area must also be prevented or corrected. The ICU management of acute ischaemic stroke patients, therefore, focuses on the optimization of systemic physiological homeostasis, management of intracranial complications, and neurological and haemodynamic monitoring after reperfusion therapies. Meticulous blood pressure management is of central importance in improving outcomes, particularly in patients that have undergone reperfusion therapies.

Conclusions: While consensus guidelines are available to guide clinical decision making after acute ischaemic stroke, there is limited high-quality evidence for many of the recommended interventions. However, a bundle of medical, endovascular, and surgical strategies, when applied in a timely and consistent manner, can improve long-term stroke outcomes.

Keywords: Acute ischaemic stroke, Decompressive craniectomy, Endovascular thrombectomy, Penumbra, Thrombolysis, Intensive care, Anesthesia

Introduction

Despite reductions in mortality and disability-adjusted life years over the last decade, acute ischaemic stroke (AIS) remains the third leading cause of death and a major cause of permanent disability worldwide with enormous social and economic consequences [1].

Following AIS, a critical reduction in cerebral blood flow below the ischaemic threshold (10–25% of baseline) culminates in irreversible neuronal death in the core of the lesion [2]. The tissue surrounding this core, often referred to as the ischaemic 'penumbra', is functionally impaired and 'at risk' of further injury (Fig. 1). While blood flow and oxygen delivery to the penumbra is reduced, this tissue may remain viable because of supply from collateral arteries [3]. Therapeutic salvage is, therefore, a possibility if blood flow is restored in a

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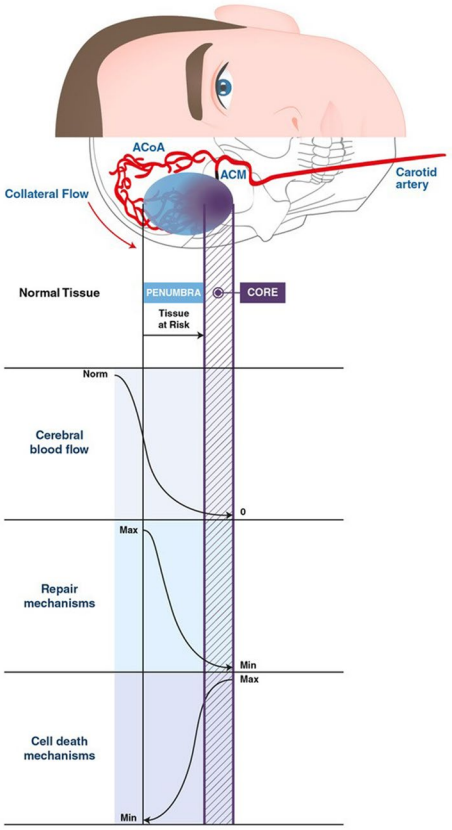

Fig. 1 Schematic showing differential blood flow to the infarct core, ischaemia penumbra and normal brain after acute ischaemic stroke, and the transition between neuronal injury and repair mechanisms

timely manner and to a sufficient degree. In addition to the reduction in blood flow, other factors, including excitotoxicity, oxidative stress and mediators of programmed cell death, also determine the likelihood of neuronal survival or death in the penumbral zone [4]. Moreover, signals that mediate cell death during the acute stage after stroke might promote repair during the recovery phase (Fig. 1). Improved understanding of the transition between injury and repair may ultimately lead to clinical therapies for neuronal recovery after AIS.

In the meantime, all therapeutic efforts are targeted to restoring blood flow to the penumbra before irreversible tissue injury has occurred ("time is brain"). This can be achieved by relieving the arterial occlusion (recanalization) and restoring blood flow (reperfusion) in a timely manner in an attempt to minimize irreversible tissue injury and improve outcomes. At the same time, secondary insults, such as hypotension, hyperthermia or hyperglycaemia, that can extend the penumbral region must be prevented or corrected. These aims are best achieved when patients are managed in an acute stroke unit.

Take-home messages

While acute interventions after acute ischaemic stroke are targeted to restoring blood flow to the ischaemic penumbra, secondary systemic physiological insults, such as hypotension, hyperthermia, or hyperglycaemia, that can extend the penumbral area must be prevented or corrected.
The critical care management of severe acute ischaemic stroke focuses on airway and ventilation management, haemodynamic and fluid optimization, fever and glycaemic control, management of anticoagulation, antiplatelet and thromboprophylaxis therapy, and surgical interventions for malignant middle cerebral artery and cerebellar infarctions, which, when applied in a timely and consistent manner, can improve long-term outcomes.

Although variations in models of care exist, management of stroke and its systemic complications by a multidisciplinary team with appropriate competencies, and coordinated rehabilitation, improves outcomes [5].

A small proportion of the overall AIS cohort, around 15–20%, needs care and interventions that cannot be provided on a stroke unit and these sickest stroke patients require admission to an intensive care unit (ICU) [6]. Even in those with the most severe strokes, a bundle of medical, endovascular, and surgical strategies, when applied in a timely and consistent manner, can improve long-term outcomes [7]. This article will review these strategies and update the reader about the rapidly developing changes in the critical care management of AIS.

Reperfusion strategies

The introduction of effective reperfusion strategies has revolutionized the management of AIS over the last 2 decades and transformed outcomes for patients.

