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REVIEW

Matthew A. Kirkman
Giuseppe Citerio
Martin Smith

The intensive care management of acute ischemic stroke: an overview

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M. A. Kirkman (✉) · M. Smith
Neurocritical Care Unit, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London WC1N 3BG, UK
e-mail: matthew.kirkman@gmail.com
Tel.: +44-78-86608978

M. A. Kirkman
Faculty of Medicine, Imperial College London, London, UK

G. Citerio
Neurointensive Care Unit, Department of Anaesthesia and Critical Care, Ospedale San Gerardo, Monza, Italy

M. Smith
NIHR University College London Hospitals Biomedical Research Centre, London, UK

Abstract *Purpose:* Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality worldwide. In part due to the availability of more aggressive treatments, increasing numbers of patients with AIS are being admitted to the intensive care unit (ICU). Despite the availability of consensus guidance for the general management of AIS, there is little evidence to support its ICU management. The purpose of this article is to provide a contemporary perspective, and our recommendations, on the ICU management of AIS. *Methods:* We reviewed the current general AIS guidelines provided by the European Stroke Organisation, the American Stroke Association, and the UK National Institute for Health and Care Excellence, as well as the wider literature, for the data most relevant to the ICU management of AIS. *Results:* There are four interventions in AIS supported by class I evidence: care on a stroke unit, intravenous tissue plasminogen activator within 4.5 h of stroke onset, aspirin within 48 h of stroke onset, and decompressive craniectomy for supratentorial malignant hemispheric cerebral infarction. However, robust evidence for specific AIS management principles in the ICU setting is weak. Management principles currently focus on airway and ventilation management, hemodynamic and fluid optimization, fever and glycemic control, management of anticoagulation, antiplatelet and thromboprophylaxis therapy, control of seizures and surgical interventions for malignant middle cerebral artery and cerebellar infarctions. *Conclusions:* We have provided our recommendations for the principles of ICU management of AIS, based on the best available current evidence. Encouragement of large-scale recruitment of patients with AIS into clinical trials should aid the development of robust evidence for the benefit of different interventions in the ICU on outcome.

Keywords Acute ischemic stroke · Endovascular therapy · Management · Neurocritical care · Thrombolysis

Introduction

Stroke is a devastating collection of clinical syndromes that represent a leading cause of mortality and morbidity worldwide [1]. Acute ischemic stroke (AIS) is the commonest subtype, accounting for 85 % of all strokes, with the remainder being hemorrhagic. Significant advances in the past two decades have resulted in the development of four interventions supported by class I evidence: care on a stroke unit, intravenous tissue plasminogen activator (rt-PA) within 4.5 h of stroke onset, aspirin within 48 h of stroke onset, and decompressive craniectomy for

supratentorial malignant hemispheric cerebral infarction [2, 3]. Expert consensus guidance for the general management of AIS is available from the European Stroke Organisation (ESO) [4], the American Stroke Association (ASA) [5], and the UK National Institute for Health and Care Excellence (NICE) [6]. In contrast, the evidence base guiding the intensive care unit (ICU) management of AIS is relatively poor despite around 15–20 % of stroke patients being admitted to an ICU [7]. This results in substantial heterogeneity in care delivery between clinicians and centers.

In 2010 guidelines for the intensivist managing stroke were published in French, based on recommendations from a group of experts [8]. However, these were not translated into English, and the evidence base has changed since the guidelines were published. To date there are no widely accepted international guidelines for managing stroke on the ICU, and the purpose of this article is to provide a contemporary perspective, and our recommendations, on the ICU management of AIS.

Pathophysiology of acute ischemic stroke

The pathophysiology of AIS is complex, and for more detailed information the reader is referred elsewhere [9]. At the tissue level there is energy failure, disruption of ion homeostasis, glutamate release, calcium channel dysfunction, free radical release, mitochondrial dysfunction, membrane disruption, activation of inflammatory cascades, as well as necrosis and apoptosis. It is vitally important to appreciate the concept of an ischemic core surrounded by an ischemic penumbral region. Blood flow to the ischemic core is too low to maintain electric activity but sufficient to preserve ion channels, whereas the hypoperfused tissue forming the surrounding penumbra has potential for complete functional recovery without lasting morphological damage if blood flow is restored in a timely manner and to a sufficient degree.

Alongside our greater understanding of the pathophysiology of AIS has been significant research for clinically effective neuroprotectants. However, clinical trials of pharmaceuticals with promising preclinical results have been disappointing, attributed to the heterogeneity of human stroke and lack of consistency in methodological design between preclinical and clinical studies [10]. The Stroke Therapy Academic Industry Roundtable criteria for the preclinical development of neuroprotective stroke agents have not prevented translational failures, most notably NXY-059, which fulfilled almost all the criteria but failed to show benefit. It remains to be seen whether ongoing studies of putative neuroprotectant agents will translate into clinical benefit.

Etiology and classification of acute ischemic stroke

Establishing the etiology of AIS is important to ensure timely and appropriate management. According to one study, 29 % of strokes relate to cardioembolic disorders, particularly atrial fibrillation (AF), 16 % to large vessel cervical or intracranial atherosclerosis with stenosis, 16 % to lacunar disease, and 3 % to other causes such as migraine, malignancy, and hypercoagulable states [11]. Although the etiology is unclear in one-third of patients, many of these likely have undiagnosed paroxysmal AF.

The Oxford (or Bamford) Stroke Classification system is often used to classify AIS based on clinical signs and symptoms into lacunar (LACS), partial anterior circulation (PACS), total anterior circulation (TACS), and posterior circulation stroke (POCS). This classification predicts the extent of the stroke, region affected, underlying etiology, and prognosis [12].

