Evidence-Based Neurocritical Care

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Abstract

Neurocritical care is a pioneering subspecialty dedicated to the treatment of patients with life-threatening neurological illnesses, postoperative neurosurgical complications, and neurological manifestations of systemic disease. The care of these patients requires specialized neurological monitoring and specific clinical expertise and has generated a body of literature commensurate with the expansion of the field. This article reviews landmark studies over the last 10 years in the management and treatment of common acute neurological illnesses including massive cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, and status epilepticus.

Keywords

neurocritical care, status epilepticus, cerebrovascular trauma, subarachnoid hemorrhage, intracranial hemorrhage

Neurocritical care is a pioneering subspecialty dedicated to the treatment of patients with life-threatening neurological illnesses, postoperative neurosurgical complications, and neurological manifestations of systemic disease. The care of these patients requires specialized neurological monitoring and specific clinical expertise and has generated a body of literature commensurate with the expansion of the field. This article reviews landmark studies over the last 10 years in the management and treatment of common acute neurological illnesses including massive cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and status epilepticus.

Methods

Trials were identified from an Ovid/Medline search, and large multicenter randomized clinical trials were selected preferentially. The following title word search terms were used: intracerebral hemorrhage or intracerebral haemorrhage, cerebral hemorrhage or cerebral haemorrhage, subarachnoid aneurysm or aneurysmal subarachnoid, aneurysmal subarachnoid hemorrhage or aneurysmal subarachnoid haemorrhage, cerebral vasospasm, traumatic brain injury, acute severe traumatic brain injury, acute traumatic brain injury, severe brain injury, and status epilepticus. Additionally, the subject headings middle cerebral artery infarction and surgical decompression were used. Search terms were limited to English language, humans, adults, and randomized controlled trial or multicenter study. Trials that focused on intensive care unit (ICU) management published between 2003 and May 2013 in high-impact journals were preferentially selected for inclusion in this review.

Surgical Management of Malignant Middle Cerebral Artery Infarction

Mortality from malignant cerebral edema after middle cerebral artery (MCA) infarction has been reported to be as high as 80%.¹ Consideration of early surgical intervention to treat malignant edema prompted 3 randomized controlled trials of decompressive hemicraniectomy for malignant MCA infarction.²⁻⁴ Pooled analysis of these European trials was incorporated into each study design. All 3 studies defined a time window of 48 hours from ictus to surgical intervention, and all used functional outcome, rather than mortality, as the primary end point.⁵ Surgery doubled the probability of a good functional outcome with a modified Rankin scale (mRS) of ≤ 3 (43% vs 21%) and increased survival from 22% to 71% in the pooled analysis ($P < .001$). However, the probability of moderately severe disability (mRS of 4) also increased more than 10 times, although the risk of very severe disability (mRS of 5)

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Table 1. Practice Points for Decompression of Malignant MCA Syndrome.

Inclusion Criteria	Functional Outcome
1. 2/3 of MCA territory involved	1. Increases probability of mRS ≤ 3 (able to walk unassisted)
2. Age less than 60	2. Also increases probability of mRS 4 (unable to walk unassisted or attend to bodily needs)
3. Ictus to surgery ≤ 48 hours	

Abbreviations: MCA, middle cerebral artery; mRS, modified Rankin scale.

was not increased. Numbers needed to treat were found to be 4 for survival with a mRS ≤ 3 , 2 for survival with a mRS ≤ 4 , and 2 for survival irrespective of the functional outcome. These studies excluded patients older than 60 years who represent nearly 50% of those with severe space-occupying MCA infarcts. The ongoing DEcompressive Surgery for the Treatment of malignant Infarction of the middle cerebral artery (DESTINY) II trial aims to evaluate patients older than 60 years.

The DESTINY, performed in Germany, and DEcompressive Craniectomy In MALignant MCA Infarction (DECIMAL), performed in France, trials were published individually in 2007.^{2,3} Inclusion criteria were similar, and both showed a trend toward functional improvement in the surgical group. However, Hemispheric Craniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial (HAMLET), performed in the Netherlands and published in 2009, allowed surgery up to 4 days from ictus. In that study, surgical decompression had no effect on functional outcome despite a reduction in case fatality rates.⁴ The wider window to surgery may have attenuated the benefits observed in the other 2 trials (Table 1).

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for only 10% to 15% of strokes annually but carries a 30-day mortality rate of 40% with a majority of survivors left with severe disability.⁶ Hematoma volume and hemorrhagic expansion are major determinants of outcome in these patients.