IV thrombolysis

Intravenous (IV) administration of the tissue plasminogen activator (tPA) Alteplase (0.9 mg/kg) within 4.5 h of AIS onset increases the odds of good functional outcome [modified Rankin score (mRS) 0–1] at 3–6 months by about one-third without increasing mortality despite higher rates of symptomatic intracerebral haemorrhage [8]. Earlier treatment (<3 h) is associated with greater proportional benefits. The number needed to treat for good outcome is 10 when IV thrombolysis is initiated less than 3 h after stroke onset and 19 between 3 and 4.5 h. Tenecteplase, a modified plasminogen activator with higher fibrin specificity (which decreases the risk of systemic bleeding) and longer half-life compared to tPA has been shown to increase rates of reperfusion and improved functional outcomes (mRS 0–1) compared to Alteplase [9]. However, tPA is currently the only licensed agent for IV thrombolysis after AIS.

Under current guidelines [7], tPA is used to treat AIS in patients without extensive areas of hypo-attenuation on computed tomography (CT) scan only if the time of symptom onset is known to be less than 4.5 h [7]. Magnetic resonance imaging (MRI) or CT perfusion has been used to evaluate the efficacy and safety of IV tPA in patients with uncertain time of stroke onset, or for extending treatment window. IV tPA guided by a mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) in the region of ischaemia resulted in significantly better 90-day functional outcomes compared to placebo in patients with unclear time of stroke onset despite a higher rate of intracranial haemorrhage in the tPA group (as seen in all thrombolysis trials) [10]. More recently, a multicentre, randomized, placebo-controlled trial including AIS patients with hypoperfused but salvageable regions of brain detected on automated perfusion imaging found that the use of Alteplase between 4.5 and 9.0 h after stroke onset, or at the time the patient awoke with stroke symptoms, resulted in a higher percentage of patients with no or minor neurologic deficits compared to placebo [11].

Endovascular thrombectomy

tPA frequently fails to achieve recanalization in patients with large vessel occlusion (LVO), i.e., internal carotid and middle cerebral (segment 1) arteries. The addition of endovascular thrombectomy (EVT) to IV tPA within 6 h of stroke onset doubles the rate of angiographic revascularisation at 24 h and functional independence at 90 days [12, 13]. Specifically, EVT is associated with a 2.5 times increase in the likelihood of a one or more point improvement in the mRS without increasing the rate of symptomatic intracerebral haemorrhage or all-cause mortality. This effect is consistent among all age groups and in patients ineligible for tPA. Optimised patient selection by the confirmation of LVO with CT or MR angiography, shorter times to revascularisation, and the use of newer devices and techniques (e.g., stent retrievers) that enable higher rates of reperfusion have all contributed to improved EVT outcomes [14].

Whether IV tPA can be safely omitted prior to EVT remains a matter of debate. A meta-analysis of 20 studies including 5279 patients found that direct thrombectomy offered similar safety and efficacy compared with tPA bridging therapy [15]. IV tPA results in successful reperfusion in 1 in 10 EVT-eligible patients, negating the need for endovascular intervention in some [16]. However, initiation of IV thrombolysis may delay the start of mechanical thrombectomy and risk thrombus extension. Current guidelines recommend EVT in all appropriate patients (supplementary material 1), and that eligible patients should receive tPA even if EVT is being considered [7].

Extended treatment windows

Endovascular thrombectomy was previously only considered in patients with stroke symptoms present for less than 6 h on the basis that ischaemic tissue is probably infarcted by this time and the risk for haemorrhagic transformation on restoration of blood flow likely outweighs any benefits from revascularization. When considering eligibility for EVT, stroke onset time is often considered to be that at which the patient was last known to be well. In practice, actual stroke onset times can be shorter (e.g., wake-up stroke) excluding many patients from an intervention from which they might gain benefit.

Two important trials have demonstrated benefit of EVT in anterior circulation LVO stroke beyond 6 h from symptom onset based on mismatch between clinical symptoms and neuroimaging. The DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial randomized 206 patients with LVO and a small ischaemic core determined by perfusion imaging but severe clinical symptoms suggestive of large penumbral volume (referred to as core:clinical mismatch), and were within 6–24 h of last being known well, to receive best medical management with ($n = 107$) or without ($n = 99$) EVT [17]. Thrombectomy was associated with a greater than 70% relative reduction in disability and higher likelihood of functional independence (mRS 0–2) compared to medical treatment alone (48.6% vs. 13.1%). The number need to treat was 2.8 to produce an additional patient with functional independence at 90 days, and 2 to improve 90-day disability score. Similarly, in the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE-3) trial, patients with anterior circulation LV who fulfilled predefined criteria of a mismatch between infarct core and penumbral tissue volumes, and were last known to be well 6–16 h previously, were also randomized to receive best medical therapy with ($n = 92$) or without ($n = 90$) EVT [18]. Thrombectomy was again associated with a highly significant benefit compared to medical treatment alone; there was a shift in mRS score distribution toward better 90-day outcome and a greater proportion of patients with mRS scores 0–2. These studies provide strong evidence for the use of EVT beyond 6 h from stroke onset based on neuroimaging eligibility criteria and identify a new cohort of patients who might benefit from this intervention.

Despite the possibility for extended treatment windows, functional outcomes are greatly improved by

shorter stroke onset to treatment times [19]. It is, therefore, imperative that EVT occurs as quickly as possible. Unlike tPA, endovascular interventions require specialized services not available in most hospitals. There is uncertainty whether outcomes are improved if patients are transported directly to the closest comprehensive stroke centre capable of delivering both tPA and EVT or receive early tPA in a primary stroke centre before secondary transfer to the comprehensive stroke centre for EVT (the 'drip and ship' approach). This is a particularly important issue in communities sited long distances from a comprehensive stroke centre. A recent systematic review and meta-analysis found that AIS patients admitted directly to a comprehensive stroke centre may have better 90-day outcomes than those receiving initial IV thrombolysis in a primary stroke centre, with no differences between the treatment pathways in rates of successful reperfusion, symptomatic intracranial haemorrhage, or 90-day mortality [20]. However, the authors noted major limitations of current evidence (retrospective studies and selection bias) and highlighted a need for adequately powered, multicenter randomized controlled trials to answer this question.

