CRITICAL CARE

REVIEW

Year in review 2011: *Critical Care* – neurocritical care

Salah G Keyrouz* and Michael N Diringer

Abstract

Contributions from the neurosciences to *Critical Care* in 2011 covered an array of topics. We learned about potential biomarkers for, and the effect of cerebral oxygen metabolism on, delirium, in addition to treatment of the latter. A group of investigators studied surface cooling in healthy awake volunteers, and incidence of infection associated with therapeutic hypothermia. The effects of statin and erythropoietin on stroke were revisited, and the role of adhesion molecule in the inflammatory reaction accompanying intracerebral hemorrhage was scrutinized. Biomarkers in subarachnoid hemorrhage and their relationship to vasospasm and outcome, and effect of daylight on outcome in this patient population, as well as a new meta-analysis of statin therapy were among the research in subarachnoid hemorrhage. Moreover, 2011 witnessed the publication of a multidisciplinary consensus conference's recommendations on the critical care management of subarachnoid hemorrhage. Results of studies regarding the diagnosis and vascular complications of meningitis were reported. Traumatic brain injury received its share of articles addressing therapy with hypertonic saline and surgical decompression, the development of coagulopathy, and biomarkers to help with prognostication. Finally, research on the treatment of Guillain-Barre syndrome in children, prediction of long-term need of ventilatory support, and pathophysiology of critical illness polyneuropathy and myopathy were reported.

Introduction

This past year's contributions from the field of Neuroscience to *Critical Care* have been varied, covering an array of topics and diseases. These include stroke, subarachnoid hemorrhage, hypothermia, meningitis, peripheral nervous system diseases, and delirium, which captured the lion's share. We review these articles, discuss their scientific contribution to the field, and their clinical relevance below.

Delirium

Delirium is a common condition in the ICU, though likely more encountered in general ICU than neuro-intensive care units. Among other things, it is associated with increased length of stay and mortality [1,2]. Because of its high prevalence and morbid consequences, delirium is an important topic in critical care research. In 2011, five articles addressing issues including pathophysiology, diagnosis and treatment of delirium were published in *Critical Care*.

McGrane and colleagues [3] sought to investigate a possible relationship between serum procalcitonin, C-reactive protein and delirium. Procalcitonin and C-reactive protein are inflammatory biomarkers that have been linked to many acute neurological conditions, like stroke, and other critical illnesses [4]. This prospective cohort study was part of a double-blind, randomized controlled trial comparing dexmedetomidine and lorazepam for sedation of mechanically ventilated patients (Maximizing Efficacy of Target Sedation and Reducing Neurological Dysfunction or MENDS) [5]. Data were analyzed for 87 (of 103) patients enrolled in MENDS. Higher levels of procalcitonin, but not C-reactive protein, were associated with fewer delirium/coma free days (odds ratio (OR) 0.5, 95% confidence interval (CI) 0.3 to 1.0; $P = 0.04$), but neither biomarker showed a relationship with 28-day survival. Some of these results were contradicted by another study led by Van den Boogaard and colleagues [6], which was a prospective observational single center study of 100 critically ill patients (50 with and 50 without delirium). These patients were further divided into two groups, 'inflamed' and 'non-inflamed' based on the presence of at least two systemic inflammatory response syndrome (SIRS) criteria and a positive culture. The reason for this dichotomy is the suspected difference in levels of inflammatory mediators between the groups. Multivariate regression analysis showed that IL-8 was independently associated with delirium in 'inflamed' patients (OR 9, 95% CI 1.8 to 44; $P \leq 0.05$), and similarly IL-10 (OR 2.6, 95% CI 1.1 to

*Correspondence: keyrouzs@neuro.wustl.edu
Neurology/Neurosurgery Intensive Care Unit, Department of Neurology, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8111, St Louis, MO 63110, USA

5.9; $P \leq 0.05$) and the amyloid beta protein $A\beta_{1\text{-}42/40}$ (OR 0.03, 95% CI 0.002 to 0.50; $P \leq 0.05$) in 'non-inflamed' patients. Procalcitonin was an important biomarker that predicted delirium, although this variable did not make it through the multivariate analysis. Based on these results, the authors speculate that the pathophysiology of delirium in different patient populations could vary, and thus potential therapy might need to be more targeted. Nonetheless, the recent studies prove that, to date, the optimal biomarker that could predict the occurrence of delirium remains elusive.

In another prospective observational study investigating the relationship between imbalance in cerebral oxygen supply/demand ratio and occurrence of delirium, Schoen and colleagues [7] used near infrared spectroscopy to measure pre- and intraoperative cerebral oxygen saturation (ScO_2) in 231 patients undergoing on-pump cardiac surgery looking for a relationship between these measurements and development of post-operative delirium. In an earlier study, preoperative ScO_2 was associated with postoperative morbidity and mortality in a similar cohort of patients [8]. The current investigation found that older age, lower mini mental status examination (MMSE) score, history of neurologic or psychiatric disease, and lower preoperative ScO_2 were independent predictors of postoperative delirium, irrespective of hemoglobin or amino-terminal pro B-type natriuretic peptide levels, the latter being a marker of cardiac insufficiency. One important limitation of this study is that it did not account for postoperative analgesia use, which is a known risk factor for delirium.

Two papers addressed treatment of delirium using quetiapine. The first is a *post hoc* analysis of a double blind, randomized, placebo controlled study [9,10]. The authors had already shown that delirium resolves faster when quetiapine is added to as-needed haloperidol [9]. In the current analysis, they sought to investigate the effect of quetiapine on individual delirium symptoms of the Intensive Care Delirium Screening Checklist (ICDSC). Their results suggest that quetiapine may lead to a shorter time to first resolution of symptom fluctuation, inattention, and disorientation, but a longer time to first resolution of agitation and hyperactivity. This could be relevant when one considers that certain symptoms could be disruptive to patient care and maybe even injurious to patient and healthcare provider, and hence there is a greater urgency to control them.