Reperfusion therapy

In the past two decades reperfusion therapy, including intravenous and intraarterial thrombolysis, and mechanical clot-removing devices, has emerged as an important treatment option for patients presenting early after symptom onset. The intention of reperfusion therapy is to restore impaired blood flow to the ischemic penumbra before irreversible neuronal death occurs. There is class I evidence supporting the use of intravenous rt-PA as soon as possible but within 4.5 h of stroke onset, following exclusion of a hemorrhagic stroke by noncontrast computed tomography (CT) scan [3, 13]. A pooled analysis of four trials confirms that the odds ratio of a favorable 3-month outcome decreases as time to treatment increases, emphasizing the benefits of earlier treatment [3]. Endovascular therapy (including intraarterial thrombolysis, mechanical embolectomy, and angioplasty/stenting) represents an alternative therapy to intravenous rt-PA, but US guidelines restrict its use to those who are not candidates for rt-PA, or who fail to improve after full rt-PA therapy [5]. It is generally accepted that intraarterial thrombolysis should be performed within 6 h and thrombectomy within 8 h of symptom onset. Several trials have shown endovascular therapy (either combined with intravenous thrombolysis or alone) to be no better than intravenous thrombolysis in terms of outcomes, which may result from the additional time required to undertake the procedure [14–16].

Key recommendations rt-PA can be given within 4.5 h of symptom onset, but the earlier the better [3, 13]. Intraarterial thrombolysis can be used within 6 h and mechanical embolectomy within 8 h of symptom onset in those who are not candidates for rt-PA or who fail to

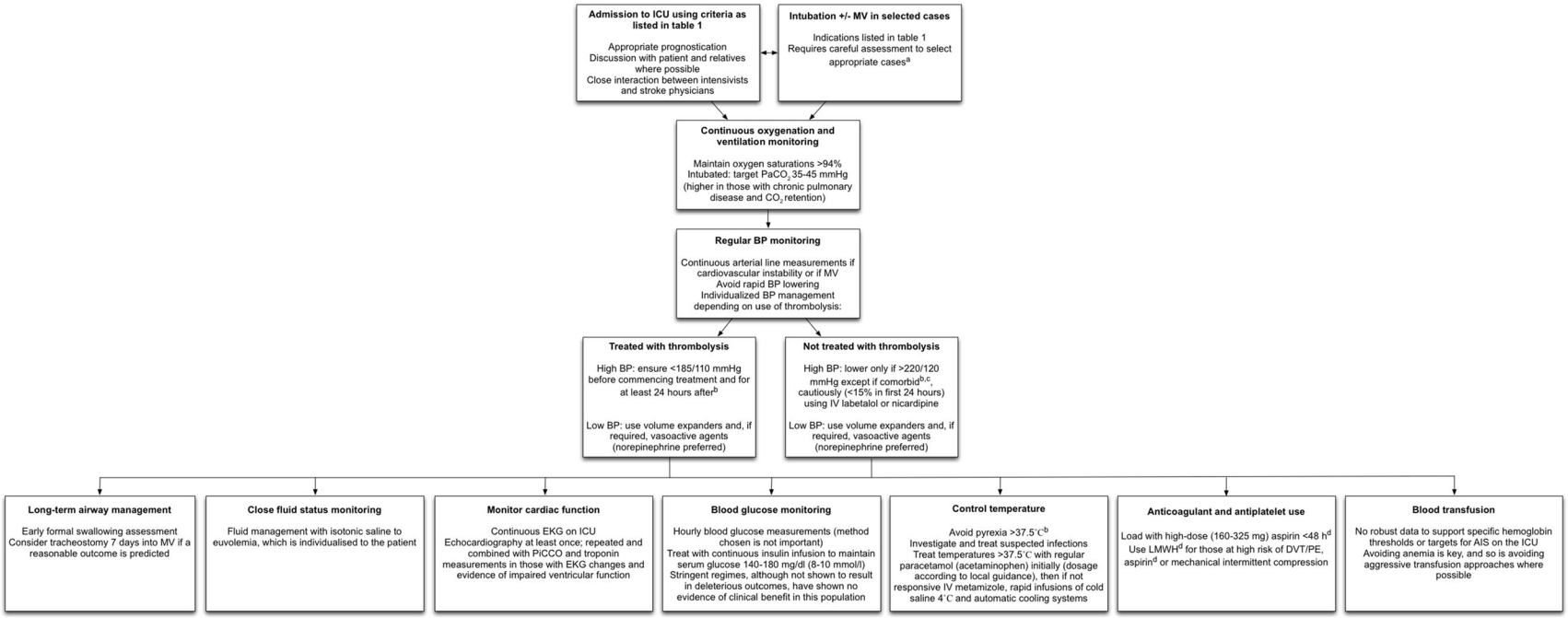

Fig. 1 Monitoring and management of systemic physiology in the patient with acute ischemic stroke on the intensive care unit. *a* Assessment of eligibility is based on careful neurological examination to exclude cases where intervention would be futile, and from considering relevant comorbidities as well as patient and family wishes; *b* European Stroke Organisation guidelines [4]. Can use intravenous labetalol and nicardipine as first-line antihypertensives; *c* including severe cardiac failure, aortic dissection, or hypertensive encephalopathy; *d* if given thrombolysis, withhold for the first 24 h postthrombolysis. *AIS* acute ischemic stroke, *BP* blood pressure, *COPD* chronic obstructive pulmonary disease, *EKG* electrocardiography, *ICU* intensive care unit, *IV* intravenous, *LMWH* low-molecular-weight heparin, *MV* mechanical ventilation, *TH* therapeutic hypothermia