Anesthesia for endovascular thrombectomy

The choice of general anesthesia (GA) or conscious sedation (CS) for EVT remains a matter of debate and the impact on outcomes inconclusive. The relative advantages and disadvantages of GA and CS are shown in Table 1.

Multiple retrospective studies demonstrated that GA was associated with worse neurological outcomes compared to CS, but these findings have not been replicated in subsequent prospective randomized controlled trials [21]. The important studies investigating GA and CS during EVT are summarised in supplementary material 2. When GA is integrated into routine workflow and systolic blood pressure (BP) maintained > 140 mmHg, patients who receive GA do not have less favourable outcomes after EVT compared to those who receive CS [21]. Given this equipoise, and as recommended by the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) [22], anesthetic technique during EVT should be individualized.

The goals of anesthesia during EVT are shown in supplementary material 3. Any pre-procedure assessment or intervention, including arterial line placement for BP monitoring, should not delay the start of the procedure given the time-limited, emergency nature of EVT. Irrespective of anesthetic technique, meticulous haemodynamic control is critical during EVT; guidelines recommend that systolic BP should be maintained between 140 and 180 mmHg, irrespective of the previous IV tPA [22]. Collateral perfusion maintains penumbral viability until reperfusion is accomplished, and this is likely BP dependent in many patients. Thus, avoiding hypotension by maintaining BP at presentation values until reperfusion occurs is a cardinal management goal [23]. A greater than 10% reduction in mean BP from baseline is a strong risk factor for poor outcome in patients having EVT under CS [24]. A single-centre study found that intervention was required to maintain BP within the target range in almost 40% of patients during CS, arguing for the routine presence of anaesthesiologists during all EVT procedures [25]. Similarly, even small reductions in mean BP are associated with poor outcomes after EVT under GA. In one study, a 10 mmHg reduction in mean BP below baseline was associated with a 1.67 times lower odds of good outcome [26]. The association between minimum BP before reperfusion and functional outcomes appears to be dependent on presentation National Institutes of Health Stroke Scale score (NIHSS); those with more severe stroke are most likely unable to tolerate even modest reductions in BP [24]. It has been suggested

Table 1 Advantages and disadvantages of general anesthesia and conscious sedation for endovascular thrombectomy

Technique	Advantages	Disadvantages
General anesthesia	Maximise patient comfort Immobilisation to minimize risk of guide-wire vessel perforation Airway protection and controlled ventilation ? shorter time to recanalization Potential reduction in radiation exposure	May delay start of intervention Inability to perform neurological assessment during procedure Haemodynamic fluctuations—need for vasopressor/inotropes Potential for inadvertent hypoxia/hypocapnea
Conscious sedation	Allows intra/post-procedure neurological assessment Avoids delay in start of intervention Minimal interference with systemic physiology Quicker recovery and discharge for neurointerventional suite	Patient discomfort/lack of cooperation Patient movement Unprotected airway/risk of aspiration Risk of hypoxemia/hypercarbia with sedation

that better functional outcome might be achieved by targeting intra-procedure BP > 20% of pre-procedure levels in patients receiving GA [27]. Importantly, BP targets should be readjusted (lowered) in communication with the neurointerventionalist following successful recanalization to minimize the risk of hyperperfusion and haemorrhagic conversion [22].

Close monitoring of oxygenation and ventilation is also critical during EVT. FiO_2 should be no higher than required to maintain normoxia, i.e., $SpO_2 > 92\%$ and $PaO_2 > 60$ mmHg [22], and hyperventilation/hypocapnea avoided [28]. Euglycaemia should be maintained according to institutional protocols (see below). If standard extubation criteria are met, patients should be awakened and extubated at the end of the procedure to allow early neurological assessment [28].

Anaesthesiologists should be prepared to rapidly convert from CS to GA if needed to protect the airway, maintain oxygenation and ventilation parameters, or manage intracranial pressure (ICP). In addition, EVT-related complications should be anticipated and rapidly treated. In case of catheter-induced intracerebral haemorrhage, heparin should be reversed immediately with protamine and systolic BP maintained > 140 mmHg to minimize the risk of further ischaemic damage [22].

Intensive care management

A more interventional approach to AIS management has resulted in increasing numbers of stroke patients being admitted to the ICU [6]. The indications for ICU admission may vary from centre to centre depending on the level of care that can be provided in the local stroke unit. Some common indications for admission to ICU are shown in Table 2. In addition to clinical status, decisions to admit a stroke patient to the ICU should be based on likely prognosis and known wishes of the patient [6]. Although there is no specific evidence to guide post-EVT management, an ICU setting allows more frequent neurological assessment as well as more aggressive BP monitoring and management [29]. The Glasgow coma scale score is frequently to assess global neurological status on the ICU, but a stroke severity rating scale, such as the NIHSS, quantifies stroke-related impairment more objectively [7]. The NIHSS is a 42 point scale comprising 11 items, each of which scores a specific ability between 0 and 4; it is used to assess stroke severity and prognosis and for serial assessment [30].

The ICU management of AIS patients focuses on the optimization of systemic physiological homeostasis, management of intracranial complications, and neurological monitoring after reperfusion therapies (Figs. 2, 3). Coordination of management by specialized neurointensive care teams has been associated with improved outcomes after AIS [31].

