33 Evidence-Based Practice of Neuroanesthesia and Neurointensive Care

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33.1 Introduction

Advent of anesthesia and evidence-based medicine (EBM) are two of the 15 landmark milestones in medical history [1]. The first public demonstration of anesthesia on 16th October 1846 and its subsequent publication a month later in the Boston Medical and Surgical Journal (the current New England Journal of Medicine) [2] suggests the early integration of EBM into anesthesia practice. With publication of high-quality studies over the last few decades from across the world, practice of neuroanesthesia and neurocritical care is moving from experience and eminence-based practice to evidence-based clinical practice (EBCP). This chapter provides an overview about EBM and discusses relevant aspects of the current best evidence in certain important clinical domains of neuroanesthesia and neurocritical care. More details and explanations regarding these EBCP guidelines are available in the cited references.

33.2 Evidence-Based Medicine and Evidence-Based Clinical Practice

EBM is a systematic approach to clinical problem-solving that allows integration of the best available research evidence with clinical expertise and patient values [3]. EBCP overcomes deficiencies in patient care that is largely based on expert opinions or inappropriate use of available evidence and provides in its place a structured framework for assessment and application of the current available evidence to inform patient care decisions [4].

33.2.1 Step-Wise Approach to Evidence-Based Clinical Practice

A scientific and structured approach to a clinical problem is a pre-requisite for EBCP. The 5A technique describes the process of using medical literature to guide patient care and involves the following steps: asking a structured question, acquiring relevant evidence, appraising the evidence (distinguishing the more from the less trustworthy), evaluating the applicability of findings to a given patient, and acting on the evidence by taking into consideration clinician expertise and patient preference [5]. The 6th "A" involves "*A*ssessing" the patient performance at conclusion of this process [4].

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33.2.2 Finding the Current Best Evidence

Finding current best evidence is critical to inform effective implementation of evidence for patient care at bedside. With >2000 articles being indexed with PubMed daily [6], identifying current best evidence quickly becomes extremely difficult. For example, a PubMed search on "cerebral vasospasm" provides more than 7000 citations (including guidelines, reviews, randomized trials, cohort studies, experimental studies, and case reports) making selection of relevant evidence for applying into healthcare practice, challenging. Pre-appraised evidence-based resources provide quick and efficient way of finding answers for clinically important questions and facilitate optimal implementation into patient care. In this regard, high-quality recommendations consisting of good evidence summaries using grading of recommendation, assessment, development, and evaluation (GRADE) become important resources for direct clinical application. GRADE framework provides transparent method to evaluate quality of evidence for various outcomes in systematic reviews [7].

In the hierarchy of EBM resources for finding answers to research or clinical questions, systems and guidelines form the top of the pyramid, pre-appraised research (synopses and systematic reviews) is placed at the mid-level, and non-pre-appraised research (case reports and cohort or controlled studies) occupy the bottom of the pyramid. The 5s model provides information about the hierarchy of levels of evidence for identifying, informing, and implementing clinical care decisions [8].

33.2.3 Application of EBM in Neuroanesthesia and Neurocritical Care Practice

With increasing publication of high-quality studies in neuroanesthesia and neurocritical care, pre-appraised evidence-based tools such as practice guidelines are now available for most of the common clinical conditions. Guidelines makes it easier for clinicians to directly implement care decisions for their patients without having to go through the laborious exercise of searching for the evidence and appraising the quality of evidence before using them for patient care. The pre-appraised guidelines inform various aspects of patient care for a particular clinical condition. Where evidence is poor or absent, guidelines provide practice framework for implementing clinical care decisions. This chapter informs certain important recommendations in the management of neurological conditions such as traumatic brain injury (TBI), stroke, aneurysmal subarachnoid hemorrhage (aSAH) and provides overview of management principles based on current evidence where guidelines are lacking.

33.3 Traumatic Brain Injury

TBI encompasses a broad range of pathologic injuries to the brain of varying clinical severity that result from head trauma. The management of patients with TBI is largely based on the guidelines provided by the Brain Trauma Foundation (BTF) [9], and the key practice recommendations are listed in Table 33.1. A three-level system is used to rate individual studies during synthesis of evidence and accordingly, well-designed randomized controlled trials (RCTs) and meta-analyses of RCTs are rated as level I evidence, poor quality RCTs and prospective cohort studies are designated as level II evidence, and case-control studies, case reports, or expert opinion are classified as level III evidence.

33.4 Acute Ischemic Stroke (AIS)

Stroke is one of the commonest causes of disability and death worldwide. Early diagnosis and prompt neurological and systemic management have shown to improve outcomes after AIS. The

Table 33.1 Management of patients with acute traumatic brain injury: current recommendations for treatment, monitoring, and thresholds based on BTF guidelines