Recombinant factor VIIa (rFVIIa), a promoter of hemostasis, studied in the phase III multicenter Femoral Artery Stenting Trial (FAST) failed to show any improvement in mortality or functional outcome and only achieved a modest decrease in hematoma expansion despite the success of the previous safety trial.^{6,7} Moreover, the treatment group had a significantly higher incidence of arterial thromboembolic events. The negative results of the phase III trial (after the positive phase 2b trial) may have been due to failure of randomization (with lower Glasgow Coma Scale [GCS] score and more intraventricular hemorrhage [IVH] in the rFVIIa groups), inclusion of very elderly patients, and improved outcomes in the placebo group possibly related to improved neurological ICU in general.

Hypertension is a known determinant of ICH expansion; however, the optimal blood pressure targets to maintain

cerebral perfusion pressure while limiting early hematoma expansion remain unknown. Current guidelines recommend a blood pressure goal of 160/90 mm Hg in the absence of elevated intracranial pressure (ICP).⁸ The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) II, a phase III multicenter trial, randomized 2839 patients with a baseline systolic blood pressure (SBP) of >150 mm Hg to an SBP goal of <140 mm Hg or <180 mm Hg within 6 hours of ictus despite ad hoc analysis of the safety trial which suggested early BP reductions within 3 hours in patients with a baseline SBP >180 mm Hg were associated with better outcomes.^{9,10} The trial showed no significant reduction in death or major disability with a suggestion of improved functional outcomes in the intensive group in ordinal analysis. Intensive treatment was not associated with increased mortality or serious adverse events.

The INTERACT results confirmed preliminary findings of the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) study, a US-based pilot study of blood pressure lowering in ICH. A total of 60 patients were randomized to 3 different SBP targets (200-170 mm Hg, 170-140 mm Hg, 140-110 mm Hg) within 6 hours of ictus in patients with a baseline SBP of >170 mm Hg and evidence of chronic hypertension.¹¹ The much anticipated phase III trial, ATACH-II, has narrowed the time to treatment to 3 hours of ictus and has changed the target blood pressure goals to ≤ 180 mm Hg or ≤ 140 mm Hg, similar to the INTERACT design. The results will likely determine whether acute blood pressure lowering in fact correlates with ICH expansion and/or outcome.

Radiographic assessments of hematoma expansion may provide an alternate therapeutic target in the treatment of ICH. The ongoing double-blind, double arm Spot Sign for Predicting and Treating ICH Growth (STOP-IT) study randomizes patients with ICH within 6 hours of ictus and a spot sign on computed tomography (CT) angiography to receive rFVIIa or placebo. The spot sign is an area of contrast enhancement within the hematoma that suggests a radiographic focus of ongoing bleeding. The second arm is a prospective observational study of hematoma expansion among patients without a spot sign. The trial should be completed in the next 3 to 5 years.

Stereotactic minimally invasive surgery for ICH can safely and effectively permit aspiration of the hematoma, allow delivery of thrombolytic medication, and enhance clot drainage. In preliminary study, minimally invasive surgery plus recombinant tissue plasminogen activator (rt-PA) for evacuation of ICH has been shown to reduce clot size (50% vs 6%) without significant adverse events.¹² Patients were randomized to stereotactic catheter placement and clot aspiration followed by ventriculostomy placement. A dose of 0.3 mg of rt-PA was administered through the ventriculostomy catheter every 8 hours, with a maximum of 9 doses, until the clot was reduced by 80% or it measured less than 15 cm³. However, outcome data were not reported and final analyses of the planned enrollment of 60 patients are yet to be published.

Intraventricular hemorrhage complicates ICH in 40% of the cases,¹³ and mortality estimates range from 50% to 80%.¹⁴ Minimally invasive procedures in the treatment of IVH have shown promise as once hemorrhagic obstruction of the third and fourth ventricle is removed, clot lysis rates increase dramatically in rt-PA-treated patients. Preliminary report of the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR-IVH) trial showed that repeated administration of low-dose rt-PA through an external ventricular drain was safe in 78 patients.¹⁵ However, analyses of the completed phase II study are yet to be published.