Airway and respiratory management

AIS is associated with a high rate of respiratory complications [32], which can arise from both neurological and non-neurological causes including dysphagia, pneumonia, pulmonary aspiration, oedema and embolism, acute distress respiratory syndrome, and respiratory muscles weakness [33]. The need for respiratory support and airway protection is associated with worse outcomes after AIS, and many physicians remain reluctant to initiate endotracheal intubation and mechanical ventilation if the probability of survival with a meaningful quality of life is extremely low [34]. In the absence of high-quality data, the decision to intubate should be triggered by clinical features such as low Glasgow Coma Scale score, loss of protective airway reflexes, signs of increased ICP, infarct size > 2/3 of middle cerebral artery territory or midline shift, hypoxic or hypercarbic respiratory failure, or seizures [35].

Targets for ventilation are unclear, although maintenance of normocapnia ($PaCO_2$ 35–45 mmHg) and $SpO_2 > 94\%$ is usually recommended [7]. Hypoxaemia ($SpO_2 < 90\%$) in the first few hours after hospital admission is associated with a doubling of mortality after AIS [36]. A large randomized controlled trial found no benefit of routine supplementary oxygen [37], and oxygen supplementation can be detrimental in some cases. Thus, guidelines recommend that oxygen therapy should be avoided in non-hypoxaemic AIS patients, and

Table 2 Common indications for ICU admission of patients with acute ischemic stroke

Intubation and ventilation	Decreased level of consciousness (GCS < 8), airway protection, acute respiratory failure, evidence of brainstem dysfunction
Optimising systemic physiology	Blood pressure, fluid balance, glucose, temperature, haemoglobin
Systemic organ support	Cardiac dysfunction, mechanical ventilation/NIV, renal replacement therapy
Severe stroke	NIHSS > 17, large MCA infarct volume (> 145 cm^3)
Management of intracranial complications	Seizures and status epilepticus, haemorrhagic transformation, malignant MCA syndrome, post decompressive craniectomy

GCS Glasgow coma score scale, *MCA* middle cerebral artery, *NIHSS* National Institutes of Health stroke scale, *NIV* non-invasive ventilation