The second article, describing a single institution's use of quetiapine in a small cohort of patients with delirium without comparative analysis, reported a reduction in need for other antipsychotics once quetiapine was introduced [11]. Adverse events were minor and transient. Despite the mixed results from these two studies, overall quetiapine has a beneficial role, at least in alleviating certain delirium symptoms and maybe reducing the need for other, sometimes less benign anti-psychotics.

Hypothermia

Therapeutic hypothermia (TH) has become a standard practice for out of hospital ventricular fibrillation cardiac arrest. TH improves neurological outcome when initiated soon, and maintained for 12 to 24 hours after successful resuscitation [12,13]. Studies suggest that TH could be also beneficial in other conditions like stroke and myocardial infarction [14-16]. Unlike patients who survive cardiac arrest and are comatose, however, those suffering a stroke or myocardial infarction are awake and therefore could perceive discomfort during cooling. Testori and colleagues [17] investigated the feasibility and safety of inducing mild hypothermia (32 to 34°C) in healthy conscious volunteers using a novel, non-invasive surface cooling method. This prospective study, which was sponsored by the manufacturer of the cooling pads (EMCOOLSpad®, Emcools AG, Pfaffstaetten, Austria), enrolled 16 healthy men aged 18 to 70 years. The pads were 20 × 30 cm each and consisted of multiple cooling cells filled with a patented cooling gel. They were applied on the back, thorax, abdomen, and thighs and were exchanged when thawed. Volunteers were medicated with meperidine, buspar to combat shivering. The active cooling and maintenance period was set at 6 hours, during and after which volunteers' biomarkers (for example, esophageal temperature, blood pressure, and so on), comfort level, and skin condition were monitored.

Although all individuals achieved temperatures <35°C, a target temperature of 32 to 34°C set by the investigators was reached in only 6 despite using magnesium sulfate infusion in some. Cooling pads had to be exchanged often because they were completely thawed before reaching temperatures <35°C. Temperature decreased from baseline median 36.2°C to 35°C within a median time of 53 minutes (median cooling rate of 1.1°C/h). Heart and respiratory rates, oxygen saturation and blood pressure decreased significantly during cooling, although none of the volunteers reported complaints. Furthermore, none felt discomfort that necessitated termination of cooling. Mild to moderate skin irritation improved over a follow-up period of 7 days. Shivering occurred in four volunteers, although increasing the dose of meperidine easily controlled it.

In conclusion, healthy, conscious volunteers did not describe active cooling using a novel surface method as uncomfortable. The method was safe, but only partially effective; an algorithm different from the one used by the investigators will be needed to achieve preset temperatures.

To address the issue of infections, a widely feared complication of TH, Kamps and colleagues [18] studied

the effect of selective decontamination of the digestive tract (SDD) in a group of severely brain-injured patients treated with prolonged mild TH on incidence of infection. Hypothermia increases the risk of infectious complications by interfering with leukocyte function and proinflammatory cytokine release [19,20].

This retrospective case-control study compared the incidence of infectious complications in adults with severe brain injury treated with TH (n = 35) to those not treated with TH (n = 169). Cooling was initiated by chilled Ringer's lactate infusion and maintained for a median duration of 107 hours (55 to 168 hours) using surface methods. Both groups received SDD, which included intravenous cefotaxim and oropharyngeal and enteral polymixin, tobramycin, and amphotericin B.

Matching cases and controls using propensity scoring that was based on known outcome predictors yielded 2 relatively homogenous groups of 35 patients each; however, more patients in the hypothermia group received parenteral nutrition (68.6% versus 37.1%; $P = 0.013$), and the maximum dose of midazolam was higher in that group too (0.31 ± 0.10 mg/kg/h versus 0.25 ± 0.11 mg/kg/h; $P = 0.043$).

Despite a higher rectal (but not oropharyngeal or bronchial) bacterial colonization rate in the TH group (51.4% versus 25.7%; $P = 0.049$), these patients were not more likely to develop an infectious complication (20% versus 34.3%; $P = 0.267$).

Still the potential biases in this study, which include its retrospective, non-randomized and uncontrolled design, unbalanced baseline characteristics (for example, parenteral nutrition, more severe intracranial hypertension necessitating TH, and higher doses of vasoactive drugs), and higher mortality in the TH group, favor the normothermia group. Therefore, the results carry some relevance by making the case for using SDD in brain-injured patients at high risk for infectious complications.

Stroke

Despite the availability of acute therapy, ischemic stroke remains a major public health issue worldwide. This is partly because of its high prevalence and morbidity, coupled with the still meager use of intravenous thrombolysis, continuously fueling interest in neuroprotection and other therapies. Tsai and colleagues [21] investigated the effect of 3-hydroxy 3-methyl-glutaryl coenzyme-A (HMG-CoA) reductase inhibitor, or statin, treatment before and after stroke on platelet function. They measured expression of CD62P and CD63 surface molecules [21], which play an important part in platelet adhesion and activation during and after stroke [22].

The prospective non-randomized and uncontrolled cohort study compared blood samples and 90-day outcomes of 43 patients who were using different forms and doses of statins before stroke to those of 129 patients without pre-morbid statin use (66 patients administered statins within 72 hours of stroke, and 63 patients not administered statins). At baseline, patients with pre-existing statin use were more likely to have diabetes, and had significantly lower total and low density lipoprotein cholesterol levels than those who were not taking statins. In addition, the expression of platelet CD62P and CD63 molecules were, too, significantly lower. The expression of CD62P, but not that of CD63, at days 7, 30, and 90 remained significantly lower in the group with preexisting statin use. Initiation of statins after stroke did not have a significant effect on the expression of these platelet surface molecules. In a stepwise logistic regression model, severity of stroke, underlying coronary artery disease, and pre-existing statin use were independent predictors of 90-day outcome; however, the conclusion's validity is questioned by the small sample size and bias related to the study design.