Topic	Level of evidence	Recommendation
Decompressive craniectomy (DC)	Level IIA	a. Bifrontal DC is not recommended to improve outcomes (as measured by the GOS-E score at 6 months after severe TBI) in patients with diffuse injury and with ICP values >20 mmHg for more than 15 min within a 1-h period that are refractory to first-tier therapies. However, this procedure reduces ICP and minimizes days in the ICU b. A large fronto-temporo-parietal DC is recommended for improving survival and neurological outcomes c. RESCUEicp trial showed that DC in patients with TBI and raised ICP was associated with lower mortality than medical management. However, more survivors in surgical group were functionally dependent (finding after BTF guidelines)
Prophylactic hypothermia	Level IIB	Early (<2.5 h), short-duration (<48 h) prophylactic hypothermia is not recommended for diffuse injury
Hyperosmolar therapy	Level I, II, III	Though hyperosmolar therapy lowers ICP, there is inadequate evidence with regard to patient outcomes to support a particular recommendation, or a specific agent, for severe TBI
Cerebrospinal fluid (CSF) removal	Level III	a. Continuous rather than intermittent CSF drainage may be considered to reduce ICP b. CSF removal to reduce ICP may be considered when GCS is <6 during the 1st 12 h after TBI
Ventilation strategies	Level IIB	Long-term prophylactic hyperventilation to $PaCO_2$ of ≤25 mmHg is not recommended
Anesthetics, analgesics, and sedatives	Level IIB	a. Prophylactic barbiturates to achieve burst suppression for intracranial hypertension is not recommended b. High-dose barbiturate is recommended for controlling raised ICP refractory to maximal medical and surgical management subject to hemodynamic stability c. Propofol is recommended for controlling raised ICP but not for improving outcomes. High-dose propofol can result in significant morbidity
Steroids	Level I	Steroids are not recommended for improving outcome or reducing ICP
Nutrition	Level IIA Level IIB	Feeding patients to achieve basal caloric requirement by day five to day seven after TBI is recommended to decrease mortality Transgastric jejunal feeding is recommended to minimize occurrence of ventilator-associated pneumonia
Infection prophylaxis	Level IIA Level III	a. Early tracheostomy is recommended to reduce ventilator days but this does not reduce mortality or nosocomial pneumonia b. Povidone-iodine oral care is not recommended to reduce ventilator-associated pneumonia Antimicrobial-impregnated catheter may be considered to prevent external ventricular drainage-related infection
Deep vein thrombosis (DVT) prophylaxis	Level III	a. LMWH or unfractionated heparin may be used in combination with mechanical prophylaxis. However, risk for expansion of intracranial hemorrhage exists b. Current evidence does not support recommendations for choice of agent, dose, or timing of pharmacologic prophylaxis

(continued)

Table 33.1 (continued)

Topic	Level of evidence	Recommendation
Seizure prophylaxis	Level IIA	a. Prophylactic phenytoin or valproate is not recommended to prevent late-onset PTS b. Phenytoin is recommended to decrease early PTS (<7 days) c. Evidence is insufficient to recommend levetiracetam over phenytoin
Intracranial pressure monitoring	Level IIB	Management of severe TBI patients guided by ICP monitoring is recommended to minimize in-hospital and 2-week post-TBI mortality
Cerebral perfusion pressure monitoring	Level IIB	Management of severe TBI using CPP monitoring is recommended to reduce 2-week mortality
Advanced cerebral monitoring	Level III	$AVDO_2$ monitoring from jugular bulb may be considered to decrease mortality and improve outcomes at 3 and 6 months after TBI
Blood pressure thresholds	Level III	Maintaining SBP ≥100 mmHg, for patients aged 50–69 years old or ≥110 mmHg for patients aged 15–49 years or aged >70 years may be considered to reduce mortality and improve outcome
Intracranial pressure threshold	Level IIB	ICP >22 mmHg should be treated as this is associated with increased mortality
Cerebral perfusion pressure threshold	Level IIB Level III	a. The CPP value between 60 and 70 mmHg is recommended to improve outcomes. The CPP threshold within this range depends on patient's autoregulatory status b. Aggressive maintenance of CPP >70 mmHg with fluids and vasopressors should be avoided
Advanced cerebral monitoring thresholds	Level III	Jugular venous saturation of <50% may be avoided to reduce mortality and improve outcomes

TBI traumatic brain injury, *ICP* intracranial pressure, *ICU* intensive care unit, *BTF* brain trauma foundation, $PaCO_2$ arterial partial pressure of carbon dioxide, *CBF* cerebral blood flow, $SjvO_2$ jugular venous oxygen saturation, $PbtO_2$ partial pressure of brain tissue oxygen, *EEG* electroencephalogram, *LMWH* low molecular weight heparin, *PTS* post-traumatic seizures, $AVDO_2$ arterio-venous oxygen difference, *CPP* cerebral perfusion pressure, *SBP* systolic blood pressure, *CT* computed tomography

recent guidelines from the American Heart Association/American Stroke Association (AHA/ASA) provide comprehensive set of recommendations for clinicians caring for adult patients with AIS. The strength of recommendation is classified as I (strong; benefit >>> risk), IIa (moderate; benefit >> risk), IIb (weak; benefit ≥ risk), III-No benefit (moderate; benefit = risk), and III-Harm (strong; risk > benefit) based on the level of evidence (A = well-designed RCTs and meta-analyses of RCTs; B = randomized and non-randomized studies and meta-analyses of such studies; C = observational or registry studies with limited data or consensus of expert opinion). The key recommendations particularly relevant to neuroanesthesiologists and neurointensivists are summarized in Table 33.2, and the readers are advised to go through the detailed guidelines here [10].

33.5 Intracerebral Hemorrhage (ICH)

ICH is the second most common cause for stroke and is associated with high mortality and morbidity. The initial management goals include preventing expansion of hematoma, and detection and control of raised intracranial pressure (ICP) apart from treatment of associated complications.

33.5.1 General Management Issues

As per the AHA/ASA guidelines, patients with ICH should be monitored and managed in an intensive care unit [11] with the availability of neurosurgical care within the hospital. Evidence suggests that vigilant monitoring and management in a stroke unit results in improved outcomes after ICH [12].