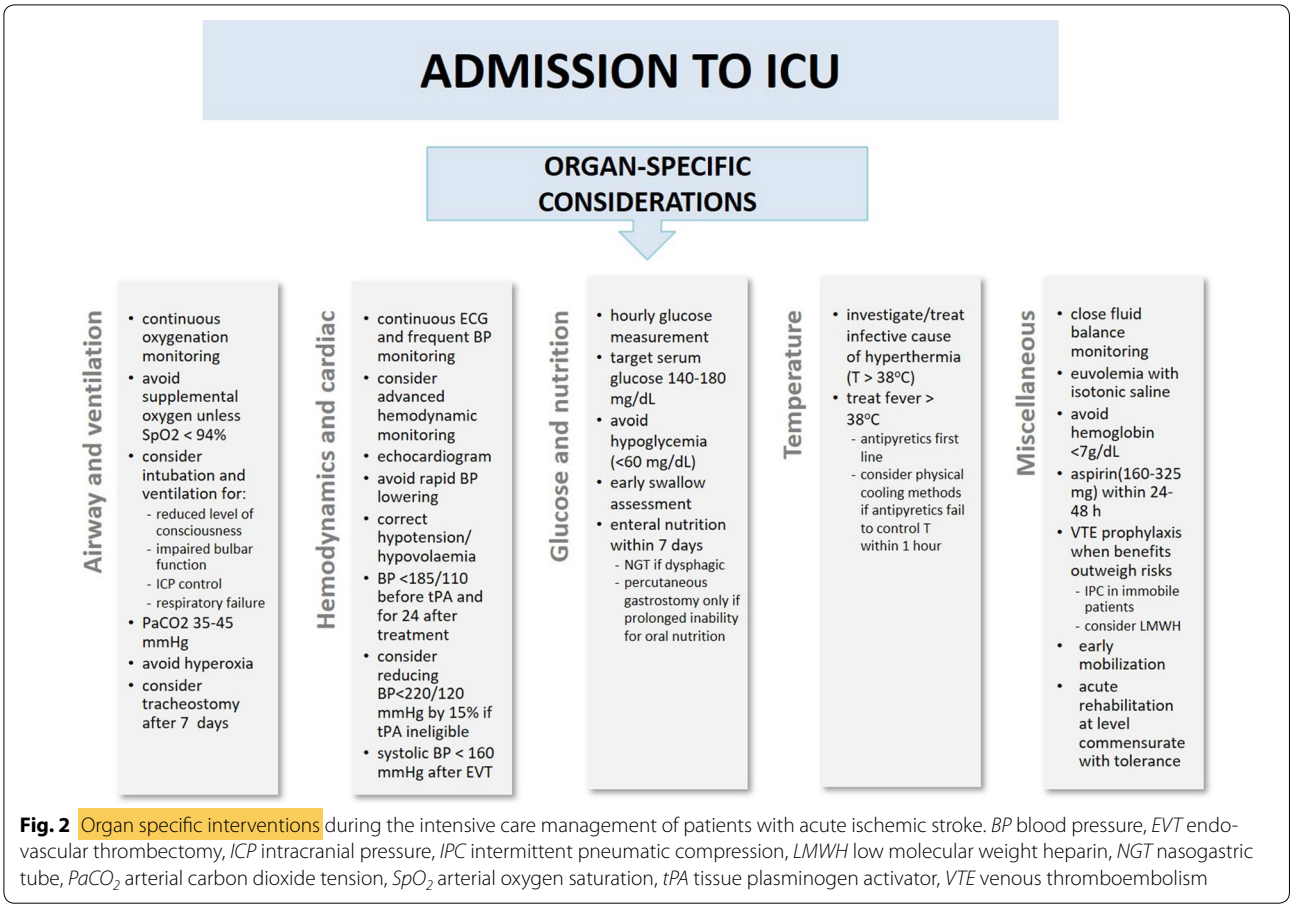

Fig. 2 Organ specific interventions during the intensive care management of patients with acute ischemic stroke. *BP* blood pressure, *EVT* endovascular thrombectomy, *ICP* intracranial pressure, *IPC* intermittent pneumatic compression, *LMWH* low molecular weight heparin, *NGT* nasogastric tube, *$PaCO_2$* arterial carbon dioxide tension, *SpO_2* arterial oxygen saturation, *tPA* tissue plasminogen activator, *VTE* venous thromboembolism

supplemental oxygen provided only to maintain oxygen saturation > 94% [7].

AIS patients should be extubated as soon as is practical and safe. Some may require tracheostomy when prolonged ventilation or airway protection is required, although optimal timing of tracheostomy remains unclear. The Stroke-related Early Tracheostomy vs. Prolonged Orotracheal Intubation in Neurocritical care Trial 2 (SETPOINT2) aims to identify the optimal timing of tracheostomy in ventilated stroke patients and clarify whether benefits in functional outcome can be achieved by early tracheostomy [38]. Decannulation requires endoscopic confirmation of adequate swallow or, if absent, consideration of feeding via a percutaneous gastrostomy. A recent randomized controlled trial demonstrated that pharyngeal electrical stimulation improves swallow function after AIS and increases the proportion of patients whose tracheostomy can be decannulated [39].

Blood pressure management

Almost 80% of AIS patients present with systolic BP > 140 mmHg from a variety of causes, including pre-existing hypertension and/or neuroendocrine stress responses, sympathetic hyperactivity, or elevated ICP. Severe hypertension has many adverse effects, including increasing the risk of cardiorespiratory complications and cytotoxic oedema and haemorrhagic transformation of infarcted tissue. However, as noted earlier, elevated BP may be beneficial in augmenting blood flow to the ischaemic penumbra following LVO. Return of BP to baseline after restoration of flow suggests that increased BP is closely linked to the presence of cerebral ischaemia [40]. Hypertension is associated with adverse outcome after AIS, particularly after EVT. In a retrospective study of 228 patients with anterior circulation stroke, higher maximum systolic BP in the first 24 h post-EVT was independently associated with worse 90-day functional outcome and higher rates of haemorrhagic complications [41]. Even modest post-procedure BP elevations appear to have adverse outcome effects. In a prospective study of 217 patients with LVO, a 10% increment in systolic BP in the first 24-h after EVT was independently associated with a higher likelihood of 3-month mortality (OR 1.49) and lower odds of 3-month functional independence (OR 0.70) [42]. Moreover, achieving a systolic BP target