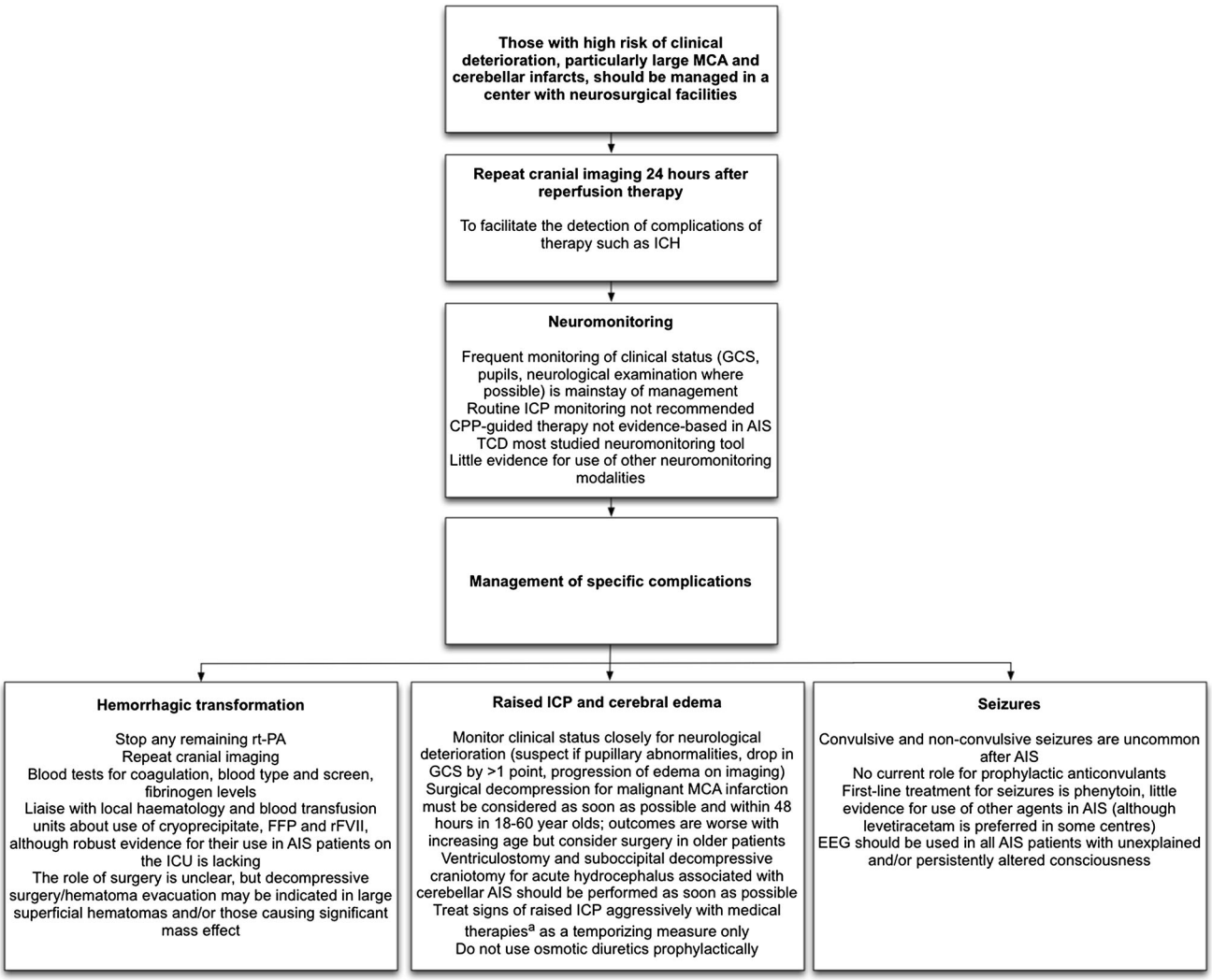

Fig. 2 Management of intracranial issues and complications in acute ischemic stroke on the intensive care unit. *a* These include normal saline, mannitol, thiopentone, and therapeutic hypothermia. *AIS* acute ischemic stroke, *CPP* cerebral perfusion pressure, *EEG* electroencephalography, *FFP* fresh frozen plasma, *GCS* Glasgow Coma Scale, *ICH* intracranial hemorrhage, *ICP* intracranial pressure, *rFVII* recombinant factor VII, *rt-PA* tissue plasminogen activator, *TCD* transcranial Doppler

improve after full rt-PA therapy [5]. Patients should have cranial imaging in the first 24 h following reperfusion therapy to detect hemorrhage or other complications of therapy [5].

Stroke units

There is class I evidence that outcomes after AIS are improved if patients are managed by multidisciplinary teams in an acute stroke unit [17]. Although variations in models of care exist, characteristics of organized inpatient stroke unit care include care provision by a multidisciplinary team with competencies in the management of stroke and its systemic complications, coordinated multidisciplinary rehabilitation, meetings between multidisciplinary team members, and regular educational and training programs.

Intensive care management of acute ischemic stroke

An increasing proportion of patients with severe stroke require admission to an ICU for neurological monitoring and management of poststroke complications. The ICU management of AIS focuses on monitoring and optimization of systemic physiological homeostasis, and monitoring and management of intracranial complications (Figs. 1, 2).

Table 1 Indications for intensive care unit admission following acute ischemic stroke: our recommendations

Need for intubation and/or mechanical ventilation due to
Decreased conscious level (GCS ≤8) or evidence of brainstem dysfunction or any other cause of a threatened airway
To prevent aspiration pneumonia in any of the above
Adjuvant therapy for intracranial hypertension or significant cerebral edema
Acute respiratory failure, for example, due to pulmonary edema (neurogenic or cardiogenic)
Generalized tonic–clonic seizures or status epilepticus
Apneic episodes
Severe stroke (National Institutes of Health Stroke Score >17)
Reperfusion therapy (intravenous or intraarterial), if multiorgan failure present ("strong agreement"[a]), to manage complications of therapy (hemorrhagic transformation), and in those undergoing local intraarterial therapy
Large middle cerebral artery infarct volume (>145 cm^3)[b] that predicts a malignant course
Persistent extremes of blood pressure [systolic >220 (not undergoing thrombolysis) or >185 (undergoing thrombolysis) or <90 mmHg] that are difficult to manage in a ward setting
Management of organ support, particularly renal replacement therapy and noninvasive ventilation (needed either due to a previous underlying condition, or acute pulmonary edema, for example) ("strong agreement"[a]), and cardiac dysfunction
Postoperatively following decompressive craniectomy ("strong agreement"[a])
Management of the patient with massive stroke and a high risk of mortality in whom organ retrieval/harvesting is planned ("weak agreement"[a])

Adapted and developed from evidence in [5, 18, 95, 96]

[a] These strengths of agreement in parenthesis are adapted from French expert consensus recommendations published in 2010, where recommendations were rated by experts according to the methodology of the RAND/UCLA Appropriateness Method [8]

[b] This is typically quantified using diffusion-weighted magnetic resonance imaging. On computed tomography, it has been shown that manual tracing of the perimeter of infarction (and multiplication by slice distance to obtain total volume) is the most reproducible method for quantifying infarct volumes [97]

Table 2 Common causes of hypoxemia following stroke

Respiratory infections
Aspiration
Acute lung injury/acute respiratory distress syndrome
Pulmonary embolus
Pulmonary edema (neurogenic or cardiogenic)
Altered central regulation of respiration
Sleep apnea
Respiratory muscle weakness

Indications for admission to intensive care and prognostication

Whilst the majority of patients with AIS are managed in the ward setting, some patients require care and interventions that cannot be provided on a stroke unit and therefore require admission to an ICU. Although variability exists between centers in the specific criteria for ICU admission, universal criteria are decreased conscious level and the need for mechanical ventilation, intensive hemodynamic management, and invasive neurological and systemic monitoring. We recommend applying the admission criteria listed in Table 1 equally to new hospital admissions and transfers from stroke units.