In a prospective randomized and placebo-controlled trial, Yip and colleagues [23] investigated the safety and effect of yet another drug, erythropoietin (EPO), on outcome and level of circulating endothelial progenitor cells (EPCs) following ischemic stroke. Among EPO actions is mobilization of EPCs. The authors had shown in a previous study that an increase in circulating levels of EPCs was associated with a favorable outcome in patients with ischemic stroke [24].

By comparing patients receiving two doses of 5,000 IU each of EPO (n = 83) to those receiving placebo (n = 84) and to age and gender-matched healthy volunteers (n = 60), the authors reported no adverse events related to EPO. Baseline EPC levels were higher in patients suffering an ischemic stroke compared to healthy volunteers. In addition, whereas EPC levels early after ischemic stroke were comparable between the two study groups, that level rose significantly in the active treatment group by day 21. Although patients treated with EPO were more likely to have less disability from their stroke 90 days later, this study did not provide longer-term follow-up that is more appropriate when considering events like recurrent stroke. Furthermore, a relationship between EPC levels and recurrent stroke or death 90 days after ischemic stroke is unclear.

Intracerebral hemorrhage (ICH) is another, yet fortunately less common, type of stroke. It is responsible for a disproportionate number of deaths and staggering morbidity. Despite interest, enthusiasm and large trials, a proven therapy for ICH remains elusive. Early morbidity and mortality from ICH is related to structural damage caused by the hemorrhage, edema, and inflammation.

An increase in levels of circulating adhesion molecules is thought to contribute to an inflammatory response in a number of diseases affecting the central nervous system.

Adhesion molecules facilitate movement of activated mononuclear cells across endothelial cells of the blood brain barrier [25]. In a retrospective study, Wang and colleagues [26] revealed that concentrations of soluble intercellular cell adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) were higher at baseline and increased through day 10 in patients with hypertensive ICH. Furthermore, sICAM-1 was independently associated with outcome. However, the latter, defined as a modified Rankin scale score of 0 or 1, was only measured at discharge. Furthermore, the patient cohort had relatively small ICH volumes (median volume of 10 ml). These limitations might have impacted the study results, which do not offer a clear link between levels of adhesion molecules, pathophysiology, and ultimate outcome that should be measured at least 90 days after hemorrhage.

Subarachnoid hemorrhage

Despite its relatively low prevalence, subarachnoid hemorrhage (SAH) remains a serious illness with high morbidity and mortality. Securing aneurysms, rupture of which is to blame for the hemorrhage, has come a long way. However, our ability to treat the myriad complications that accompany SAH, particularly vasospasm (VSP) and delayed cerebral ischemia, is still disappointing [27]. Hence, it is not surprising to read about many publications addressing SAH and the treatment of its complications in *Critical Care* in 2011.

First, a landmark paper published the recommendations of a Neurocritical Care Society's multidisciplinary consensus conference on the critical care management of SAH [28]. Based on the best available evidence, coupled with their expert opinion, a group of experienced clinicians and researchers addressed issues including medical measures to prevent re-bleeding, prophylactic use of anticonvulsant drugs, monitoring and managing intravascular volume status and cardiopulmonary complications, temperature and glucose control and sodium homeostasis, current use of statins and magnesium sulfate, monitoring and managing delayed cerebral ischemia, and finally anemia and transfusion, and endocrine dysfunction in SAH. The purpose of these recommendations is to offer guidance to clinicians when making diagnostic and management decisions in the absence of high quality data.

Touching on one of the themes addressed in the Neurocritical Care Society's multidisciplinary consensus conference paper, an updated meta-analysis of six randomized clinical trials of magnesium sulfate in the treatment of VSP was carried out by Wong and colleagues [29]. Magnesium is a physiologic antagonist of calcium that in *in vitro* and animal studies causes arterial vasodilation and is neuroprotective [30]. Studies of magnesium sulfate in VSP have thus far yielded conflicting and largely disappointing results [31-34]. Not surprisingly, and in keeping with results of most individual trials, the authors found no evidence to lend support for a beneficial effect of magnesium sulfate on the incidence of delayed ischemic deficits or overall outcome.

Despite meager scientific evidence, emphasis on availability of natural light in the ICU environment is universal [35]. An interesting single center study tested the hypothesis that care in an ICU room with a window contributes to better outcome in patients with SAH [36]. This was a retrospective study that mined data on 789 patients from a large prospective SAH database at Columbia University. Care in a room with a window had no effect on outcome, measured by modified Rankin Scale score at discharge, 3 months and 1 year. Furthermore, it had no effect on other secondary endpoints like length of mechanical ventilation (MV), delirium, ICU length of stay, and mortality. The results were the same in a subgroup analysis that included patients admitted during the months of the year with more than 12 hours of daylight, and those with better Hunt-Hess grade SAH.

Continuing with outcome studies, a group of investigators assessed the ability of copeptin, the carboxy-terminal portion of the arginine vasopressin precursor peptide, in predicting outcome and incidence of VSP in patients with SAH [37]. Recent data found that plasma copeptin levels were elevated in patients with traumatic brain injury (TBI), ICH and ischemic stroke [38-43].

The authors reviewed medical records of 303 patients with aneurysmal SAH whose copeptin levels were compared to those of 150 sex- and age-matched healthy volunteers. Plasma copeptin levels on admission were significantly higher compared to healthy controls (21.2 ± 9 pmol/L versus 6.4 ± 1.8 pmol/L; $P < 0.001$). A multivariate analysis identified World Federation of Neurological Surgeons (WFNS) score, modified Fisher score, and plasma copeptin levels as independent predictors of occurrence of VSP, and in-hospital and one-year mortality. However, copeptin levels did not improve the predictive power of either WFNS or the modified Fisher score when the variables were combined. Conversely, plasma levels of copeptin, along with WFNS and modified Fisher score, independently predicted poor outcome at one year (defined as a Glasgow Outcome Scale (GOS) score of 1 to 3), and copeptin significantly added to the predictive power of WFNS ($P = 0.018$) and modified Fisher score ($P = 0.029$) in this case. Despite these encouraging results, using copeptin levels to help with prognostication in SAH is not ready for primetime yet. Further studies to validate and confirm these findings are needed.