Table 33.2 Management of patients with acute ischemic stroke: current recommendations based on the AHA/ASA guidelines

Topic	Class of recommendation; level of evidence (LOE)	Recommendation
Emergency triage and initial evaluation	Class I; B	Clinical assessment and neurological evaluation by an acute stroke team. Administer intravenous alteplase ≤60 min of arrival in the ED in ≥50% of patients Use stroke rating scale, preferably the NIHSS Mandatorily assess blood glucose. Electrocardiogram recommended but should not delay alteplase
	Class IIb; B	Usefulness of chest radiographs in the absence of evidence of acute cardio-pulmonary disease is not known Telestroke consultation guided IV alteplase may be safe and beneficial
Early diagnosis: cerebro-vascular imaging	Class I; B	Brain imaging <20 min of ED arrival in ≥50% of patients who may be candidates for alteplase and/or mechanical thrombectomy
	Class I; A	Non-contrast CT to exclude ICH Noninvasive vascular study during initial imaging evaluation if intra-arterial fibrinolysis or thrombectomy is contemplated CT perfusion, DW-MRI, or MRI perfusion for anterior circulation AIS <6–24 h of last known normal
	Class III; B	CT hyperdense MCA sign, and hypoattenuation or ischemic changes should not lead to withholding of IV alteplase Routine MRI before alteplase is not recommended. Multimodal imaging should not delay alteplase use CT and MRI perfusion, and diffusion imaging for mechanical thrombectomy <6 h is not recommended
	Class II; B	CT angiography in patients without history of renal impairment if large vessel occlusion is suspected
	Class IIa; C	For mechanical thrombectomy, imaging of both intracranial and extracranial vessels
	Class I; C	Brain imaging interpretation <45 min of patient arrival to the ED
General care and treatment of complications	Class I; B	Cardiac monitoring for at least first 24 h for potentially serious cardiac arrhythmias Systolic BP should be <185 mmHg and diastolic BP <110 mmHg before fibrinolytic therapy is initiated and maintained <180/105 mmHg for ≥ first 24 h after intravenous alteplase
	Class I; C	Airway and ventilatory support to patients who have bulbar dysfunction Oxygen to maintain oxygen saturation >94% Sources of hyperthermia be identified and treated In patients who do not receive fibrinolysis, BP should be lowered by 15% during first 24 h after stroke Medications should be withheld unless systolic BP is >220 mmHg or diastolic BP is >120 mmHg Hypovolemia corrected with normal saline, and arrhythmias reducing cardiac output be corrected Blood glucose <60 mg/dL should be treated
	Class IIa; B	Restarting antihypertensive medications after first 24 h for preexisting hypertension and are stable neurologically
	Class IIa; C	No data to recommend BP lowering drugs Achieve blood glucose levels of 140–180 mg/dL and closely monitor to prevent hypoglycemia
	Class IIb; C	Data to guide recommendations for treatment of hypertension in patients not undergoing reperfusion strategies are inconclusive or conflicting
	Class III; C	Supplemental oxygen not recommended in non-hypoxic patients

(continued)

Table 33.2 (continued)

Topic	Class of recommendation; level of evidence (LOE)	Recommendation
Intravenous fibrinolysis	Class I; A	Intravenous alteplase (0.9 mg/kg, maximum 90 mg with 10% as bolus over 1 min) patients who may be treated <3 h of AIS Door-to-needle time <60 min from arrival
	Class I; B	Exclusion for alteplase administration in the time period of 3–4.5 h after stroke onset—age >80 y, oral anticoagulants, baseline NIHSS score >25, imaging suggestive of ischemic injury involving >1/3 of MCA territory and history of both stroke and diabetes mellitus Promptly manage side effects of iv alteplase (bleeding and angioedema)
	Class IIa; B	In patients with 1–10 microbleeds on brain MRI, IV alteplase is reasonable IV alteplase may be beneficial for AIS with known sickle cell disease
	Class IIb; B	In patients with >10 microbleeds on MRI, alteplase may increase risk of ICH
	Class III; B	Abciximab and alteplase should not be administered concurrently
	Class IIa; C	Seizure is not a contraindication for iv alteplase
	Class IIb; C	Fibrinolysis may be considered in patients with mild stroke deficits, rapidly improving stroke symptoms, major surgery in preceding 3 months and recent MI, weighing the risks and benefits
	Class III; A	Streptokinase for stroke treatment not recommended
	Class IIb; B	Tenecteplase 0.4 mg/kg bolus is an alternative to alteplase in patients with minor neurological impairment without major occlusion
	Class III; B	Sonothrombolysis is not recommended with IV thrombolysis
Endovascular interventions	Class I; A	Patients eligible must be administered iv alteplase despite considering intra-arterial treatments. Mechanical thrombectomy with stent retriever be considered if following criteria are met: (1) pre-stroke mRS score of 0 or 1; (2) occlusion of ICA or MCA segment; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated <6 h of symptom onset
	Class I; B	Intra-arterial fibrinolysis benefits patients with major AIS of <6 h duration from MCA occlusion who are ineligible for iv alteplase
	Class IIb; B	Though stent retrievers remain the first choice other mechanical thrombectomy devices may be considered
	Class IIb; C	Rescue intra-arterial fibrinolysis or mechanical thrombectomy are reasonable for large-artery occlusion not responding to intravenous fibrinolysis
	Class IIa, B	For minor stroke, dual antiplatelet therapy started <24 h and continued for 21 days can benefit in early secondary stroke prevention for 90 days
	Class III; B	Ticagrelor is not recommended for acute treatment of minor stroke
Mechanical flow augmentation	Class I; C	Vasopressors may be considered in patients with systemic hypotension resulting in neurological sequelae, close monitoring is recommended when drug-induced hypertension is used
	Class IIb; B	Role of high-dose albumin is not clear
	Class III; A	Hemodilution by volume expansion is not recommended
	Class III; A	Pentoxifylline is not recommended

Table 33.2 (continued)