Crucial to the ICU admission decision-making process is assessment of the likely neurological prognosis, the presence or absence of nonneurological organ system dysfunction or failure, the wishes of the patient and their relatives, and relevant comorbidities [8]. Prognostication relies on thorough neurological assessment after identifying and correcting potentially reversible causes of altered neurological state, including hypoxemia, hypotension, seizures, use of sedatives, sepsis, and hydrocephalus, and should be performed by intensivists and stroke physicians in collaboration. Coma resulting directly from the AIS and National Institutes of Health Stroke Score (NIHSS) >17 on admission are associated with poor prognosis [8], but there are exceptions such as cerebellar infarcts which can respond favorably to decompressive surgery [18].

Prognostic assessment may be difficult or impossible in the acute setting, and where there is uncertainty a proactive approach is favored. However, early aggressive treatment should be linked to compassionate end-of-life care if a satisfactory degree of clinical recovery does not occur within an appropriate time scale. Patients with catastrophic strokes are increasingly being admitted to ICU to facilitate organ donation in those who have previously expressed a wish to donate.

Key recommendations Specific locally agreed criteria should guide decisions to admit to ICU (Table 1). Prognostication is vital for determining suitability for ICU admission, and relies on regular clinical assessment, the patient's premorbid status, documented discussions with patient and relatives, and collaboration between intensivists and stroke physicians.

Oxygenation and ventilation

Hypoxemia is common after AIS, has myriad causes (Table 2), and adversely affects outcome [19]. However, routine oxygen supplementation does not improve outcome [20, 21] and appears to be detrimental irrespective of stroke severity [20, 22]. Although semantics differ, current ESO, ASA, and NICE guidance support oxygen supplementation only if SpO_2 falls below 94 % [4–6]. Hypocapnia is associated with poor outcomes following AIS [23]. Although hypercapnia may increase cerebral perfusion [24], no data currently support its use to improve AIS outcomes. Intubation and mechanical ventilation (MV) is indicated for some patients (Table 1), although to date no trial has tested its utility in severe stroke. Continuous monitoring of systemic oxygenation is

essential for all AIS patients on the ICU using pulse oximetry, and mechanical ventilation should additionally be guided by regular arterial blood gas (ABG) monitoring. Although no data support AIS-specific ABG targets, maintenance of SpO_2 >94 % and normocapnea seem reasonable.

The mortality rate of intubated and ventilated AIS patients has been variously reported to be between 40 and 80 % [25], but most studies are old and comprise small cohorts. Although robust data are lacking, the introduction of more aggressive management strategies such as decompressive craniectomy may improve these figures [25]. In a prospective study of 58 patients requiring MV after AIS, stupor/coma, bilateral absence of corneal reflexes preintubation, and presence of ischemic cardiopathy were independent predictors of mortality [26]; although this suggests the need for careful neurologic examination, including assessment of brainstem reflexes, to identify appropriate patients for MV, these should not form absolute contraindications.

Between 15 and 35 % of AIS patients managed in the ICU require tracheostomy [25], usually those with severe dysphagia and bulbar palsies (often resulting from brainstem and large hemispheric infarcts) or those who require prolonged periods of MV. It is not possible to predict reliably those who will require prolonged ventilation or to ascertain the outcome benefits of early tracheostomy because of the paucity of evidence. However, it has been suggested that the need for tracheostomy should be assessed 1 week after the institution of MV [25]. It is anticipated that an ongoing randomized controlled trial (RCT) assessing the role of early tracheostomy versus prolonged orotracheal intubation in AIS, subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH), the SETPOINT trial, will resolve some of these uncertainties.

Dysphagia is common after both hemispheric [27] and brainstem [25] stroke, and increases the risk of aspiration pneumonia. All patients should undergo a swallow assessment soon after admission, and remain nil by mouth until an adequate swallow has been confirmed. A systematic review found that the water test (administration of a prespecified aliquot of water to assess the adequacy of swallowing) combined with pulse oximetry to detect aspiration, whilst using coughing, choking, and voice alteration as endpoints, to be the best screening method for dysphagia [28]. Adequate nutrition is crucial, but a recent Cochrane systematic review found no difference in death or dependency between early and late feeding in patients with acute and subacute stroke [29].

Key recommendations Continuous monitoring of oxygenation with pulse oximetry for all AIS patients on the ICU. Oxygen supplementation should be reserved for those with SpO_2 <94 %. Continuous monitoring of mechanical ventilation with regular arterial blood gas analysis. Maintain normocapnea—target $PaCO_2$ 35–45 mmHg (higher in those with chronic pulmonary disease and CO_2 retention). Endotracheal intubation and mechanical ventilation is indicated in patients with decreasing conscious level, severe bulbar palsies, and intracranial hypertension, but should be assessed on an individual basis depending on likely outcome and patient and family preferences. All patients should undergo a formal swallow assessment on admission by an appropriately qualified individual (not necessarily a speech therapist). Tracheostomy should be considered after 1 week of mechanical ventilation if a reasonable outcome is predicted.