Another paper investigated risk factors for VSP in patients with bleeding from arteriovenous malformations

[44]. While VSP commonly complicates aneurysmal SAH, its incidence, risk factors and consequences in ruptured arteriovenous malformation are unknown. A single center, retrospective observational study from a busy neurosurgical practice in Paris, France found that of 72 patients with ruptured arteriovenous malformation, 12 (17%) had VSP defined by transcranial Doppler (TCD) blood flow velocity >120 cm/s in any cerebral artery. Four patients underwent digital subtraction angiography with results confirming TCD findings. Furthermore, 6 (8%) of the patients with abnormal TCD findings went on to develop cerebral infarcts. Multivariate analysis identified three risk factors for developing TCD-defined VSP: a low Glasgow Coma Score (GCS), female gender, and younger age. Amount of subarachnoid, intraventricular or intraparenchymal blood had no effect on risk of VSP, and outcome was not affected by the development of VSP, though the sample size was small and a possible effect could not be excluded.

The need for better tools to monitor critically ill patients, mitigate deterioration before or as they occur, and predict and improve outcome has led to the development of an array of neuromonitoring devices to use in the neurointensive care unit. However, and despite the enthusiasm those devices have generated, clinicians have struggled to meaningfully incorporate them in daily practice to ultimately impact outcome. This is mainly because of a complex link between monitored function or marker, intervention and outcome.

A group of researchers studied the utility of combined, continuous electroencephalogram (EEG) and somatosensory evoked potential (SSEP) recording in 68 critically ill patients with SAH (51 patients) and ICH (17 patients) [45]. Recordings were carried out for an average of 10 ± 4 days. As expected, EEG and SSEP changes preceded clinical deterioration, intracranial pressure (ICP) elevation, and/or new abnormalities on imaging studies in the majority of patients. In addition, combined EEG and SSEP monitoring increased the odds of predicting deaths when deterioration did occur. SSEP and GCS score changes significantly predicted GOS. A caveat to these findings is that specific interventions to prevent and treat deteriorations were not discussed. Continuous data monitoring of such tests could prove cumbersome, and may be impossible in certain settings and institutions.

Meningitis

Bacterial meningitis is associated with many complications like seizure, hydrocephalus, cerebral venous thrombosis, empyema, and stroke. These complications add to the already high morbidity of the disease. Different mechanisms underlie the development of stroke, the most common being arterial narrowing caused by an inflammatory vasculitis. Klein and colleagues [46] reviewed medical records of 94 patients with bacterial meningitis cared for at one institution looking for the incidence of arterial narrowing. Patients underwent TCD of commonly insonated cerebral vessels. Although it is unclear when and how often TCD was performed, 43% of patients had elevated systolic Doppler velocities (222 ± 45 cm/s), almost half of whom were diagnosed within the first two days. The authors found that elevated TCD velocities were more often seen in sicker patients and those who were treated with corticosteroids, though the latter was associated with the former and multivariate analysis was not performed. In addition, elevated velocities increased the risk of stroke and poor outcome, which treatment with nimodipine did not reduce.

Another paper investigated the early diagnosis of meningitis [47]. Appropriate therapy of bacterial meningitis relies on early diagnosis. Direct cerebrospinal fluid (CSF) examination only identifies a bacterial pathogen in 60 to 80% of cases, and results of cultures are delayed for days [48,49]. An earlier study by Viallon and colleagues [50] suggested that serum procalcitonin and CSF lactate levels could differentiate bacterial from viral meningitis on presentation in patients who have negative direct CSF examination. Their current study was aimed at validating the value of these markers in accurately making the diagnosis of bacterial meningitis upon admission. This was an observational study comparing patients with bacterial (n = 35) to those with viral (n = 218) meningitis treated at one hospital over a span of 12 years. The authors concluded that a CSF lactate level of 3.8 mmol/L had a sensitivity of 94% and a specificity of 97% when differentiating the two types of meningitis. Similarly, the sensitivity and specificity of a serum procalcitonin of 0.28 ng/ml was 97% and 100%, respectively. Although the number of patients with bacterial meningitis in this study is small, the results are nonetheless clinically relevant, especially when other parameters like leucocyte count, glucose and protein levels, albeit less sensitive, are also suggestive of a bacterial etiology. Thus, these findings could offer some hope for an earlier diagnosis, and therefore timely appropriate therapy, in those patients with unrevealing CSF, or blood, culture results.

Traumatic brain injury

Acute coagulopathy is a dreaded complication of TBI. Its prevalence ranges between 10% and 90%, depending on how it is defined, and is more often encountered in severely injured patients. A retrospective review by a group of investigators sought to determine the incidence of coagulopathy in TBI and understand its relationship with outcome [51]. Of 107 patients with isolated TBI, 65% of whom had severe injury, coagulopathy was present on admission in 24%. Another 40% of those

without coagulopathy on admission developed abnormalities in their coagulation parameters within 24 hours of admission. Coagulopathy upon admission was associated with death (OR 3.75; $P = 0.04$), though there was no interaction between severity of TBI and death that one would expect. Finally, because of its retrospective nature, information about other consequences and treatment of coagulopathy was lacking.

An interesting retrospective review by Roquilly and colleagues [52] described the authors' 9-year experience in treating severe TBI-related refractory intracranial hypertension in 50 patients with an algorithm-guided continuous hypertonic saline infusion. The authors used an algorithm that considered natriuresis, diuresis and patient's weight, and adjusted the infusion rate of a 20% saline solution based on intracranial pressure and the difference between pre-set and current sodium level. Though the paper was purely descriptive, the authors indicated that the approach was successful in quickly lowering ICP, and did not result in major adverse events. Validating this algorithm by comparing the approach to bolus administration of hypertonic saline should be considered the next step, especially in light of the controversy regarding the effectiveness of mannitol compared to hypertonic saline and its adverse events [53].