Topic	Class of recommendation; level of evidence (LOE)	Recommendation
Neuroprotective agents	Class IIa; B	Continue statin therapy if already taking
	Class IIb; B	Induced hypothermia for AIS is not well established
	Class III; A	Neuroprotective pharmacological agents are not efficacious in improving outcomes after ischemic stroke
Surgical interventions	Class IIb; B	Urgent CEA for AIS is not established
General stroke care	Class I; A	Patients with pneumonia or UTIs should receive appropriate antibiotics
	Class I; B	Enteral feeding should be initiated <7 days of admission Patients who cannot take feed orally should receive nasogastric, nasoduodenal, or PEG tube feedings
	Class IIa; A	Aspirin is reasonable when anticoagulants are contraindicated for DVT prophylaxis
	Class IIa; B	Consider nutritional supplements if malnourished
	Class IIa; C	Assessment of swallowing before patient begins oral intake is recommended NG tube feeding preferred for 2–3 weeks after stroke
	Class IIb; B	Oral hygiene reduces risk of pneumonia
	Class III; B	Compression stockings and routine prophylactic antibiotics are not beneficial
	Class III; C	Routine bladder catheters not recommended
	Class IIa; C	Patients and families with stroke should be referred to palliative care if applicable
Treatment of acute neurological complications	Class I; B	Decompressive surgery of space-occupying cerebellar infarction and for malignant edema of cerebral hemisphere is effective and lifesaving
	Class I; C	Ventricular drain is useful for acute hydrocephalus
	Class IIa; C	Brief hyperventilation (PCO_2 30–34 mmHg) may be considered during acute neurological deterioration from brain swelling
	Class III; A	Corticosteroids are not recommended for cerebral edema and raised ICP
	Class III; C	Prophylactic anticonvulsants are not recommended

ED emergency department, *NIHSS* National Institute of Health Stroke Scale, *CT* computed tomography, *ICH* intracranial hemorrhage, *DW-MRI* diffusion weighted magnetic resonance imaging, *AIS* acute ischemic stroke, *MCA* middle cerebral artery, *BP* blood pressure, *mRS* modified Rankin score, *ASPECTS* Alberta Stroke Program Early CT Score, *CEA* carotid endarterectomy, *UTIs* urinary tract infections, *PEG* percutaneous endoscopic gastrostomy, *DVT* deep vein thrombosis, *NG* nasogastric, $PaCO_2$ arterial partial pressure of carbon dioxide

33.5.2 Specific Recommended Interventions [11]

1. *Fever management*: Sources of fever should be treated, and antipyretic medications should be used to achieve normothermia in febrile patients with stroke.
2. *Glucose management*: Hyperglycemia during the initial 24 h after stroke contributes to adverse outcomes; insulin treatment should target serum glucose level between 140 and 180 mg/dL. Hypoglycemia should be avoided.
3. *Venous thromboembolism (VTE) management*: Intermittent pneumatic compression is the mainstay for prevention of VTE in patients with acute ICH.
4. *Fluid management*: Normal saline should be used for maintenance and replacement; hypotonic fluids and hypervolemia are avoided as they exacerbate cerebral edema and ICP [12].
5. *Aspiration pneumonia*: Dysphagia is common and is a major risk factor for developing aspiration pneumonia. Prevention of

aspiration includes initial nil-per-oral status until swallowing function is evaluated.

6. *Reversal of anticoagulation*: The summary of recommendations for reversal of antithrombotic agents in patients with ICH is detailed in Table 33.3 and details are available here [13].
7. *Blood pressure (BP)*: For patients with systolic BP >200 mmHg or mean BP >150 mmHg, aggressive reduction of BP with intravenous infusion of medication accompanied by frequent (every 5 min) BP monitoring is considered. For patients with systolic BP >180 mmHg or mean BP >130 mmHg and evidence or suspicion of elevated ICP, monitoring ICP and reducing BP using intravenous medication to keep cerebral perfusion pressure (CPP) between 60 to 80 mmHg should be considered. For patients with systolic BP >180 mmHg or mean BP >130 mmHg and no evidence or suspicion of elevated ICP, reduction of BP (target mean BP of 110 mmHg or BP of 160/90 mmHg) using intravenous medication is considered, and patient is clinically re-examined every 15 min. In patients presenting with systolic BP of 150–200 mmHg, lowering to 140 mmHg is probably safe.
8. *Seizure prophylaxis and treatment*: Seizures are more common in lobar as compared to deep hemorrhage [14]. If seizures occur, use intravenous fosphenytoin or phenytoin. The 2010 guidelines recommend against prophylactic use of antiepileptic drugs.
9. *Intracranial pressure*: Increased ICP can result from hematoma or edema, and may contribute to brain injury and neurologic deterioration. Current guidelines recommend head of the bed elevation by 30° once hypovolemia is excluded, along with analgesia and sedation, particularly in intubated patients. Mild hypernatremia should be tolerated. Glucocorticoids should not be used to lower the ICP. Invasive monitoring and treatment of ICP should be considered for patients with GCS <8. Intravenous mannitol is the treatment of choice to lower increased ICP. The goal of therapy is to achieve plasma hyperosmolarity (300–310 mosmol/kg) while maintaining adequate plasma volume. Barbiturate anesthesia can be used if mannitol fails to lower ICP to an acceptable range. Hyperventilation ($PaCO_2$ 25–30 mmHg) causes rapid lowering of ICP. CSF drainage by intraventricular catheter is effective for lowering the ICP.
10. *Surgery*

Cerebellar hemorrhage: Surgical removal of hematoma with cerebellar decompression should be performed for cerebellar hemorrhages >3 cm in diameter who are deteriorating, or have brainstem compression and/or hydrocephalus [12].