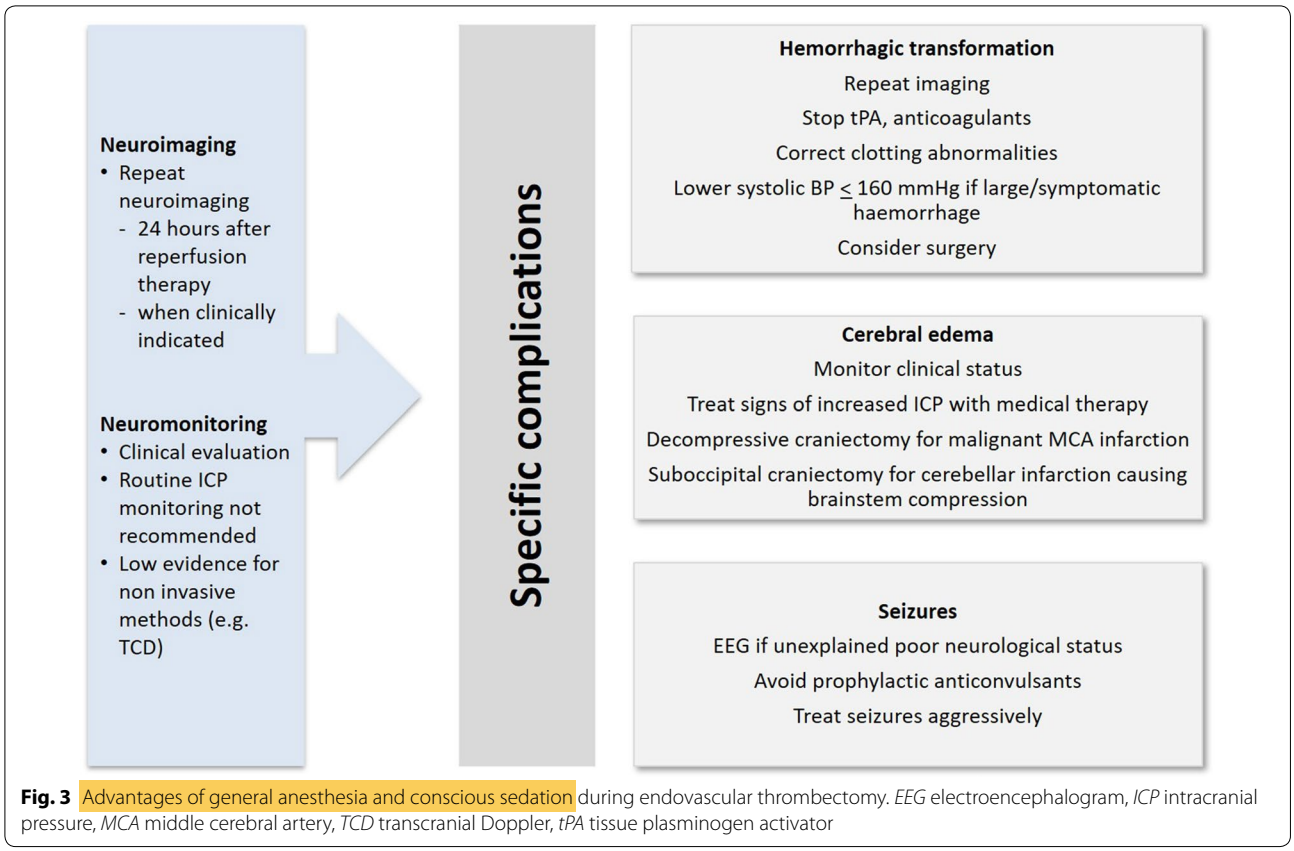

Fig. 3 Advantages of general anesthesia and conscious sedation during endovascular thrombectomy. *EEG* electroencephalogram, *ICP* intracranial pressure, *MCA* middle cerebral artery, *TCD* transcranial Doppler, *tPA* tissue plasminogen activator

< 160/90 mmHg during this period was independently associated with lower rates of 3-month mortality. Blood pressure variability as well as absolute BP influences stroke outcomes. In a single-centre study, large BP fluctuations in the first 24 h post-EVT were associated with worse outcomes in patients with failed LVO recanalization [43].

Guidelines recommend that BP should be reduced below < 185/110 mmHg prior to IV tPA and maintained at that level for 24 h thereafter [7]. There is no clear evidence to guide BP management after EVT, but it seems prudent to maintain systolic BP < 160 mmHg in the early post-procedure period with a proviso that this target is individualized based on degree of revascularization, collateral blood flow, extent of infarction post-EVT, use of thrombolytics, and pre-existing cardiac and renal comorbidities. The benefits of initiating antihypertensive treatment in patients that do not receive thrombolysis or have no other indications for acute BP lowering (e.g., myocardial ischaemia or heart failure) is unknown, and guidelines recommend tolerating BP up to 220/120 mmHg in such patients [7]. However, it seems reasonable to reduce BP by 15% in the first 24 h after stroke onset for BP above these values and to start or restart antihypertensive medications after 24 h in patients that remain hypertensive but neurologically stable [7].

Some observational studies have suggested an association between low BP and worse outcomes after AIS [44]. However, a recent single-centre study found that 88% of patients had systolic BP below the recommended target during EVT, but that neither duration nor number of episodes of systolic BP < 140 mmHg affected discharge outcome [28]. No studies have addressed the treatment of low BP after AIS [7]. While it is imperative to treat symptomatic hypotension, there are no data to support the use of induced hypertension or choice of vasopressor/inotrope [29]. Further investigation is required to identify optimal BP targets to avoid unnecessary administration of vasopressors; cumulative vasopressor dose has been associated with unfavourable outcomes after EVT [45].

A survey of StrokeNet sites in the USA found that the majority of institutions do not have standardized protocols for post-EVT BP control, although BP management is individualized based on reperfusion status in many [46]. Future research should focus on understanding the impact of BP variability and cerebral autoregulatory status on stroke outcomes, and determining whether BP is a therapeutic target or merely a marker of injury severity/poor outcome [47].

Fever

Fever frequently complicates AIS. Temperature > 37.5 °C has been reported in up to one quarter of patients in first 6 h after stroke onset and in about one-third by 24 h. Higher body temperature at admission and increases in temperature during the first 24 h after stroke onset are associated with worse outcomes [48].

While AIS-related fever may have a neurogenic origin, an infective cause should always be sought and treated [49]. Irrespective of origin, fever accelerates the ischaemic cascade and worsens neuronal injury. Thus, guidelines include a strong recommendation for prompt fever treatment in stroke patients [7]. First-line therapy is with antipyretic medications, although early and late treatment with paracetamol has not been found to be of benefit [50]. It is recommended that targeted temperature management should be initiated if antipyretic agents fail to control neurogenic fever > 37.5 °C within 1 h, and maintained for as long as there is potential for secondary brain damage [49].

Many preclinical studies support a neuroprotective role of therapeutic hypothermia in AIS [51], but its effective translation into clinical management is unproven [7]. The Endovascular Reperfusion and Cooling in Cerebral Acute Ischemia (ReCCLAIM I) study found no benefits from intravascular hypothermia after reperfusion therapy for AIS [52]. Infection is a significant complication of stroke and therapeutic hypothermia increases these baseline risks, particular for pneumonia [53].

Antiplatelet agents, anticoagulation, and thromboprophylaxis

Aspirin administration within 24–48 h from stroke onset is recommended with level 1 of evidence of a 50% reduction in rate and severity of early recurrent stroke (6–12 weeks) [7]. The role of other antiplatelet agents, or dual therapy, is not established. The clopidogrel in high-risk patients with acute non-disabling cerebrovascular events' (CHANCE) randomized trial found that short-term dual platelet therapy with aspirin and clopidogrel started within 24 h and continued for 21 days after stroke onset and had a potential beneficial effect on 90-day secondary stroke prevention in a Chinese population [54]. In a subsequent study in an international population of patients with minor ischemic stroke or at high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischaemic events, but a higher risk of major haemorrhage at 90 days compared to those who received aspirin alone [55]. Based on such evidence, it seems likely that dual antiplatelet therapy will become the treatment of choice in the future. Canadian guidelines already recommend a combination of clopidogrel and aspirin for 21–30 days in patients with minor stroke (NIHSS 0–3) of non-cardioembolic origin, followed by de-escalation to antiplatelet monotherapy [56]. Antiplatelet therapy is often avoided in the first 24 h following reperfusion therapy [6], but this approach requires further evaluation.