Similarly, surgical management of TBI using a bifrontotemporoparietal decompressive craniectomy was evaluated in a randomized controlled study by Cooper and colleagues [54]. The long awaited results disappointed most who are intimately involved in caring for patients with TBI. The study recruited adult patients with severe non-penetrating TBI with a GCS between 3 and 8 and elevated ICP that is refractory to standard therapy. Patients were randomized within the first 72 hours after TBI to either undergo an extensive decompressive craniectomy and durotomy plus standard care (n = 73) or standard care alone (n = 82), while allowing crossover from the latter to the former group. Decompressive craniectomy decreased ICP, duration of mechanical ventilation and ICU length of stay in comparison to medical therapy alone, although 6-month outcome measured by the extended GOS was worse in the surgical group (OR for a worse functional outcome, defined as a score of 1 to 4 on the extended GOS, was 1.84; 95% CI, 1.05 to 3.24; $P = 0.03$). This unexpected result could have been the product of many variables, as suggested by criticism that the study received; these included enrolling a small subset of TBI patients with ICP that was not very elevated, and possibly suboptimal medical management before craniectomy, long accrual time before surgery, the operative technique that did not involve division of the sagittal sinus and falx cerebri, and possibly worsening vasogenic edema following craniectomy and decompression of the brain. In clinical practice, decompressive craniectomy in TBI is typically an intervention of last resort. The results of this study, considering its shortcomings, are unlikely to change the current practice.

Prognostication early in the course of TBI remains a vexing and frustrating issue. The available tools, including clinical examination and brain imaging, are far from being perfect and reliable [55]. A multi-center prospective study investigated the value of serum ubiquitin C-terminal hydrolase-L1 neuronal protein (UCH-L1), and glial fibrillary acidic protein (GFAP) levels in predicting outcome in severe TBI [56]. Eighty-one patients with severe TBI with or without minor extracranial injury were recruited from four centers. Serial (every 6 hours) measurements of both serum UCH-L1 and GFAP were collected in the first 24 hours and compared to those from 167 healthy volunteers. The authors found significant elevation in levels of both biomarkers in their cohort of brain-injured patients. In addition, GFAP was higher in patients with focal mass lesions, whereas UCH-L1 was higher in patients with diffuse injury, potentially suggesting different susceptibility of neurons and glia to different patterns of injury. Secondary elevations and sustained high levels of either biomarker within the first 24 hours were linked to secondary insults and surgical intervention. UCH-L1 was an independent predictor of mortality at discharge; a level of 1.89 ng/ml had a specificity and sensitivity of 96% and 52% in predicting early deaths. Finally, a predictive model including age, GCS and UCH-L1 levels accurately classified patients as dead versus alive at 6 months 94% of the time. Findings of this study are interesting; if validated in a larger cohort, a combination of clinical findings, brain imaging and biomarkers could aid in early prognostication in patients with TBI.

Peripheral nervous system

A handful of papers published in *Critical Care* last year addressed questions related to the peripheral nervous system. Two of these dealt with Guillain-Barre syndrome (GBS). The first, by El-Bayoumi and colleagues [57], described the results of a single center randomized trial of intravenous immunoglobulin (IVIg) versus plasma exchange (PE) in ventilated children with GBS. In adults, treatment with IVIg or PE leads to comparable outcomes [58,59], and similar duration of MV [60]. The aim of the study was to understand the effect of the two immunotherapies on duration of MV, ICU length of stay and overall outcome in children. With a small sample size (IVIg 20 patients; PE 21 patients), the investigators found that outcome, measured by the ability to ambulate independently 4 weeks after discharge from ICU, was similar in the 2 groups; yet children treated with PE had a significantly shorter duration of MV compared to those treated with IVIg (11 ± 1.5 days versus 13 ± 2.1 days;

P = 0.037). Confirmation of these findings by larger randomized trials could have an important impact on how we treat children with severe GBS.

The second study sought to answer an important question that clinicians caring for patients with GBS are faced with: how to decide early in the course of the illness who will need a tracheostomy. Fourrier and colleagues [61] reviewed medical records of 61 adult patients with GBS treated at their institution between 1996 and 2009. Of those, 40 patients required MV, 12 for equal or less than, and 28 for more than 15 days. Three of the 12 patients in the shorter MV group and 25 of the 28 patients in the longer MV group underwent tracheostomy. The authors found that the combination of a sciatic nerve conduction block on electromyography and lack of foot flexion after completion of immunotherapy was an excellent predictor of prolonged MV (100% specificity). This finding awaits validation before being used to predict prolonged MV and hence the need for tracheostomy in this patient population.

Critical illness polyneuropathy and myopathy (CIPNM) is another cause of flaccid paralysis in the ICU, though unlike GBS, which is the reason for admission, CIPNM develops during a long ICU stay. The exact pathophysiology of CIPNM is yet to be elucidated, although risk factors like use of neuromuscular blocking agents, aminoglycosides, and high dose corticosteroids have been incriminated [62,63]. More recently, calcium homeostasis disturbances in critically ill, septic patients have been suggested to play a role in the pathogenesis of CIPNM [64].

Anastasopoulos and colleagues [65] prospectively followed 190 consecutive critically ill patients with ICU length of stay longer than 7 days who were admitted to their institution over a 9-month period. Forty of the 190 patients developed CIPNM, which was confirmed by electromyography. Patients with CIPNM had a longer duration of MV (32.88 ± 22.2 days versus 14.4 ± 9 days; $P < 0.05$) than those without CIPNM. Episodes of prolonged hypocalcemia were common, especially among patients with septic shock. Logistic regression analysis showed that hypocalcemia, hypercalcemia and septic shock were independently associated with the development of CIPNM. The severity of hypocalcemia, however, did not correlate with that of CIPNM. The proposed mechanism by which hypocalcemia could lead to CIPNM involves elevated intracellular calcium concentration interfering with proteolysis of myosin thick filament. Finally, whether hypocalcemia is a cause or byproduct of severe illness during which CIPNM is more likely to occur remains unclear, and more studies are needed to prove a cause-effect relationship.