Supratentorial hemorrhage: Craniotomy only for those with lobar clots >30 mL within

Table 33.3 Reversal of antithrombotic agents in intracranial hemorrhage

Antithrombotic agent	Reversal drug
Vitamin K antagonist	For INR >1.4, intravenous vitamin K 10 mg + 3–4 PCC or FFP 10–15 ml/kg if PCC unavailable
Factor Xa inhibitor	Activated charcoal (50 g) within 2 h, PCC 50 U/kg
Direct thrombin inhibitor	For dabigatran-activated charcoal (50 g) within 2 h and idarucizumab 5 g. Hemodialysis or repeat idarucizumab if persistent bleeding
Unfractionated heparin	Protamine 1 mg for every 100 U of heparin given in last 2–3 h
LMWH	Enoxaparin dosed >8 h—protamine 1 mg IV for every 1 mg enoxaparin, for 8–12 h—0.5 mg for every 1 mg of enoxaparin Dalteparin, nadroparin, and tinzaparin dosed within 3–5 half lives of LMWH protamine 1 mg/100 anti Xa U of LMWH or recombinant factor VIIa (rFVIIa) 90 mcg/kg
Thrombolytic agents	Cryoprecipitate 10 U or tranexamic acid 10–15 mg/kg over 20 min or epsilon aminocaproic acid 4–5 g
Antiplatelet agent	DDAVP (desmopressin) 0.4 mcg/kg IV or platelet transfusion (one apheresis unit) if neurosurgical intervention is planned

PCC prothrombin complex concentrate, *FFP* fresh frozen plasma, *INR* international normalized ratio, *rFVIIa* recombinant factor VIIa, *LMWH* low molecular weight heparin

1 cm of the surface. No other patient group is recommended for surgery. The routine evacuation of supratentorial ICH in the first 96 h is not recommended.

Intraventricular hemorrhage: Patients with intraventricular extension of ICH are at risk for hydrocephalus, especially if third and fourth ventricles are involved. Such patients should be closely monitored.

11. *Hemostatic therapy*: Hemostatic therapy stops ongoing hemorrhage and prevents hemorrhage enlargement; however, trials demonstrate mixed results. Recombinant factor VIIa for acute ICH that is not associated with warfarin should not be used.
12. *Resumption of antiplatelet therapy*: Aspirin therapy can be resumed after acute phase of ICH, provided BP is well controlled and indication for antiplatelet treatment is strong (potential benefit outweighs the increased risk of recurrent ICH).
13. *Resumption of anticoagulation*: For patients who require anticoagulation soon after ICH, the AHA/ASA guidelines conclude that intravenous heparin may be safer than oral anticoagulation. Oral anticoagulants may be resumed 3–4 weeks after the onset of ICH with rigorous monitoring and maintenance of international normalized ratio (INR) in lower end of therapeutic range.
14. *Treatment of hypertension*: This is the most important step to reduce the risk of ICH, and its recurrence. Cessation of smoking, alcohol, and cocaine is also recommended.

33.6 Aneurysmal Subarachnoid Hemorrhage

The classic presentation of aSAH is as follows: Abrupt onset of a sudden, severe headache which might be associated with neck pain, nausea and vomiting, transient loss consciousness, or coma. Examination should include Glasgow Coma Scale (GCS) score, pupil evaluation, fundoscopy for retinal hemorrhages, and neck examination for meningismus. Clinical severity of aSAH can be determined using World Federation of Neurological Surgeons or Hunt and Hess Scale. Once aSAH is diagnosed, bed rest is advised (Class 2B). Pre-operative laboratory evaluation includes complete blood count, platelets, coagulation parameters, electrolytes, blood urea and serum creatinine, cardiac enzymes, and 12-lead electrocardiogram. Nimodipine 60 mg per oral or via nasogastric tube every 4 h (watch for hypotension) should be started within 4 days of ictus and continued for 21 days. Antiepileptic drug is administered until the aneurysm is secured (Class 2B). However, phenytoin use has been associated with worse cognitive outcomes. When aSAH patients present with coagulopathy, platelets should be administered for platelet count $<50 \times 10^9$/L [15].

33.6.1 Anesthetic Management of aSAH

Patients with aSAH may exhibit physiologic derangements that affect anesthetic management, including neurologic dysfunction, cardiac abnormalities, electrolyte disturbances, anemia, and seizures. The goals during anesthesia for surgery or coiling are hemodynamic stability, avoiding hypertension and aneurysm rupture, and maintaining cerebral perfusion. An arterial catheter, placed prior to induction of anesthesia, allows continuous BP monitoring. Precise guidelines for BP management do not exist [16]. In patients with unruptured aneurysm or ruptured aneurysm with normal ICP, systolic BP should be maintained $\leq$140 mmHg with mean BP $\geq$60 mmHg. Short acting, titratable medications such as labetalol or nicardipine are recommended for BP control. However, over-zealous treatment of BP can lead to brain ischemia (especially if hydrocephalus is present). For ruptured aneurysm with suspected or known intracranial hypertension, passive hypertension should not be actively treated. Hypertension in response to noxious stimulation and iatrogenic hypertension should be avoided, and CPP of 50–60 mmHg should be maintained. A temporary clip may be placed on

a feeding vessel to facilitate dissection and permanent clipping. If neuromonitoring (somatosensory evoked potentials) shows ischemic changes during temporary clipping, increasing mean BP by 10–20% may be appropriate. The administration of anesthetic drugs for neuroprotection during temporary clipping is controversial, and practice varies. Induced hypothermia has been shown not to improve outcomes for patients who undergo aneurysm clipping [16]. Adenosine, 0.4–0.6 mg/kg IV, may be administered to induce temporary bradycardia or cardiac arrest to reduce or suspend flow through the aneurysm or in the event of intraoperative aneurysm rupture [17].