Hemodynamic and fluid management

Approximately 80 % of AIS patients are hypertensive [systolic blood pressure (BP) >140 mmHg] at presentation [30], and this may be related to chronic hypertension, stress, raised intracranial pressure (ICP), or a neuroendocrine response. Severe hypertension likely contributes to cardiorespiratory complications and promotes cytotoxic edema and hemorrhagic transformation within infarcted tissue, although the associated risk of hemorrhagic transformation has not been demonstrated in the clinical setting. There is a U-shaped relationship between BP and outcome after AIS, with both high and low BP having adverse effects on outcome [30]. Although high BP is independently associated with poor outcome after AIS, the effect of acute blood pressure lowering is not clear. Some studies suggest improved [31], some unchanged [32], and others worsened [33, 34] long-term outcomes. Conversely, severe hypotension will compromise cerebral perfusion and potentially increase infarct volume. Some patients may benefit from BP augmentation, for example, those with severe carotid stenosis [35], but further data are required to assess long-term outcomes. European, US, and UK guidelines vary in their approaches to BP management after AIS (Supplementary Table 1), reflecting the controversy surrounding optimal BP targets and the reluctance to lower BP in the acute setting, except in relation to thrombolysis where ESO guidance recommends that BP should be <185/110 mmHg before commencing and for 24 h after treatment [4].

Regular BP monitoring should be undertaken after AIS. We recommend continuous BP monitoring via an arterial line in those with unstable BP and those who are intubated and ventilated, where it has the advantage of facilitating ABG analysis. There are currently no data to suggest significant risks with the use of arterial lines in those undergoing thrombolysis.

Fluid balance should be carefully monitored and managed to maintain euvolemia. Despite many AIS patients being in a state of relative hyperviscosity, a meta-analysis of 18 trials suggested that intentional hemodilution does not improve outcome [36]. European and US guidelines recommend the use of 0.9 % ("normal") saline

for fluid replacement after AIS [4, 5], and dextrose-containing fluids should always be avoided except in the presence of hypoglycemia. Despite promising preclinical data on the use of 25 % albumin in AIS, a large RCT found no benefit on outcomes at 90 days compared with saline [37]. Fluid replacement should be monitored closely and special caution exercised in those with cardiovascular disease and cerebral edema. Daily fluid replacement should be individualized based on the patient's ideal body weight, clinical status, and comorbidities, rather than administered as a fixed volume per day.

Key recommendations Regular noninvasive BP monitoring in all AIS patients on the ICU; continuous BP via an arterial line in patients with cardiovascular instability and those who are mechanically ventilated. There are currently no data to suggest significant risks with the use of arterial lines in those undergoing thrombolysis. There are no data to guide a specific BP target during the ICU management of AIS, and hemodynamic management should be individualized and take into account thrombolytic therapy and premorbid BP whilst avoiding extremes of pressure as indicated below. BP lowering is not indicated in those not undergoing thrombolysis unless ≥220/120 mmHg or in the presence of significant comorbidities, particularly severe cardiac failure, aortic dissection, or hypertensive encephalopathy. If performed, BP lowering should be cautious, i.e., <15 % in the first 24 h in those not receiving thrombolysis. BP should be lowered <185/110 mmHg before and for at least 24 h after thrombolysis. Intravenous labetalol and nicardipine are reasonable first-line agents to lower BP. Sublingual nifedipine should be avoided as it can abruptly and inconsistently decrease BP. Hypotension (defined by the individual's normal BP, but systolic BP <90 mmHg is a reasonable threshold) should be treated with fluid resuscitation in the first instance, and with vasoactive agents such as norepinephrine if unresponsive to volume replacement. Fluid management with 0.9 % saline to euvolemia.

Myocardial complications

Cardiac problems commonly coexist with AIS, either as a trigger for the disease (e.g., cardioembolic stroke) or as a result of the stroke itself. Dysrhythmias are present in 57 % of patients after AIS [38], elevated cardiac troponin levels in up to 17.5 % [39], and at least 12 % have abnormal left ventricular function on echocardiography [40]. There is no detailed specific guidance available on how to manage these complications.

A history of cardiovascular disease may predispose to sudden death after AIS, an important but underrecognized phenomenon. Sudden death after AIS is thought to result from interaction between cardiovascular and neurological pathology and be related to impaired central autonomic control, especially when the insular cortex is involved, resulting in cardiac damage and cardiac arrhythmias [41]. Further evidence is required to understand the exact pathophysiological mechanisms in order to better modulate autonomic function after AIS.

Key recommendations All AIS patients on ICU should undergo continuous electrocardiography (EKG) and have echocardiography at least once during the course of their admission (repeated if abnormal ventricular function identified). Cardiac troponin should be measured in patients with EKG changes and echocardiographic evidence of impaired ventricular function. Noninvasive monitors, such as PiCCO, may aid hemodynamic and fluid management in patients with cardiovascular abnormalities.

Glycemic control

Hyperglycemia occurs in more than 40 % of AIS patients [42] and, as a marker of illness severity, is associated with a range of deleterious effects, including increased cortical toxicity, larger infarct volumes [43], and susceptibility to infection. Poststroke hyperglycemia is independently associated with increased mortality and morbidity at 90 days, and postthrombolysis ICH [44], and may also attenuate the benefits of intraarterial thrombolysis [45]. The effects of hyperglycemia may depend on stroke subtype, as moderate hyperglycemia appears to be associated with favorable outcomes following lacunar stroke [46].

Regular blood glucose monitoring and careful glycemic control is required in all AIS patients, but treatment targets vary between guidelines (Supplementary Table 1). Randomized controlled trials investigating the clinical efficacy of intensive insulin therapy (IIT) after AIS have been inconclusive, and the risk of hypoglycemia is a concern. A meta-analysis of seven trials including 1,296 patients demonstrated that, although tight glucose control regimens (72–135 mg/dl) did increase the risk of symptomatic and asymptomatic hypoglycemia, this did not affect functional outcome, death or final neurological deficit after AIS [47].