To evaluate weakness in critically ill patients, clinicians and researchers use the Medical Research Council (MRC) sum score, which is the average MRC strength score combined for 12 specified muscle groups [66]. The feasibility and reliability of this score was tested in patients with GBS, and in outpatient survivors of critical illness. A recent study suggested that performing manual strength testing for the MRC sum score is not feasible in a large number of patients in the ICU [67]. This is most often related to impaired attention and comprehension. In addition, albeit the sample size was small (n = 30) and patients developing weakness were few, the interobserver agreement for individual muscle group and the total MRC sum score was poor, especially when patients were uncooperative. This study raises an important issue, given that the MRC sum score is widely used and reported in investigations of weakness in the ICU. This leaves room for speculation about the validity of results of such studies.

Conclusion

The unrelenting interest in neuroscience research was the impetus behind many good quality investigations published in *Critical Care* in 2011. These expanded our knowledge about delirium, its risk factors and different pathophysiologic mechanisms, therapy for vasospasm, and stroke, complications of TBI, diagnosis of meningitis, and respiratory failure in GBS. Some of these articles could be the precursor to larger trials that advance our knowledge of diseases, their treatment and outcome in the neurointensive care unit.

Abbreviations

CI, confidence interval; CIPNM, critical illness polyneuropathy and myopathy; CSF, cerebrospinal fluid; EEG, electroencephalogram; EPC, endothelial progenitor cell; EPO, erythropoietin; GBS, Guillain-Barre syndrome; GCS, Glasgow Coma Score; GFAP, glial fibrillary acidic protein; GOS, Glasgow Outcome Score; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IL, interleukin; IVIg, intravenous immunoglobulin; MRC, medical research council; MV, mechanical ventilation; OR, odds ratio; PE, plasma exchange; SAH, subarachnoid hemorrhage; ScO_2, cerebral oxygen saturation; SDD, selective decontamination of the digestive tract; sICAM, soluble intercellular cell adhesion molecule; SSEP, somatosensory evoked potentials; sVCAM, soluble vascular cell adhesion molecule; TBI, traumatic brain injury; TCD, transcranial Doppler; TH, therapeutic hypothermia; UCH-L1, ubiquitin C-terminal hydrolase-L1 neuronal protein; VSP, vasospasm; WFNS, World Federation of Neurological Surgeons.

Competing interests

The authors declare that they have no competing interests.

Published: 10 December 2012

References

1. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS: **Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.** *JAMA* 2004, **291:**1753-1762.
2. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, Truman B, Dittus R, Bernard R, Inouye SK: **The impact of delirium in the intensive care unit on hospital length of stay.** *Intensive Care Med* 2001, **27:**1892-1900.
3. McGrane S, Girard TD, Thompson JL, Shintani AK, Woodworth A, Ely EW, Pandharipande PP: **Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients.** *Crit Care* 2011, **15:**R78.

4. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L: **Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction.** *Crit Care* 2004, **8:**R234-242.
5. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW: **Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial.** *JAMA* 2007, **298:**2644-2653.
6. van den Boogaard M, Kox M, Quinn KL, van Achterberg T, van der Hoeven JG, Schoonhoven L, Pickkers P: **Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients.** *Crit Care* 2011, **15:**R297.
7. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger KU: **Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial.** *Crit Care* 2011, **15:**R218.
8. Heringlake M, Garbers C, Kabler JH, Anderson I, Heinze H, Schon J, Berger KU, Dibbelt L, Sievers HH, Hanke T: **Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery.** *Anesthesiology* 2011, **114:**58-69.
9. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E: **Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study.** *Crit Care Med* 2010, **38:**419-427.
10. Devlin JW, Skrobik Y, Riker RR, Hinderleider E, Roberts RJ, Fong JJ, Ruthazer R, Hill NS, Garpestad E: **Impact of quetiapine on resolution of individual delirium symptoms in critically ill patients with delirium: a post-hoc analysis of a double-blind, randomized, placebo-controlled study.** *Crit Care* 2011, **15:**R215.
11. Wan RY, Kasliwal M, McKenzie CA, Barrett NA: **Quetiapine in refractory hyperactive and mixed intensive care delirium: a case series.** *Crit Care* 2011, **15:**R159.
12. **Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.** *N Engl J Med* 2002, **346:**549-556.
13. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K: **Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.** *N Engl J Med* 2002, **346:**557-563.
14. Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, Mayberg MR, Furlan AJ: **Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke.** *Stroke* 2001, **32:**1847-1854.
15. Ly HQ, Denault A, Dupuis J, Vadeboncoeur A, Harel F, Arsenault A, Gibson CM, Bonan R: **A pilot study: the Noninvasive Surface Cooling Thermoregulatory System for Mild Hypothermia Induction in Acute Myocardial Infarction (the NICAMI Study).** *Am Heart J* 2005, **150:**933.
16. Steiner T, Friede T, Aschoff A, Schellinger PD, Schwab S, Hacke W: **Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery.** *Stroke* 2001, **32:**2833-2835.
17. Testori C, Sterz F, Behringer W, Spiel A, Firbas C, Jilma B: **Surface cooling for induction of mild hypothermia in conscious healthy volunteers - a feasibility trial.** *Crit Care* 2011, **15:**R248.
18. Kamps M, Bisschops LA, van der Hoeven JG, Hoedemaekers CW: **Hypothermia does not increase the risk of infection: a case control study.** *Crit Care* 2011, **15:**R48.
19. Diestel A, Roessler J, Berger F, Schmitt KR: **Hypothermia downregulates inflammation but enhances IL-6 secretion by stimulated endothelial cells.** *Cryobiology* 2008, **57:**216-222.
20. Ishikawa K, Tanaka H, Shiozaki T, Takaoka M, Ogura H, Kishi M, Shimazu T, Sugimoto H: **Characteristics of infection and leukocyte count in severely head-injured patients treated with mild hypothermia.** *J Trauma* 2000, **49:**912-922.
21. Tsai NW, Lin TK, Chang WN, Jan CR, Huang CR, Chen SD, Cheng KY, Chiang YF, Wang HC, Yang TM, Lin YJ, Lin WC, Chang HW, Lee LH, Lu CH: **Statin pre-treatment is associated with lower platelet activity and favorable outcome in patients with acute non-cardio-embolic ischemic stroke.** *Crit Care* 2011, **15:**R163.
22. Marquardt L, Ruf A, Mansmann U, Winter R, Schuler M, Buggle F, Mayer H, Grau AJ: **Course of platelet activation markers after ischemic stroke.** *Stroke* 2002, **33:**2570-2574.
23. Yip HK, Tsai TH, Lin HS, Chen SF, Sun CK, Leu S, Yuen CM, Tan TY, Lan MY, Liou CW, Lu CH, Chang WN: **Effect of erythropoietin on level of circulating endothelial progenitor cells and outcome in patients after acute ischemic stroke.** *Crit Care* 2011, **15:**R40.
24. Yip HK, Chang LT, Chang WN, Lu CH, Liou CW, Lan MY, Liu JS, Youssef AA, Chang HW: **Level and value of circulating endothelial progenitor cells in patients after acute ischemic stroke.** *Stroke* 2008, **39:**69-74.
25. Cannella B, Cross AH, Raine CS: **Upregulation and coexpression of adhesion molecules correlate with relapsing autoimmune demyelination in the central nervous system.** *J Exp Med* 1990, **172:**1521-1524.
26. Wang HC, Lin WC, Lin YJ, Rau CS, Lee TH, Chang WN, Tsai NW, Cheng BC, Kung CT, Lu CH: **The association between serum adhesion molecules and outcome in acute spontaneous intracerebral hemorrhage.** *Crit Care* 2011, **15:**R284.
27. Johnston SC, Selvin S, Gress DR: **The burden, trends, and demographics of mortality from subarachnoid hemorrhage.** *Neurology* 1998, **50:**1413-1418.
28. Diringer MN, Bleck TP, Claude Hemphill J 3rd, Menon D, Shutter L, Vespa P, Bruder N, Connolly ES Jr, Citerio G, Gress D, Hänggi D, Hoh BL, Lanzino G, Le Roux P, Rabinstein A, Schmutzhard E, Stocchetti N, Suarez JI, Treggiari M, Tseng MY, Vergouwen MD, Wolf S, Zipfel G; Neurocritical Care Society: **Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference.** *Neurocrit Care* 2011, **15:**211-240.
29. Wong GK, Boet R, Poon WS, Chan MT, Gin T, Ng SC, Zee BC: **Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage: an updated systemic review and meta-analysis.** *Crit Care* 2011, **15:**R52.
30. Keyrouz SG, Diringer MN: **Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage.** *Crit Care* 2007, **11:**220.
31. Veyna RS, Seyfried D, Burke DG, Zimmerman C, Mlynarek M, Nichols V, Marrocco A, Thomas AJ, Mitsias PD, Malik GM: **Magnesium sulfate therapy after aneurysmal subarachnoid hemorrhage.** *J Neurosurg* 2002, **96:**510-514.
32. Wong GK, Boet R, Poon WS, Chan MT: **Trial design in "magnesium sulphate in aneurysmal subarachnoid hemorrhage: a randomized controlled trial".** *Stroke* 2005, **36:**2530-2531; author reply 2531-2532.
33. Wong GK, Poon WS, Chan MT, Boet R, Gin T, Ng SC, Zee BC: **Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial.** *Stroke* 2010, **41:**921-926.
34. Westermaier T, Stetter C, Vince GH, Pham M, Tejon JP, Eriskat J, Kunze E, Matthies C, Ernestus RI, Solymosi L, Roosen K: **Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: a randomized, placebo-controlled, clinical study.** *Crit Care Med* 2010, **38:**1284-1290.
35. **Guidelines for intensive care unit design. Guidelines/Practice Parameters Committee of the American College of Critical Care Medicine, Society of Critical Care Medicine.** *Crit Care Med* 1995, **23:**582-588.
36. Wunsch H, Gershengorn H, Mayer SA, Claassen J: **The effect of window rooms on critically ill patients with subarachnoid hemorrhage admitted to intensive care.** *Crit Care* 2011, **15:**R81.
37. Zhu XD, Chen JS, Zhou F, Liu QC, Chen G, Zhang JM: **Detection of copeptin in peripheral blood of patients with aneurysmal subarachnoid hemorrhage.** *Crit Care* 2011, **15:**R288.
38. Katan M, Fluri F, Morgenthaler NG, Schuetz P, Zweifel C, Bingisser R, Müller K, Meckel S, Gass A, Kappos L, Steck AJ, Engelter ST, Müller B, Christ-Crain M: **Copeptin: a novel, independent prognostic marker in patients with ischemic stroke.** *Ann Neurol* 2009, **66:**799-808.
39. Urwyler SA, Schuetz P, Fluri F, Morgenthaler NG, Zweifel C, Bergmann A, Bingisser R, Kappos L, Steck A, Engelter S, Müller B, Christ-Crain M, Katan M: **Prognostic value of copeptin: one-year outcome in patients with acute stroke.** *Stroke* 2010, **41:**1564-1567.
40. Katan M, Christ-Crain M: **The stress hormone copeptin: a new prognostic biomarker in acute illness.** *Swiss Med Weekly* 2010, **140:**w13101.
41. Zweifel C, Katan M, Schuetz P, Siegemund M, Morgenthaler NG, Merlo A, Mueller B, Christ-Crain M: **Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage.** *BMC Neurol* 2010, **10:**34.
42. Dong XQ, Huang M, Yang SB, Yu WH, Zhang ZY: **Copeptin is associated with mortality in patients with traumatic brain injury.** *J Trauma* 2011, **71:**1194-1198.
43. Dong XQ, Huang M, Yu WH, Zhang ZY, Zhu Q, Che ZH, Du Q, Wang H: **Change in plasma copeptin level after acute spontaneous basal ganglia hemorrhage.** *Peptides* 2011, **32:**253-257.