Intraoperative aneurysm rupture occurs most commonly during aneurysm dissection and clipping. Goals for management are to rapidly create a bloodless field to facilitate clipping, and to protect the brain. Esmolol 10–20 mg intravenously may be used to induce hypotension targeted to a mean BP of 50–60 mmHg. Propofol 20–60 mg IV followed by >125 mcg/kg/min infusion may be used to maintain reduced cerebral metabolic rate. If electroencephalogram (EEG) monitoring is used, propofol can be titrated to burst suppression. After aneurysm clipping, IV fluids and blood products are administered to achieve euvolemia and hemoglobin ≥8 g/dL. The guidelines provided by Neurocritical Care Society [18], American Heart Association [15], and European Stroke Organization [19] regarding perioperative management of aSAH are summarized here [20].

33.7 Stupor and Coma

Stupor and coma reflect impaired or absent responsiveness to external stimulation and present as difficulty in arousal necessitating prompt intervention to preserve life and brain function. Most often, patients present to an emergency department following trauma, cerebrovascular disease, intoxications, infections, and metabolic derangements [21].

33.7.1 Management

Basic care should be administered based on the clinical findings and laboratory investigations. Patients with a GCS ≤8 require intubation to protect the airway. Intubation is also necessary if hypoxemia (peripheral oxygen saturation of <90%), vomiting, or poor cough/gag reflex are present. Hypotension (mean BP <70 mmHg) is managed with intravenous fluids or vasopressors or both. Dextrose bolus 25 g (as 50 mL of a 50% solution) should be administered while awaiting blood reports to identify cause of coma. Thiamine 100 mg should be administered in malnourished patients to manage potential Wernicke's encephalopathy. Naloxone (0.4–2.0 mg IV) and flumazenil are appropriate for known or suspected drug toxicity [22]. Gastric lavage and activated charcoal are considered in suspected toxic or drug ingestions. If cerebral herniation is evident on clinical examination or imaging, urgent treatment is recommended. Hyperthermia (>38.5 °C) can aggravate brain damage; antipyretics and/or cooling blankets should be promptly instituted. Empiric therapy is recommended for bacterial meningitis [23] (e.g., ceftriaxone 2 g IV twice daily and vancomycin 2 g/day IV 6 hourly) or viral encephalitis [24] (acyclovir 10 mg/kg IV thrice a day) until these conditions are excluded. Phenytoin or fosphenytoin (15–20 mg/kg) is recommended for seizure management. If non-convulsive seizures are suspected and EEG is unavailable, phenytoin or lorazepam (1–2 mg IV) may be considered [25]. Definitive therapy should be considered after a confirmatory diagnosis. Patients with coma either recover or progress to brain death, persistent vegetative state, or minimally conscious state.

33.8 Meningitis and Encephalitis

Patients having hyper-acute (hours) and acute (hours to days) onset of headache with altered mentation should be suspected of having meningitis or encephalitis. Other signs such as

meningismus, fever, rash, focal neurological deficits, or seizure significantly increase the possibility of central nervous system (CNS) infection. Patients with altered mental status should be monitored for needing airway management. Similarly, patients with bacterial meningitis are likely to have lung or bloodstream infections with the same pathogen, hence cardio-respiratory parameters should be monitored closely to diagnose sepsis. Bacterial meningitis and herpes encephalitis should be recognized early (< 1st hour), as prompt treatment can improve the outcome.

If the patient develops systemic inflammatory response syndrome, 20–30 ml/kg of intravenous crystalloids should be administered over 20–30 min and vital signs, mental status, and airway should be reassessed frequently during this treatment. Dexamethasone 10 mg should be administered 15 min before antibiotic therapy particularly in *Streptococcus pneumoniae* meningitis [26]. Selection of antibiotics/antivirals is based on (a) course of CNS infection, (b) age, and (c) other infectious risk factors [27]. Children <3 months are susceptible for group B streptococci, *Escherichia coli*, *Listeria monocytogenes, Streptococcus pneumonia, and Neisseria meningitidis;* ampicillin, gentamycin, and cefotaxime should be used. In children >3 months, causes include *Streptococcus pneumoniae*, *Neisseria meningitides,* and *Haemophilus influenzae*. Vancomycin with either cefotaxime or ceftriaxone is the preferred antibiotic choice in this population. Broader empiric antibiotics should be considered in children with immune deficiency, recent neurosurgery, penetrating head trauma, or anatomic defects. Young patients suspected of bacterial meningitis from *Haemophilus influenza, Neisseria meningitidis,* and *Streptococcus pneumoniae* should receive CNS doses of third-generation cephalosporin and vancomycin. Adults are at risk of *Streptococcus pneumoniae* infection while the elderly and immunosuppressed are at risk for *Streptococcus pneumoniae* and *Listeria monocytogenes* and should be treated with CNS doses of ampicillin, a third-generation cephalosporin and vancomycin. Vancomycin and trimethoprim-sulfamethoxazole are alternatives in patients with penicillin allergy. For suspected CNS infections that evolve over days, Herpes simplex encephalitis should be considered, and treatment begun with thrice a day acyclovir 10 mg/kg. Adequate hydration with intravenous fluids avoids acyclovir-associated renal failure. In immunosuppressed patients with CNS infections that evolve over days, fungal meningitis should be considered and empiric Amphotericin B can be administered. A lumbar puncture (LP) establishes diagnosis and helps in tailoring the therapy.