Urgent anticoagulation is not effective in preventing neurological deterioration or early stroke recurrence, or improving outcomes, after AIS [57]. There is also no evidence of benefit from anticoagulation in patients with severe stenosis of an internal carotid artery or non-occlusive extracranial intraluminal thrombus [7].

Venous thromboembolism (VTE) is a potentially life-threatening complication, varyingly reported to occur in 10–75% of AIS patients [58]. As in other patient cohorts, prevention of thromboembolism is facilitated by early hydration and mobilisation [6]. Specific VTE prophylaxis should be considered in all patients when the potential benefits outweigh risks (e.g., intracranial haemorrhage) [7]. The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial found that, compared to routine care, intermittent pneumatic compression was associated with a reduction in the rate of deep-vein thrombosis (relative risk reduction 0.65, 95% CI 0.51–0.84; $p = 0.001$), a significant improvement in 6-month survival (hazard ratio: 0.86; 95% CI 0.73–0.99; $p = 0.042$) but not disability, with an increased incidence of skin breaks (3.1% vs. 1.4%, $p = 0.002$) [59]. Guidelines strongly recommend intermittent pneumatic compression in immobile stroke patients without contraindications [7]. Any benefits of prophylactic unfractionated or low molecular weight heparins are not well established. While pharmacological prophylaxis reduces the rate of deep venous thrombosis and pulmonary embolism in AIS patients, it is not associated with reduced mortality or improved neurological outcomes because of increased risk of intra- and extracranial bleeding [60]. A recent randomized trial including more than 2000 general ICU patients receiving pharmacologic thromboprophylaxis found that adjunctive intermittent pneumatic compression did not result in a significantly lower incidence of proximal lower limb deep-vein thrombosis compared with pharmacologic thromboprophylaxis alone [61]. Whether the findings of this study are applicable to AIS patients remains to be determined.

Glycaemic control and nutrition

The brain is dependent on a constant and adequate supply of glucose for oxidative metabolism. Acute hypoglycaemia can activate a cascade of events resulting in functional brain failure [62], whereas hyperglycaemia worsens intracellular acidosis, increases brain oedema and infarct size, disrupts the blood–brain barrier, and is associated with higher rates of infection [63].

Hyperglycaemia during the first 24 h after AIS onset is associated with worse outcomes [64]. It increases the risk of reperfusion injury and haemorrhagic transformation, and is associated with impaired recanalization. The importance of uncontrolled hyperglycaemia after AIS is reflected in guidelines which recommend that only assessment of blood glucose should precede the initiation of IV thrombolysis [7]. Optimal glycaemic management and blood glucose targets after AIS remain controversial, particularly in critically ill stroke patients. Preliminary data from the Stroke Hyperglycemia Insulin Network Effort (SHINE) study, which recruited 1151 patients from 63 stroke units in the US, show that intensive glucose control (80–130 mg/dL) with insulin infusion does not improve 90-day functional outcome compared to standard control (< 180 mg/dL) with intermittent subcutaneous insulin [65]. In addition, intensive glucose control increased the risk of hypoglycaemia (< 40 mg/dL) and required increased supervision from nursing staff in this study.

Current guidelines recommend close monitoring of blood glucose after AIS and treatment of hyperglycaemia to maintain glucose in the range of 140–180 mg/dL, with avoidance or immediate treatment of hypoglycaemia (< 60 mg/dL) [7]. It seems reasonable to use IV insulin to control blood glucose in stroke patients on the ICU, where such practice is routine and the risk of hypoglycaemia likely lower than in other clinical areas such as stroke units. Higher glucose levels are more deleterious in patients with good collaterals compared to those with poor collaterals, raising the intriguing possibility that good collateral circulation at presentation might be an indication for more intensive glycaemic control [66].

The provision of adequate hydration and nutrition is crucial, but often limited by dysphagia which occurs in 23–50% of AIS patients [67]. Dysphagia increases the risk for pulmonary aspiration, pneumonia and malnutrition, adversely affects quality of life, and increases morbidity and mortality. All AIS patients should undergo an early nurse-led swallow assessment followed by fibreoptic evaluation in those at risk for aspiration [7]. Patients should be maintained nil orally until an effective swallow is confirmed. Enteral feeding within 7 days from admission is associated with a 5.8% reduction in mortality after AIS. In patients with impaired swallow, enteral nutrition should initially be provided via a nasogastric tube [68], with percutaneous endoscopic gastrostomy reserved for those in whom persistent dysphagia is anticipated [7].

There is no clear evidence to guide optimum volume, duration, or mode of parenteral fluid administration in patients with poor oral fluid intake. Infusion of isotonic saline to maintain euvolaemia is recommended, with avoidance of hypotonic glucose-containing solutions and albumin [69].

Acute rehabilitation

Early mobilisation reduces post-stroke complications. Acute rehabilitation should be provided by organised, interprofessional stroke teams at intensities commensurate with tolerance and anticipated benefit [7]. High-dose, early mobilisation (sitting, standing and walking) providing at least three out-of-bed sessions compared to usual care, and initiated within 24 h of stroke onset, reduces the odds of a favourable 3-month outcome compared to standard care [70]. Speech and language therapy improves functional communication in patients with post-stroke aphasia.