44. Chhor V, Le Manach Y, Clarencon F, Nouet A, Daban JL, Abdennour L, Puybasset L, Lescot T: **Admission risk factors for cerebral vasospasm in ruptured brain arteriovenous malformations: an observational study.** *Crit Care* 2011, **15:**R190.
45. Bosco E, Marton E, Feletti A, Scarpa B, Longatti P, Zanatta P, Giorgi E, Sorbara C: **Dynamic monitors of brain function: a new target in neurointensive care unit.** *Crit Care* 2011, **15:**R170.
46. Klein M, Koedel U, Pfefferkorn T, Zeller G, Woehrl B, Pfister HW: **Arterial cerebrovascular complications in 94 adults with acute bacterial meningitis.** *Crit Care* 2011, **15:**R281.
47. Viallon A, Desseigne N, Marjollet O, Birynczyk A, Belin M, Guyomarch S, Borg J, Pozetto B, Bertrand JC, Zeni F: **Meningitis in adult patients with a negative direct cerebrospinal fluid examination: value of cytochemical markers for differential diagnosis.** *Crit Care* 2011, **15:**R136.
48. Spanos A, Harrell FE Jr, Durack DT: **Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations.** *JAMA* 1989, **262:**2700-2707.
49. Hoen B, Viel JF, Paquot C, Gerard A, Canton P: **Multivariate approach to differential diagnosis of acute meningitis.** *Eur J Clin Microbiol Infect Dis* 1995, **14:**267-274.
50. Viallon A, Zeni F, Lambert C, Pozzetto B, Tardy B, Venet C, Bertrand JC: **High sensitivity and specificity of serum procalcitonin levels in adults with bacterial meningitis.** *Clin Infect Dis* 1999, **28:**1313-1316.
51. Greuters S, van den Berg A, Franschman G, Viersen VA, Beishuizen A, Peerdeman SM, Boer C: **Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury.** *Crit Care* 2011, **15:**R2.
52. Roquilly A, Mahe PJ, Latte DD, Loutrel O, Champin P, Di Falco C, Courbe A, Buffenoir K, Hamel O, Lejus C, Sebille V, Asehnoune K: **Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study.** *Crit Care* 2011, **15:**R260.
53. Marko NF: **Hyperosmolar therapy for intracranial hypertension: time to dispel antiquated myths.** *Am J Respir Crit Care Med* 2012, **185:**467-468.
54. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, Kossmann T, Ponsford J, Seppelt I, Reilly P, Wolfe R; DECRA Trial Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: **Decompressive craniectomy in diffuse traumatic brain injury.** *N Engl J Med* 2011, **364:**1493-1502.
55. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW: **Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors.** *Neurosurgery* 2005, **57:**1173-1182; discussion 1173-1182.
56. Mondello S, Papa L, Buki A, Bullock MR, Czeiter E, Tortella FC, Wang KK, Hayes RL: **Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study.** *Crit Care* 2011, **15:**R156.
57. El-Bayoumi MA, El-Refaey AM, Abdelkader AM, El-Assmy MM, Alwakeel AA, El-Tahan HM: **Comparison of intravenous immunoglobulin and plasma exchange in treatment of mechanically ventilated children with Guillain Barre syndrome: a randomized study.** *Crit Care* 2011, **15:**R164.
58. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA: **Immunotherapy for Guillain-Barre syndrome: a systematic review.** *Brain* 2007, **130:**2245-2257.
59. van der Meche FG, Schmitz PI: **A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group.** *N Engl J Med* 1992, **326:**1123-1129.
60. **Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange/ Sandoglobulin Guillain-Barre Syndrome Trial Group.** *Lancet* 1997, **349:**225-230.
61. Fourrier F, Robriquet L, Hurtevent JF, Spagnolo S: **A simple functional marker to predict the need for prolonged mechanical ventilation in patients with Guillain-Barre syndrome.** *Crit Care* 2011, **15:**R65.
62. de Letter MA, Schmitz PI, Visser LH, Verheul FA, Schellens RL, Op de Coul DA, van der Meche FG: **Risk factors for the development of polyneuropathy and myopathy in critically ill patients.** *Crit Care Med* 2001, **29:**2281-2286.
63. Weber-Carstens S, Deja M, Koch S, Spranger J, Bubser F, Wernecke KD, Spies CD, Spuler S, Keh D: **Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study.** *Crit Care* 2010, **14:**R119.
64. Zink W, Kaess M, Hofer S, Plachky J, Zausig YA, Sinner B, Weigand MA, Fink RH, Graf BM: **Alterations in intracellular Ca2+-homeostasis of skeletal muscle fibers during sepsis.** *Crit Care Med* 2008, **36:**1559-1563.
65. Anastasopoulos D, Kefaliakos A, Michalopoulos A: **Is plasma calcium concentration implicated in the development of critical illness polyneuropathy and myopathy?** *Crit Care* 2011, **15:**R247.
66. Kleyweg RP, van der Meche FG, Schmitz PI: **Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome.** *Muscle Nerve* 1991, **14:**1103-1109.
67. Hough CL, Lieu BK, Caldwell ES: **Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement.** *Crit Care* 2011, **15:**R43.

doi:10.1186/cc11825
Cite this article as: Keyrouz SG, Diringer MN: **Year in review 2011: *Critical Care* – neurocritical care.** *Critical Care* 2012, **16:**245.