33.9 Convulsive Status Epilepticus

Generalized convulsive status epilepticus is a medical emergency that requires prompt evaluation and treatment [28, 29]. The assessment and treatment in status epilepticus should proceed simultaneously. Initial treatment with a benzodiazepine (Grade 1A) is recommended with hemodynamic and respiratory monitoring to avoid side effects of therapy. When intravenous access is available, lorazepam is preferred (Grade 2C). The loading dose is 0.1 mg/kg infused at ≤2 mg/min, allowing 1 min for assessing the effect before deciding additional doses. Alternatively, 4 mg fixed dose may be administered in adults. In addition to benzodiazepines, a loading dose of a longer-acting anti-seizure drug is recommended to control seizures (Grade 1B). Fosphenytoin (20 mg/kg phenytoin equivalents [PE]) is the preferred anti-seizure drug (Grade 2C). Valproic acid (20–40 mg/kg IV) and levetiracetam (40–60 mg/kg) are alternatives in patients with phenytoin hypersensitivity or history of primary generalized epilepsy. In patients who are actively seizing despite two doses of benzodiazepine, a midazolam or propofol infusion should administered simultaneously with fosphenytoin, valproic acid, or levetiracetam, since the primary role of non-benzodiazepine anti-seizure drug is to prevent recurrence rather than to terminate the seizures.

Most patients begin to recover responsiveness within 10–20 min after generalized convulsions, but there is a broad range. The two most common reasons for prolonged post-ictal recovery are sedation due to medications and continuation of (non-convulsive) seizures. All patients who do not attain consciousness after initial treatment should be monitored by EEG to determine ongoing seizure and adequacy of treatment. Following recovery, a full neurologic examination and head imaging should be performed to look for underlying etiology. A LP is warranted if the clinical presentation is suggestive of CNS infection or if the patient has a history of a malignancy with possible metastasis to the meninges.

The optimal duration of treatment for refractory status epilepticus is not well established. In general, infusions are continued for 24 h of clinical and EEG seizure suppression and then gradually tapered over 12–24 h. The prognosis depends on the underlying etiology, but there is some evidence that status epilepticus is independently associated with mortality and neurologic sequelae.

33.10 Acute Non-traumatic Weakness

Weakness is a common, nonspecific complaint arising from both neurologic and non-neurologic diseases. A structured approach involving detailed history, physical examination, and if necessary, imaging studies is needed to arrive at a diagnosis of acute non-traumatic weakness arising from neurologic and neuromuscular processes. The intensivist's first responsibility is to rule out life-threatening or permanently disabling causes of weakness that require urgent treatment. The immediate life threats from acute neuromuscular weakness include inability to protect or maintain the airway, respiratory failure from thoracic and diaphragmatic muscle weakness, and circulatory collapse from autonomic instability. Once life-threatening problems have been addressed or ruled out, the clinician should approach the patient with objective weakness in a systematic manner. The first important step in this approach is to determine whether the weakness is unilateral (asymmetric) or bilateral (symmetric), and to look closely for signs of central neurologic involvement. When assessing acute weakness, it is helpful to begin cephalad and centrally and then progress caudal and peripherally. This approach provides a reliable framework for neuroanatomic localization and accurate diagnosis. If unilateral weakness is identified, signs suggestive of cortical, subcortical (lacunar), or brainstem lesions should be searched. If these are absent, a peripheral process (radiculopathy or peripheral nerve injury) most likely accounts for the patient's symptoms. If bilateral weakness is identified, patient's mental status and signs of upper or lower motor neuron lesions and associated abnormalities should be evaluated. The constellation of examination findings should allow approximate identification of the site of the lesion and determination of the need for imaging studies, specialist consultation, and treatment [30].

33.11 Cervical Spine Injury

Spinal injury should be suspected after trauma, especially following motor vehicle collisions, assaults, falls, and sports-related injuries. Immobilization of the spine using backboard, rigid cervical collar, and lateral head supports should begin at the scene, and maintained until instability related spine injury is excluded [31]. Unstable lesions above C3 may cause immediate respiratory paralysis while lower cervical lesions may cause delayed respiratory distress. In the obtunded adult patient, flexion-extension imaging should not be used to assess for a possible isolated ligamentous injury or spinal cord injury without radiographic abnormality of the cervical spine. In cases of less severe trauma, the history, physical examination, and clinical decision rules are used to determine if spinal imaging is necessary. Both the National Emergency X-Radiography Utilization Study (NEXUS) low-risk criteria and the Canadian C-spine rule are well validated and sensitive. Conservative treatment of cervical fractures

Table 33.4 Electrophysiological monitoring for surgery of spinal column and spinal cord

Recommendation	Level of evidence
MIOM, SSEPs, and MEPs during spinal cord/spinal column surgery are a reliable and valid diagnostic adjunct to assess spinal cord integrity	Level I
MEP recordings are superior to SSEP recordings	Level I
SSEP recordings during spinal cord/spinal column surgery are reliable and valid diagnostic adjuncts to describe spinal cord integrity	Level II
MIOM, including SSEPs and MEP recording, during spinal cord/spinal column surgery does not improve gross total tumor resection or improve neurological outcome, when utilized during intramedullary tumor resection procedures	Level II

MIOM multimodality intraoperative monitoring, *SSEPs* somatosensory evoked potentials, *MEPs* motor evoked potentials

consists of closed reduction under fluoroscopic guidance and halo-vest immobilization. If plain radiographs or computed tomography demonstrate minor spinal fracture patterns and there is no neurologic deficit, then outpatient management may be possible. Unstable fractures should be surgically fixed. The summary of recommendations for electrophysiological monitoring during surgery for spinal column or cord is listed in Table 33.4, and further details are available here [32].