Surgery remains an important therapeutic option in ICH, because it may treat or preempt intracranial hypertension and optimize cerebral perfusion. Although evidence supports the surgical evacuation of some ICH (eg, cerebellar hemorrhages),^{16,17} the role of surgery in treating other patients with ICH has been controversial. The International Surgical Trial in Intracerebral Haemorrhage (STICH) prospectively randomized 1033 patients to early surgery or a conventional medical therapy and stipulated that enrollment be contingent upon clinical equipoise.¹⁸ This trial failed to show a difference in functional outcome at 6 months between medical and surgical treatment groups. However, in subgroup analysis, surgically treated patients with superficial ICH (≤ 1 cm from the cortical surface) had improved functional outcomes, and those with low admission GCS score (≤ 8) had worse outcomes after surgery. This trial was criticized for both the high rate of surgical crossovers and the timing of surgical intervention in the treatment group. The STICH II trial randomized 601 patients with spontaneous lobar ICH ≤ 1 cm from the cortical surface with a volume of 10 to 100 cm³ within 48 hours of ictus to early surgery (within 12 hours) or best medical management.¹⁹ Enrolled patients had an admission GCS motor score of ≥ 5 and an eye score of ≥ 2 . Of the patients in the conservative group, 21% eventually had surgery typically due to neurologic deterioration. Results showed a nonsignificant increase in the number of patients with a favorable outcome at 6 months. Furthermore, post hoc analysis demonstrated benefit from surgical intervention in the subgroup of patients with a poor prognosis (composite of GCS, age, and hematoma volume); however, this subgroup was not specified a priori.

In summary, many treatments for ICH have been studied, but few have clearly and demonstrably improved outcome. Hope remains strong for therapeutic blood pressure reduction, minimally invasive surgery, and fibrinolytic therapy. Ultimately, the combination of treatment modalities may prove most effective (Table 2).

Subarachnoid Hemorrhage

The management of SAH has evolved considerably over the last 10 years. Seminal studies investigating the treatment of aneurysms, prevention of rebleeding, and treatment of delayed cerebral ischemia (DCI) have informed current practice.

Table 2. Practice Points for Treatment of ICH.

Treatment	Study Conclusions
rFVIIa	No improvement in mortality of functional outcome
SBP reduction	Treating for SBP ≤ 140 appears safe but improvement in outcome has not yet been demonstrated
Stereotactic clot aspiration	Appears safe but awaiting outcome data
Intraventricular rt-PA for IVH	Reduces clot burden and appears safe but awaiting outcome data
Surgical evacuation	May be of benefit in clots ≤ 1 cm from the cortical surface

Abbreviations: ICH, intracerebral hemorrhage; rFVIIa, recombinant factor VIIa; SBP, systolic blood pressure; rt-PA, recombinant tissue plasminogen activator; IVH, intraventricular hemorrhage.

The International Subarachnoid Aneurysm Trial (ISAT) was the first large multicenter trial to evaluate modality of aneurysm treatment.²⁰ A total of 2143 patients were randomized to either endovascular coil embolization or surgical clip placement. One-year mortality rate was lower in the endovascular treatment group than in the surgical group (23.7% vs 30.6%; $P = .0019$). This benefit persisted despite the fact that more patients in the endovascular arm required subsequent intervention. Of those initially allocated to endovascular therapy, 53 required a second endovascular procedure and 83 required a second surgical procedure on the same aneurysm. In contrast, only 34 patients allocated to surgical therapy required a second procedure.

In 2005, outcome data for the ISAT trial as well as secondary outcome data for rebleeding, mortality, epilepsy, and follow-up angiography were published.²¹ There was no significant difference in the rate of rebleeding between the 2 groups beyond 1 year. However, postprocedural rebleeding appeared to be higher in the endovascular group (3.3% vs 1.1%). Complete occlusion of the aneurysm favored surgery (82% vs 66%) with the caveat that half as many follow-up angiograms were done in the surgical group. Coil embolization carried a significantly lower risk of postprocedural seizure. Long-term follow-up of a subset of patients revealed a higher incidence of rebleeding in the endovascular group after 1 year.²² However, there was no difference in the number of deaths due to rebleeding, and the number of rebleeding events was small. Although the probability of independent survival for those alive at 5 years was similar in both the groups, there was a significant lower risk of death in the endovascular group (11% vs 14%; $P = .03$). The authors concluded that the benefit of endovascular treatment for patients with good clinical grade SAH and anterior circulation aneurysms was not lost over time despite the higher long-term rebleeding rates.

Rates of aneurysmal rebleeding have decreased significantly, in large part due to early treatment. However, despite timely neurosurgical referrals, early rebleeding remains a major cause of preventable mortality from aneurysmal SAH.