Management of intracranial complications

Neurological deterioration may occur because of seizures, extension of the infarct, haemorrhagic transformation, or worsening cerebral oedema.

Haemorrhagic transformation

Haemorrhagic transformation can occur in any patient, but is more common in those who have received tPA, EVT, or anticoagulation. Wake-up strokes and higher serum glucose levels are independent risk factors for the development of symptomatic intracranial haemorrhage after EVT, whereas complete recanalisation has a lower risk for haemorrhage compared to partial recanalisation [71].

There is no standardized management or robust evidence to guide treatment of haemorrhagic transformation. tPA should be stopped if the infusion has not been completed, and pharmacological VTE prophylaxis temporarily discontinued. Some recommend the suspension of aspirin for 5–7 days, although the risks and benefits of this approach are unknown; decisions to stop aspirin should be considered on an individual basis [29]. Lowering systolic BP targets to < 160 mmHg is also reasonable in patients with sizable or symptomatic haemorrhagic transformation [72].

In the case of worsening symptomatic haemorrhage, particularly after tPA, cryoprecipitate and tranexamic acid are recommended [73], but there is no evidence for their routine use. There are also no definitive data about the role of surgery. The decision to evacuate a haematoma is determined by the size and location of the haemorrhage, and the patient's overall clinical condition; evacuation of large hematomas may be lifesaving, whereas deeper, smaller haemorrhages are best managed conservatively.

Cerebral oedema

Although successful reperfusion reduces final infarct volume, post-EVT oedema may lead to neurological deterioration [74]. Clinically significant cerebral oedema leading to intracranial hypertension develops in a small but significant proportion of patients with AIS, typically those with distal internal carotid artery occlusion or proximal occlusion of the middle cerebral artery (MCA). The latter, often referred to as 'malignant MCA syndrome' because of its life-threatening nature, leads to clinical deterioration in two-thirds of affected patients within 48 h of stroke onset [75]. Malignant MCA syndrome has a mortality rate of almost 80% if untreated and in excess of 50% despite maximal medical management. General medical measures to limit space-occupying oedema, such as osmotherapy, are often ineffective as sole therapy, but can be useful as a bridge to surgery [76].

Decompressive hemicraniectomy significantly decreases mortality and improves functional outcome in AIS patients younger than 60 years of age. A pre-planned merged analysis of 3 trials including 93 patients younger than 60 years of age in whom treatment was initiated within 48 h of stroke onset found that hemicraniectomy was associated with lower 12-month mortality compared to conservative management (22% vs. 71%, respectively, $p < 0.0001$; 50% absolute risk reduction) and a higher proportion of patients with favourable outcomes [77]. The number needed to treat was 2 for survival with mRS 4 or better, 4 for survival with mRS 3 or better, and 2 for survival irrespective of functional outcome. The benefits of surgery were similar in patients older or younger than 50 years of age or in the presence or the absence of aphasia. A Cochrane systematic review incorporating the three original studies confirmed these findings, but cautioned that an overestimation of effect size could not be excluded because all trials were stopped early [78].

The role of decompressive craniectomy in elderly stroke patients is more controversial. In the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II (DESTINY II) trial, hemicraniectomy within 48 h of symptom onset in patients with malignant hemispheric infarction aged between 61 and 82 years resulted in lower mortality (33% vs. 70%), but a higher proportion of survivors with severe disability (mRS 4–5) compared to medical treatment [79]. No patient survived with no or minimal disability (mRS 0–2) in this study, highlighting the grave prognosis of malignant MCA infarction in the elderly. Decisions to recommend decompressive craniectomy must, therefore, be made not only in the context of its clinical indications, but also after consideration of an individual patient's preferences and quality-of-life expectations.

Ethical considerations

Stroke patients often have impaired decisional capacity or deficits which limit their ability to communicate their wishes. Decisions to provide invasive interventions, such as mechanical ventilation or decompressive craniectomy, must often be based on the clinician's assessment of likely prognosis balanced against interpretation of the patient's wishes or values. In the absence of a clear advanced directive, interpretations of a patient's wishes by family members and clinicians are often imperfect in gaining a valid understanding of what an individual patient would have chosen in this particular circumstance [80].

Individuals' attitudes to levels of disability vary considerably, although some appear to adapt to life-changing events and subsequently accept a degree of disability that they would previously have judged to be unacceptable [81]. Clinicians' attitudes to disability also vary and may be different to those of their patients; this can lead to the withholding of treatments that a patient might have been willing to accept. The importance of shared decision making based on likely outcomes of therapeutic options after AIS, prolonged recovery times, and potential post-procedure quality of life cannot be over-estimated [82].

Conclusion

Effective reperfusion strategies, including tPA and EVT, have revolutionized the management of AIS and can now be delivered in extended time windows in some patients based on neuroimaging criteria. Secondary insults, such as hypotension, hyperthermia, or hyperglycaemia, that can extend the penumbral region must be prevented or corrected. The ICU management of AIS patients, therefore, focuses on optimisation of systemic physiological homeostasis and management of intracranial complications. Meticulous blood pressure management is of central importance in improving outcomes, particularly in patients that have undergone reperfusion therapies. Together, a bundle of medical, endovascular and surgical strategies, when applied in a timely and consistent manner, can improve long-term stroke outcomes.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
MS is Editor-in-Chief of the Journal of Neurosurgical Anesthesiology. CR is a junior Editor of Intensive Care Medicine. GC is Editor-in-Chief of Intensive Care Medicine. The authors have no other conflicts to declare.

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