A recent study, the INSULINFARCT trial, concluded that continuous intravenous insulin infusion provided superior glucose control to subcutaneous insulin therapy but also resulted in larger infarct growth [48]. The rates of serious adverse events and death at 3 months were similar in the subcutaneous and intravenous insulin groups, but the study was not powered to detect clinical changes. The authors concluded that IIT cannot be recommended after AIS at the present time, but it is unclear whether these conclusions are relevant to the management of patients in the ICU (compared with stroke units) where glycemic control with insulin infusion control is routinely undertaken and well monitored. In the absence of definitive evidence from the ICU setting, we recommend the ASA

guidance and thresholds for initiating glycemic treatment, aiming to maintain serum glucose between 140 and 180 mg/dl (8.0–10.0 mmol/l), with intravenous insulin infusion whilst avoiding large swings in glucose levels.

Key recommendations Regular blood glucose monitoring is essential. Although tight glycemic control has not been shown to result in deleterious outcomes, there is no evidence of clinical benefit in this population. Treatment with continuous insulin infusion to maintain serum glucose between 140 and 180 mg/dl (8.0–10.0 mmol/l) is preferred on the ICU.

Fever

Pyrexia affects up to 50 % of patients after AIS [49], and is independently associated with poor outcome [50]. There is no widely established or accepted temperature target, but symptomatic treatment of fever is advocated after exclusion or treatment of an infective cause (Supplementary Table 1). Although a multicenter double-blind RCT of AIS patients with admission temperatures of 36–39 °C found that high-dose paracetamol (acetaminophen) within 12 h of stroke onset did not improve outcome overall, a beneficial effect was identified in those with admission temperatures between 37 and 39 °C [51]; the Paracetamol [Acetaminophen] in Stroke 2 (PAIS 2) trial is investigating the outcome effects of paracetamol in patients who fit this criterion [52]. It should be noted that the paracetamol dose in the original PAIS trial was 6 g daily, and that this is significantly higher than that recommended for routine clinical use. This is a controversial issue because of toxicity concerns, and in the USA, the Food and Drug Administration advisory committee has asked manufacturers to limit the amount of acetaminophen to 325 mg per dosage unit. Ibuprofen does not appear to reliably reduce body temperature after stroke [53].

Many preclinical studies support the neuroprotective role of therapeutic hypothermia (TH) in AIS, and technological advances have facilitated rapid and safe cooling [54]. However, definitive evidence for benefit is currently lacking, and this might be related to heterogeneous study design including differences in temperature targets, hypothermia induction methods, time windows for initiation of TH and duration of treatment, and the variable use of adjuvant treatments. Although a Cochrane systematic review found no overall benefit or harm from TH after AIS, a clinically significant effect could not be ruled out and the authors called for large clinical trials [55]. Notable ongoing studies are a phase II/III trial comparing TH and thrombolysis versus thrombolysis alone (ICTuS2/3), and a phase III trial of TH in patients eligible and ineligible for thrombolysis (EuroHYP-1). The results of these trials are awaited with interest, as in vitro data suggest that lower temperatures might impair the efficacy of rt-PA [56].

TH is not risk free. The main adverse effects include shivering, electrolyte disturbance, impaired renal function, impaired cardiac function (particularly with temperatures below 32 °C [57]), and immunosuppression. In addition, airway management presents an additional challenge to the clinician managing TH in a patient with AIS, and may be an indication for ICU admission [57]. Localized head cooling reduces the risk of systemic complications, but there is currently insufficient evidence to recommend its use outside the research setting [58].

Key recommendations Avoid pyrexia ($T > 37.5$ °C). Investigate for, and treat, infectious causes of fever. Regular paracetamol (acetaminophen) therapy as a first-line therapy in those with temperatures >37.5 °C, the dose administered being dependent on local guidance. Second-line therapy includes intravenous metamizole, rapid infusion of cold saline (4 °C), and the use of automatic cooling systems.

Anticoagulation, antiplatelet therapy, and thromboprophylaxis

Meta-analyses have suggested no significant benefit from early use of unfractionated or low-molecular-weight heparin as a treatment for AIS of presumed cardioembolic origin [59, 60], including when compared with aspirin [61]. Due to the clinical trial protocol of the National Institute of Neurological Disorders and Stroke (NINDS) trials [62], the use of anticoagulation in the first 24 h following intravenous rt-PA is currently contraindicated. However, there is risk of re-occlusion following thrombolysis, and acute coronary occlusions are often safely treated with concomitant anticoagulation and antiplatelet therapy, so further research is required to assess the safety and efficacy of such a multimodal treatment regime after AIS reperfusion therapy. The evidence for the use of direct thrombin inhibitors such as dabigatran following AIS is insufficient to allow a recommendation regarding their routine use, or timing of therapy initiation, on the ICU.

There is class I evidence that administering aspirin within 48 h of stroke is associated with overall benefit, but it should not replace rt-PA or other acute interventions and should not be used within 24 h of thrombolysis [5]. There is less evidence for the use of clopidogrel and other antiplatelet agents in the acute setting after stroke.

Patients with AIS are at increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), particularly elderly immobile patients with severe stroke. PE accounts for 10 % of deaths after stroke [5]. Prevention of thromboembolism is facilitated by early hydration and mobilization, and the use of antithrombotics and external calf compression devices. Use of heparin to prevent DVT is supported by class I evidence

[63], and subcutaneous low-molecular-weight heparin (LMWH) is more effective than unfractionated heparin [64]. Although there is no specification within existing stroke guidelines on when exactly it should be commenced, early administration seems logical, but at least 24 h after reperfusion therapy to minimize the risk of intracranial hemorrhage.

In combining two RCTs, it was recently found that graduated compression stockings do not reduce the number of thromboembolic events and confer a nonsignificantly higher risk of death [65]. In contrast, a large RCT of intermittent pneumatic compression found a reduced risk of DVT and nonsignificantly lower risk of death within 30 days of treatment ($p = 0.057$) [66].

Key recommendations Administer oral high-dose aspirin (160–325 mg loading dose) within 48 h of AIS but delay for 24 h in those receiving thrombolysis. Use of any anticoagulant is contraindicated in the first 24 h following thrombolysis, but should be considered after this (further safety and efficacy data are required). Anticoagulation for the management of systemic thrombotic disease should be discontinued in those with moderate to severe strokes due to the increased risk of intracranial bleeding; the decision to restart should be made in liaison with relevant specialists including hematology. Early mobilization reduces the risk of thromboembolic complications of AIS. All immobilized AIS patients on ICU should be treated with prophylactic-dose subcutaneous LMWH to prevent DVT and mechanical intermittent calf compression. Treatment should be started early, but LMWH should not be started until 24 h following thrombolysis.