The first multicenter prospective trial designed to investigate the early, short-term use of tranexamic acid, an antifibrinolytic, to prevent aneurysmal rebleeding was performed in 2002.²³ Five hundred and ninety-six patients with CT-confirmed SAH within 48 hours of local hospital admission were randomized to receive either placebo or tranexamic acid (1 g every 6 hours) until aneurysm treatment or up to 72 hours. Although treatment resulted in a statistically significant decrease in early rebleeding, no difference was found in functional outcome or 6-month mortality, the predetermined study end points.

Cerebral vasospasm, implicated in the pathogenesis of DCI, the major cause of morbidity and mortality after aneurysm rebleeding, has been the target of many recent drug trials. Clazosentan, an endothelin receptor antagonist, demonstrated a dose-dependent reduction in moderate or severe angiographic vasospasm but in phase III trial failed to demonstrate improvement in functional outcome despite a 65% reduction in angiographic vasospasm.²⁴ Magnesium, a noncompetitive antagonist of voltage-dependent calcium channels, was investigated in 2 randomized placebo-controlled trials. One found a lower incidence of cerebral infarction without an effect on functional outcome,²⁵ while the other failed to show improvement in functional outcome at 6 months.²⁶ Nimodipine, a calcium channel blocker, is still the only medicine shown to improve neurologic outcomes in a multicenter, double-blind, placebo-controlled trial.²⁷ In addition to drug therapy, a study of prophylactic transluminal balloon angioplasty to prevent delayed ischemia demonstrated no difference in functional outcome despite a significantly lower incidence of vasospasm.²⁸ These studies suggest that cerebral vasospasm may not be the primary cause of poor functional outcome following aneurysmal SAH (Table 3).

Traumatic Brain Injury

Severe head injury is the leading cause of death and disability after traumatic injury.²⁹ The past 30 years have witnessed a demonstrable reduction in TBI mortality from 50% to less than 25%, even when adjusted for injury severity, age, and other determinants of death in this population. The trend toward improved outcomes is likely due to the use of evidence-based protocols, such as those published by the Brain Trauma Foundation (BTF).³⁰

The BTF Guidelines emphasize the importance of intracranial pressure monitoring, although there are no high-quality data to support its use. A recent study published in the *New England Journal of Medicine* questions the efficacy of ICP monitoring on improving outcome after severe TBI.³¹ The study was performed in Ecuador and Bolivia, as a study of the current standard of care in the United States would be unethical. Surprisingly, no significant difference in functional outcome was observed between the pressure monitoring group and the imaging-clinical examination group. Criticisms of the trial may be related to the monitoring device used, the threshold for treatment, the lack of experience with such monitoring,

Table 3. Practice Points for Treatment of Aneurysmal SAH.

Treatment	Study Conclusions
Coil embolization versus clipping	Significantly lower mortality rate with coiling of good clinical grade anterior circulation aneurysms
Tranexamic acid	Decreased early rebleeding of unsecured aneurysms but no improvement in functional outcome or mortality
Clazosentan	Significant decrease in vasospasm but no improvement in functional outcome
Magnesium	No improvement in functional outcome
Nimodipine	Improved neurologic outcome in patients after 21 days of treatment
Prophylactic transluminal balloon angioplasty	Significant decrease in vasospasm but no improvement in functional outcome

Abbreviations: SAH, subarachnoid hemorrhage.

the differential use of barbiturates, or the unusual composite end point employed. Further study into the merits and benefits of ICP monitoring may be warranted.

Surgical decompressive craniectomy for the treatment of refractory ICP in patients with diffuse TBI is often considered clinically.³² In a recent trial, 155 patients with severe nonpenetrating TBI and refractory intracranial hypertension were assigned to bifrontal-temporoparietal decompressive craniectomy or standard care. Despite a significantly lower mean ICP, functional outcome was worse in the craniectomy group. A major criticism of the study was a significant difference in patients with unreactive pupils on admission in the surgical group. A post hoc analysis that adjusted for pupil reactivity at baseline found no difference in functional outcome between the groups. The authors proposed that expansion of the swollen brain outside the skull may cause axonal stretch leading to neural injury or may impair cerebral blood flow or metabolism overcoming any beneficial effect on ICP lowering.

Mild therapeutic hypothermia has been considered a promising therapy for neuroprotection after TBI but has yielded conflicting results. The National Acute Brain Injury Study evaluated the use of very early hypothermia on functional outcome at 6 months.³³ A total of 97 patients within 2.5 hours of nonpenetrating brain injury with GCS score of 3 to 8 and reactive pupils were randomized to normothermia or hypothermia (33°C for 48 hours). Enrollment was exceedingly difficult for this study and was terminated early for futility. There was no significant difference in functional outcome between the groups; however, there were significantly more episodes of elevated ICP in the hypothermia group. This may have been secondary to rigorous measures to reduce hypotension including fluid expansion and vasopressors or rebound ICP related to rewarming. Subgroup analysis demonstrated improved outcome with hypothermia in 28 patients with surgically removed hematomas.