33.12 Prophylaxis for Venous Thromboembolism in Neurocritical Care

The risk of VTE and its consequences including death is high in patients cared in the neurointensive care unit necessitating prophylaxis. The increased risk is due to venous stasis from paralysis and increased endothelial activation in this population. The risk of bleeding from prophylaxis in these patients is also high. The Neurocritical Care Society has provided guidelines regarding prophylaxis for VTE in neurocritical care setting [33], and the summary is provided in Table 33.5.

33.13 Temperature Management in Neurointensive Care

Targeted temperature management (TTM) is often used to minimize secondary injury and improve outcome in neurocritical care. Though the evidence is strong for neonatal hypoxic-ischemic encephalopathy and out-of-hospital cardiac arrest, its use for patients with TBI and stroke is increasingly evaluated. Key aspects of the guidelines for TTM provided by Neurocritical Care Society [34] are described in Table 33.6.

33.14 Conclusions

The application of EBM in neuroanesthesia and neurocritical care practice enhances possibility of optimal patient diagnosis and management and is likely to improve patient outcomes. Neuroanesthesiologists and neurointensivists should acquire knowledge and necessary skills regarding searching for good quality evidence, critical appraisal of current available evidence and identifying and implementing pre-appraised evidence such as practice guidelines to better inform clinical care decisions for improving outcomes in neurological patients.

Key Points

- Evidence-based practice of neuroanesthesia and neurocritical care improves quality of care and outcomes in patients with neurological illness.
- Neuroanesthesiologists and neurointensivists should use pre-appraised evidence such as guidelines to deliver standardized and transparent care for patients.
- Where these are not available, structured approach to finding best current evidence and integrating this evidence with clinician experience and patient values is desirable.

Table 33.5 Prophylaxis for venous thrombosis in neurocritical care patients

Diagnosis	Recommendation and level of evidence	Recommendation
Ischemic stroke	Strong; high-quality evidence Weak; low-quality evidence	a. VTE pharmaco-prophylaxis should be performed as soon as is feasible b. LMWH over prophylactic-dose UFH in combination with intermittent pneumatic compression c. When patients have received rTPA, VTE prophylaxis should be delayed for 24 h
Intracranial hemorrhage	Strong; high-quality evidence Weak; low-quality evidence	a. IPC and/or graduated compression stocking for over no prophylaxis beginning at admission b. UFH or LMWH in patients with stable hematomas and no ongoing coagulopathy beginning <48 h of admission. IPCs in patients on pharmacologic prophylaxis
Aneurysmal subarachnoid hemorrhage (aSAH)	Strong; low-quality evidence Strong; moderate-quality evidence Strong; moderate-quality evidence	a. UFH in all patients with aSAH except unsecured ruptured aneurysms b. IPCs at hospital admission c. UFH at least 24 h after securing of aneurysm
Traumatic brain injury (TBI)	Weak; low-quality evidence	IPC <24 h of TBI or <24 h after craniotomy
Brain tumors	Strong; moderate-quality evidence	LMWH or UFH upon hospitalization who are at low risk for major bleeding and who lack signs of hemorrhagic conversion
Spinal cord injury	Strong; high-quality evidence Weak; low-quality evidence	a. VTE prophylaxis at the earliest, <72 h of injury b. No mechanical measures alone c. IPC if LMWH or UFH is not possible
Neuromuscular disease	Strong; moderate-quality evidence Weak; very low-quality evidence	a. UFH, LMWH, or fondaparinux preferred b. Continuing VTE prophylaxis at least for duration of hospitalization, or until ambulation
Complicated spinal surgery	Strong; moderate-quality evidence Weak; low-quality evidence	a. IPC with LMWH or UFH b. No routine use of IVC filters c. Prophylactic IVC filter as a temporary measure only in patients with PE and DVT or those with DVT at risk for PE who cannot be anticoagulated

VTE venous thromboembolism, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *rTPA* recombinant tissue plasminogen activator, *IPC* intermittent pneumatic compression, *DVT* deep vein thrombosis

Table 33.6 Targeted temperature management (TTM) in neurointensive care

Intervention	Recommendation	Quality of evidence
Initiation of cooling	No recommendation on timing of TTM initiation	Moderate
	Use controlled normothermia to reduce fever burden	Moderate
Duration of cooling	At least 24 h of cooling in OHCA	Moderate
	No longer than >72 h or <32 °C in HIE	Moderate
	Long duration for ICP control in severe TBI	Low
Method of cooling to achieve fastest cooling	Nasal, skin or intravascular temperature modulating devices and/or cold saline infusions preferred to air blankets, cooling fans or packs for faster target temperature achievement, improving likelihood of reaching the target and minimizing overshoot	High
	Surface cooling devices preferred to passive air cooling/ice packs to achieve target temperature in HIE	High
Measurement site	Use continuous esophageal temperature probe; if not appropriate/available, use bladder probe	Low
Shivering assessment and treatment	Use bedside sedation assessment scale to assess shivering	Moderate
	Use stepwise approach prioritizing non-sedating interventions over narcotics, sedatives, or paralytics	
	Metabolic support based on disease state and estimation of metabolism, enteral nutrition <24–48 h	
Complication prevention/management	No additional interventions for gastric intolerance	Low
	Follow standard critical care guidelines for monitoring infection	Low
	Maintain serum potassium levels of 3.0–3.5 mmol/L	High
	Temperature-corrected ABG measurements, monitoring similar to critically ill, consider impact of drugs	
	Similar ICU care with respect to monitoring for bleeding	High
	Thromboelastometry helpful in measuring coagulation	Low
	Closely monitor for skin breakdown during surface cooling	Low
	Recommend cardiac monitoring during TTM	High

OHCA out of hospital cardiac arrest, *HIE* hypoxic ischemic encephalopathy, *TBI* traumatic brain injury, *ICP* intracranial pressure, *ABG* arterial blood gas

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