Anemia

In a retrospective study, anemia, defined as hemoglobin <12 g/dl in women and <13 g/dl in men by the World Health Organization, was identified in 97.2 % of severe AIS patients managed on the ICU [67]. Although evidence from general critical care populations suggests a threshold for blood transfusion in the absence of serious cardiac disease of hemoglobin concentration ~7 g/dl [68], the "transfusion trigger" in AIS remains unclear. The sensitivity of the brain to oxygen deprivation suggests that hemoglobin optimization might improve oxygenation in the penumbral region and prevent tissue loss, but robust evidence to this effect is lacking. A mathematic modeling study suggested that a hemoglobin value of 10 g/dl or below might be the most appropriate transfusion trigger in AIS [69], but there is currently no class I evidence supporting specific hemoglobin thresholds or targets and thus no recommendation regarding transfusion threshold can be made. Although anemia should be avoided, aggressive transfusion approaches are not currently recommended.

Hemorrhagic transformation

Symptomatic hemorrhagic transformation occurs in 5–6 % of patients undergoing intravenous rt-PA, intra-arterial recanalization strategies, and anticoagulant use [5, 35]. It is more common after intraarterial compared with intravenous thrombolysis [70, 71], possibly related to the use of anticoagulation and antiplatelet therapy intended to reduce the risk of thrombus formation related to intraprocedural catheter and stent use. Hemorrhagic transformation can also occur in the absence of reperfusion therapy. No standardized management guidelines or robust evidence exists to guide treatment. In theory, any combination of cryoprecipitate, fresh frozen plasma, and recombinant factor VII may be used in close cooperation with the local hematology and blood transfusion service, but there is no robust evidence base to recommend their routine use. rt-PA should of course be stopped if the infusion has not been completed. There are no definitive data from clinical trials about the role of surgery following hemorrhagic transformation, and the decision to proceed to surgical evacuation is determined by the size and location of the hemorrhage, and the patient's overall clinical condition. The evacuation of large hematomas may be lifesaving, whereas deeper, smaller hemorrhages are best managed conservatively with serial imaging.

Key recommendations Hemorrhagic transformation should be managed in the first instance by stopping any remaining intravenous rt-PA (if applicable), repeating cranial imaging, and monitoring coagulation status. The use of cryoprecipitate, fresh frozen plasma, and recombinant factor VII is not supported by robust evidence in this setting. The role of surgery is unclear, but decompressive surgery/hematoma evacuation may be indicated in large superficial hematomas and/or those causing significant mass effect.

Neuromonitoring

There are limited data to support a role for neuromonitoring after AIS, and because most patients are not sedated, invasive intracranial monitoring is impossible in the majority. More technical data on the different monitoring techniques, and their relative strengths and weaknesses, are beyond the scope of this review, and the reader is directed elsewhere [72].

Although ICP monitoring is often used in patients with large space-occupying infarcts and edema, measured ICP values are often normal (<20 mmHg) despite large ischemic tissue volumes [73]. Such findings support a role for close clinical and radiologic monitoring as opposed to reliance on ICP values. Optic nerve ultrasonography has recently been reported as a potential noninvasive alternative to traditional, invasive, ICP monitoring and may

find a role in AIS [74]. Although current ESO guidelines recommend that cerebral perfusion pressure (CPP) be maintained >70 mmHg after AIS [75], this is based on old data from patients with traumatic brain injury (TBI), a completely different pathophysiology. Brain tissue oxygen tension ($PtiO_2$) monitoring is the gold-standard bedside measure of cerebral oxygenation [72], but evidence for its utility in AIS is lacking. Near-infrared spectroscopy (NIRS) is a noninvasive monitor of cerebral oxygenation, and although early pilot data suggest that NIRS-derived cerebral oxygenation is responsive to both systemic- and stroke-related changes in AIS [76], and NIRS may have a role in assessment of cerebrovascular reactivity as a novel biomarker of cerebral autoregulation [77], further research is required before its routine bedside use can be recommended. Near-infrared spectroscopy-derived hemoglobin and tissue oxygenation indices have also been used as a noninvasive measure of cerebral autoregulation [78]. Cerebral microdialysis (MD) allows bedside monitoring of glucose and key brain metabolites to monitor bioenergetic compromise and cellular energy failure [72, 79]. Glutamate levels and lactate/pyruvate ratio are reduced by TH in severe middle cerebral artery (MCA) infarction [80] and, when elevated, predict subsequent development of massive edema and cerebral infarction [81]. Delivery of exogenous glucose through MD perfusate may reduce levels of the excitatory neurotransmitter glutamate following AIS [82], but the influence on outcome of such an intervention is currently unclear.

Transcranial Doppler (TCD) ultrasonography is a noninvasive monitor that is able to assess cerebral blood flow velocity in basal cerebral vessels and is perhaps the most promising neuromonitor after AIS. It can assist in the diagnosis of AIS through detecting acute MCA occlusions with high sensitivity and specificity, response of arterial occlusion to thrombolysis, prognostication based on the extent of arterial occlusion, assess cerebral blood flow and vasoreactivity [83], and in combination with continuous blood pressure measurement, can provide high temporal resolution as a bedside monitor of cerebral autoregulation [84].

Key recommendations Clinical and radiological monitoring are the cornerstones of identifying deterioration after AIS. Routine ICP monitoring is not recommended but can be considered in those with large infarct volumes or hemorrhagic conversion with mass effect. However, ICP values are often normal even in the presence of large infarct volumes. The risks of using invasive neuromonitoring tools such as intraparenchymal ICP monitors in those undergoing thrombolysis are currently poorly quantified. There is no evidence to support an "optimal" CPP in AIS patients managed on the ICU, or that CPP-driven therapy improves outcome. TCD has evidence of utility for establishing diagnosis and assessment of severity of AIS based on several noninvasive biomarkers. There is insufficient evidence to recommend multimodality monitoring in AIS.