In recent years, 2 small trials have investigated the use of progesterone as a neuroprotectant in acute TBI after animal

models showed improvement in cerebral edema and neuronal loss. A phase II randomized controlled trial studied 100 patients with TBI within 11 hours of injury with GCS score of 4 to 12 randomized to either progesterone or placebo.³⁴ Treatment with progesterone was associated with a modest improvement in mortality and functional outcome without an increased rate of adverse events. A similar single-center Chinese study randomized 159 severe patients with TBI within 8 hours of injury to progesterone or placebo.³⁵ Treated patients had significantly more favorable outcomes than placebo at 3 months ($P = .034$) and lower mortality at 6 months ($P < .05$). Progesterone for the Treatment of Traumatic Brain Injury (ProTECT) and Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries (SyNAPSe) are 2 ongoing multicenter phase III trial.

Steroids were a routine treatment for TBI until the landmark multicenter Corticosteroid Randomisation After Significant Head Injury (CRASH) trial.³⁶ More than 10 000 patients with a GCS score of 14 or less were randomized to 48-hour infusion of methylprednisolone or placebo within 8 hours of ictus. The trial was stopped early when an increase in mortality was observed in the steroid group. Despite similar baseline characteristics, the 14-day relative risk of death was 18% higher in the steroid group ($P = .0001$). A similar increase in the relative risk of death at 6 months was subsequently published the following year.³⁷ The results of this study have led to the prohibition of steroid use in the treatment of TBI.

Conflicting data on the mortality risk of colloid resuscitation solutions prompted the Saline versus Albumin in Fluid Evaluation (SAFE) trial.³⁸ Although the primary study found no significant difference in mortality between the 2 groups, a post hoc study of 460 patients with TBI (GCS 3-13) demonstrated significantly higher mortality at 24 months in the albumin group (33.2% vs 20.4% in the saline group, $P = .003$).³⁹ This difference in mortality was heavily influenced by the high 28-day mortality rate (41.8% vs 22.2%, $P < .001$). In addition to a mortality benefit, patients in the saline group were also significantly more likely to have a favorable functional outcome. The observed deleterious effects of albumin may be due to exacerbation of cerebral edema from a disrupted blood-brain barrier (Table 4).

Status Epilepticus

Few randomized trials have been published on the management of status epilepticus. Two studies found that intravenous (IV) valproate and IV phenytoin were equally successful in terminating motor activation within 20 minutes.^{40,41} Additionally, a study of the effectiveness of coma induction with propofol versus barbiturates for the treatment of refractory status epilepticus (RSE) found mortality and functional outcome were similar in both the groups despite recruitment of only 24 of the 150 patients planned.⁴²

Recently published guidelines for the evaluation and management of status epilepticus by the Neurocritical Care Society highlight the lack of good quality evidence.⁴³ The guidelines

Table 4. Practice Points for Treatment of TBI.

Treatment	Study Conclusions
Bifrontal-temporoparietal decompressive craniectomy for refractory ICP	Significant decrease in ICP but no improvement in functional outcome
Prophylactic hypothermia	No improvement in functional outcome
Progesterone	Modest improvement in functional outcome and mortality in phase 2 trials and awaiting phase 3 results
Methylprednisolone Saline versus albumin	Significant increase in mortality Albumin significantly increased mortality and saline significantly improved outcome

Abbreviations: ICP, intracranial pressure; TBI, traumatic brain injury.

Table 5. Practice Points for Treatment of Status Epilepticus.

Treatment	Study Conclusions
Valproate versus phenytoin	Equally terminate motor seizures
Propofol versus barbiturates for refractory status epilepticus	No difference in mortality or outcome

redefine convulsive, nonconvulsive, and RSE and strongly recommend diagnosis and treatment of underlying etiologies. Rapid, sequential treatment to terminate convulsive and electrographic seizures is recommended. Benzodiazepines should be used as emergent initial therapy followed by IV fosphenytoin/phenytoin, valproate sodium, or levetiracetam. Despite little evidence, the use of continuous antiepileptic drugs for RSE titrated to cessation of electrographic seizures or burst suppression as well as the use of continuous electroencephalography monitoring within 1 hour of status onset was also strongly recommended (table 5).

Conclusions

Although ongoing research is still needed in the burgeoning field of neurocritical care, these recent randomized controlled clinical trials have paved the way for the development of evidence-based practice guidelines. Furthermore, these landmark studies serve as the foundation from which future research and innovative treatments will develop. The next 10 years are likely to offer studies that define and redefine the clinical practice of neurocritical care.

Declaration of Conflicting Interests

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References

1. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch. Neurol.* 1996; 53(4):309-315.
2. Juttler E, Schwab S, Schmiedek P, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): a randomized, controlled trial. *Stroke.* 2007;38(9):2518-2525.
3. Vahedi K, Vicaute E, Mateo J, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL trial). *Stroke.* 2007;38(9):2506-2517.
4. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol.* 2009; 8(4):326-333.
5. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol.* 2007;6(3):215-222.
6. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2008;358(20):2127-2137.
7. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2005;352(8):777-785.
8. Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* 2010;41(9):2108-2129.
9. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med.* 2013;368(25):2355-2365.
10. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT). *Stroke.* 2010;41(2): 307-312.
11. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med.* 2010;38(2):637-648.
12. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D. Preliminary findings of the minimally-invasive surgery plus rTPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. *Acta Neurochir Suppl.* 2008;105:147-151.
13. Daverat P, Castel JP, Dartigues JF, Orgogozo JM. Death and functional outcome after spontaneous intracerebral hemorrhage: a prospective study of 166 cases using multivariate analysis. *Stroke.* 1991;22(1):1-6.
14. Tuhim S, Dambrosia JM, Price TR, et al. Intracerebral hemorrhage: external validation and extension of a model for prediction of 30-day survival. *Ann Neurol.* 1991;29(6):658-663.
15. Morgan T, Awad I, Keyl P, Lane K, Hanley D. Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. *Acta Neurochir Suppl.* 2008;105:217-220.
16. Da Pian R, Bazzan A, Pasqualin A. Surgical versus medical treatment of spontaneous posterior fossa haematomas: a cooperative study on 205 cases. *Neurol Res.* 1984;6(3):145-151.
17. Kirolos RW, Tyagi AK, Ross SA, van Hille PT, Marks PV. Management of spontaneous cerebellar hematomas: a prospective treatment protocol. *Neurosurgery.* 2001;49(6):1378-1386; discussion 1386-1377.
18. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (STICH): a randomised trial. *Lancet.* 2005;365(9457):387-397.
19. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet.* 2013;382(9890):397-408.
20. Molyneux A, Kerr R, Stratton I, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. *J Stroke Cerebrovasc Dis.* 2002;11(6):304-314.
21. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet.* 2005;366(9488):809-817.
22. Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the international subarachnoid aneurysm trial (ISAT): long-term follow-up. *Lancet Neurol.* 2009;8(5):427-433.
23. Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg.* 2002;97(4):771-778.
24. Macdonald RL, Higashida RT, Keller E, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol.* 2011;10(7):618-625.
25. Westermaier T, Stetter C, Vince GH, et al. Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: a randomized, placebo-controlled, clinical study. *Crit Care Med.* 2010;38(5):1284-1290.

26. Wong GK, Poon WS, Chan MT, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. *Stroke*. 2010;41(5):921-926.
27. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm—a controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med*. 1983;308(11):619-624.
28. Zwienenberg-Lee M, Hartman J, Rudisill N, et al. Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial. *Stroke*. 2008;39(6):1759-1765.
29. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg*. 1998;186(5):528-533.
30. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007;24(suppl 1):S1-S106.
31. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med*. 2012;367(26):2471-2481.
32. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16):1493-1502.
33. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the national acute brain injury study: hypothermia II): a randomised trial. *Lancet Neurol*. 2011;10(2):131-139.
34. Wright DW, Kellermann AL, Hertzberg VS, et al. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann Emerg Med*. 2007;49(4):391-402, 402.e391-e392.
35. Xiao G, Wei J, Yan W, Wang W, Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit Care*. 2008;12(2):R61.
36. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. 2004;364(9442):1321-1328.
37. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. *Lancet*. 2005;365(9475):1957-1959.
38. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247-2256.
39. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357(9):874-884.
40. Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure*. 2007;16(6):527-532.
41. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology*. 2006;67(2):340-342.
42. Rossetti AO, Milligan TA, Vulliemoz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care*. 2011;14(1):4-10.
43. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17(1):3-23.