Cerebral edema and hemorrhage

The main intracranial complications following AIS are the development of ICH and cerebral edema. They are the main factors influencing clinical deterioration and are associated with poor outcome. Both can result from reperfusion injury and may lead to increased ICP, although as discussed earlier, the proportion of AIS patients with intracranial hypertension detected by ICP monitoring is small, even in the presence of large malignant MCA infarction volume [73].

Early recognition of neurological deterioration is vital, not least because decompressive craniectomy, sometimes used to alleviate intracranial hypertension associated with malignant cerebral edema, is best performed early. Merging three small RCTs demonstrated the potential benefits of decompressive craniectomy for malignant MCA infarction [85]. If performed within 48 h of symptom onset in those between 18 and 60 years, decompressive craniectomy reduces mortality from 78 to 29 % and significantly improves favorable outcomes after malignant MCA infarction. Equal benefit is seen in those with dominant and nondominant hemisphere infarctions.

Ventriculostomy to relieve acute hydrocephalus, and suboccipital decompressive craniectomy with or without resection of necrotic tissue, is recommended after cerebellar infarction [18]. As in malignant MCA infarction, clinical deterioration and imaging (and not ICP monitoring) are key to determining the need for surgical intervention after cerebellar infarction.

In the presence of monitored intracranial hypertension, or clinical signs suggestive of raised ICP, medical treatment interventions include the administration of mannitol [86] and hypertonic saline [87], but there is no robust evidence that these improve outcome after AIS. Nevertheless, a small prospective study suggested that hypertonic saline is more effective than mannitol at reducing ICP after AIS [88]. This observation is supported by a meta-analysis of five prospective trials, three of which included patients with AIS [89]. However, different doses of osmotic agents were used in these studies, and a blinded RCT with equiosmolar doses and correlation with outcome after AIS is urgently required. In any case, osmotic therapies should be used primarily as a temporizing measure and not delay surgical intervention. Further, osmotic agents should not be used as prophylaxis before the detection of cerebral edema [18].

Thiopental can significantly and promptly reduce ICP in acute crises, but treatment with barbiturates requires ICP, electroencephalography (EEG), and invasive hemodynamic monitoring. TH has also been used in AIS patients with cerebral edema unresponsive to other

medical therapies [54]. Steroids have no role in the management of cerebral edema after AIS [90].

Key recommendations Frequent monitoring of clinical status is superior to ICP monitoring in detecting those requiring medical or surgical management for intracranial worsening. Patients at high risk of clinical deterioration, particularly malignant MCA infarction and edematous cerebellar AIS, should be managed in a center with immediate access to neurosurgical facilities. Suspect the need for urgent surgical intervention in those with malignant MCA infarction or cerebellar stroke if pupillary abnormalities develop, there is a drop in the Glasgow Coma Score by more than 1 point, and/or there is progression of edema on cranial imaging. Decompressive craniectomy is indicated in patients aged 18–60 years with dominant and nondominant hemisphere malignant MCA infarction and should be performed as soon as possible (but within 48 h) of clinical or radiological deterioration; outcomes are worse with increasing age, but decisions should be made on an individual basis, and intervention in those >60 years should be considered. Ventriculostomy should be performed as soon as possible for obstructive hydrocephalus associated with cerebellar AIS, and accompanied by suboccipital decompressive craniectomy. Hypertonic saline appears to be superior to mannitol at lowering ICP after AIS, but both agents should only be used as a temporizing measure prior to surgical decompression. Prophylactic use of osmotic diuretics before the detection of cerebral edema is not recommended.

Seizures

Convulsive seizures are less common after AIS than other brain injury types, and usually result from diffuse cortical infarction [91]. Seizures should be treated aggressively, but trials addressing the role of prophylactic anticonvulsants were terminated early due to poor recruitment [92]. Evidence suggests worse long-term outcomes with anticonvulsant use [93], but as most studies used phenytoin, it is not clear whether this observation holds true for other anticonvulsants such as levetiracetam. EEG should be used in all AIS patients with unexplained and/or persistently altered consciousness [94].

Nonconvulsive seizures (NCSs) are also less common after AIS than in other acute brain injury types [94], but nevertheless are more important than previously recognized. The effect of anticonvulsant therapy on long-term outcomes in NCSs remains to be elucidated.

Key recommendations Convulsive and nonconvulsive seizures are uncommon after AIS, and there is no role for prophylactic anticonvulsants. Seizures should be treated aggressively and a long-acting anticonvulsant considered. The first-line anticonvulsant is phenytoin because of the paucity of studies of other agents, but levetiracetam is now preferred in some centers. EEG should be used in all AIS patients with unexplained and/or persistently altered consciousness.

End-of-life care

Despite early aggressive treatment some patients do not have a satisfactory degree of clinical recovery, and withdrawal of life-sustaining therapies and a shift to end-of-life care is appropriate. Documented early discussion with patients and relatives to ascertain previous wishes is vital. An outcome that is acceptable to an individual patient, rather than to the clinical team, should drive decision-making regarding "do not attempt resuscitation" orders and other limitations of care.

Key recommendations A patient's wishes regarding acceptable outcome status should be sought as early as possible. Limitations or withdrawal of life-sustaining therapies should be driven by the wishes of the patient.

Conclusions

AIS is a common and devastating condition with currently limited, but rapidly expanding, therapeutic options. Despite detailed European and US guidelines for the general management of AIS, little of this guidance is focused on ICU management. With an increasing role for treatment options such as endovascular therapy, TH, and aggressive physiological optimization, it is likely that the number of patients with AIS admitted to the ICU will increase. Management principles currently focus on airway and ventilation management, hemodynamic and fluid optimization, fever and glycemic control, management of anticoagulation, antiplatelet and thromboprophylaxis therapy, control of seizures, and surgical interventions for malignant MCA and cerebellar infarctions. It remains to be seen whether multimodality neuromonitoring establishes a role in the patient with AIS, but for now clinical examination and serial imaging is the mainstay of monitoring. The results of trials of TH for AIS are greatly anticipated. Encouragement of large-scale patient recruitment into clinical trials should aid the development of robust evidence for the benefit of different interventions in the ICU on outcome.

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