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## Year in review in Intensive Care Medicine 2014: I. Cardiac dysfunction and cardiac arrest, ultrasound, neurocritical care, ICU- acquired weakness, nutrition, acute kidney injury, and miscellaneous

Received: 12 January 2015  
Accepted: 12 January 2015  
Published online: 30 January 2015  
© Springer-Verlag Berlin Heidelberg and  
ESICM 2015

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*Intensive Care Medicine* is changing. New types of papers, such as “What’s New in Intensive Care?”, “Understanding the Disease” and “My Paper 20 Years Later”, form a stable proportion of the articles published in the 2014 issues. This diversification has been received with an extraordinary enthusiasm and appreciation by the worldwide readership, as evidenced by the massive number of hits and downloads. In this first of three 2014 “Year in Review” articles, we cover those papers published in *Intensive Care Medicine* during the past year which focus on cardiac arrest, ultrasonography in critically ill patients, neurocritical care, ICU-acquired weakness, nutrition, acute kidney injury, as well as a number of miscellaneous topics.

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### Cardiac dysfunction in the intensive care unit

Two articles falling in the category “My paper 20 Years Later” highlighted two timeless cardiovascular topics, namely, the  $VO_2/DO_2$  relationship and weaning-induced cardiac dysfunction.

In the first of these articles, Vincent and De Backer [1] appraised a paper [2] they had published in 2002 assessing the presence of  $VO_2/DO_2$  dependency using a dobutamine test. In the 2014 article, the authors critically re-evaluated the  $VO_2/DO_2$  relationship. Under normal conditions, oxygen uptake ( $VO_2$ ) is independent of oxygen delivery ( $DO_2$ ) because  $O_2$  extraction rapidly adapts to changes in  $DO_2$ . However,  $VO_2$  can become  $DO_2$  dependent in acute circulatory failure. The  $VO_2/DO_2$  relationship is thus a major parameter in guiding therapy of acute circulatory failure at the bedside, even though its application in past years may now be viewed as rather too simplistic given present-day knowledge. Vincent and De Backer [1] summarize our current understanding of the  $VO_2/DO_2$  relationship in critically ill patients in simple take-home messages. First, abnormal global  $VO_2/DO_2$  dependency does not exist in stable, critically ill patients, including those with sepsis or acute respiratory distress syndrome (ARDS). Secondly, abnormal global  $VO_2/DO_2$  dependency does exist in severe cases of circulatory shock, when blood flow is significantly reduced, and it may exist globally in patients with septic shock and regionally in patients with severe sepsis. Thirdly, due to microcirculatory alterations, global determinations of  $VO_2/DO_2$  are unfortunately insufficiently precise/sensitive to guide therapy effectively, and regional measurements cannot be obtained routinely in critically ill patients. Lastly, the study of the time-course of blood lactate levels may represent a surrogate for the evaluation of cellular oxygen deficit.

In the second cardiovascular review highlighted here, Teboul [3] evaluated the impact of an article published in 1988 [4] that introduced the concept of weaning-induced cardiac dysfunction. Since publication of the latter article, weaning-induced cardiac dysfunction has been realized as an established cause of weaning failure, and relevant clinical research studies have made major contributions towards improving its diagnosis. Concepts have evolved greatly over the last 25 years, and present-day ICU physicians are well aware that weaning failure may be partially or completely due to an acute onset of cardiogenic pulmonary edema. Efforts should be made not only to accurately diagnose cardiogenic pulmonary edema but also identify the mechanisms responsible for its development during weaning. Ongoing and future technological progress in ultrasonography and biomarker research will certainly help identify this condition.

On the educational side, Perel and colleagues [5] contributed a very interesting article to “My Paper 20 Years later” in which they describe the evolution of the concept of respiratory variations in arterial pressure during mechanical ventilation, covering the period from the publication of their 1987 landmark paper until present day. This comprehensive review may help readers to understand the physiology of this phenomenon, specifically in terms of the clinical applications and limitations of  $\Delta Down$  [ $\Delta$ down; decrease in the systolic blood pressure (SBP)] and  $\Delta Up$  ( $\Delta$ up; increase in the SBP), the two main components of respiratory variations in arterial pressure. These authors also note that decisions regarding hemodynamic management should be based on the integration of parameters of various sources and not on any single parameter, taking into consideration the entire clinical and physiological picture.

In a “What’s New in Intensive Care?” paper, Dalabih and colleagues discuss the management of acute right ventricular decompensation of chronic pulmonary hypertension [6] in which readers are reminded that reducing or limiting right ventricular afterload is the key to good clinical management, regardless of the etiology. The paper includes a well-designed figure summarizing the challenges and the recommendations of good clinical management of this entity, including some which concern mechanical ventilation strategies.

For the entire period of recorded human history, the world has never been globally as aged as today. It is therefore not surprising that the proportion of elderly patients admitted to the ICU is increasing, even in circulatory shock. The usefulness of ICU admission in the aged population is a hot topic worldwide. Mortality rates are known to increase with age, but the impact of age on outcomes after circulatory shock has not been well defined. Biston et al. [7] explored this topic, performing a

secondary analysis of data from a large randomized trial that compared the effects of dopamine and norepinephrine on outcome in the ICU. Mortality rates were higher in elderly (75–84 years) and very elderly ( $\geq 85$  years) patients at 28 days, at hospital discharge and after 6 and 12 months of follow-up. Most very elderly patients were dead at 6 (92 %) and 12 months (97 %). Mortality rates increased with age in all types of shock. Using multivariable analysis, the risk of death was higher in very elderly patients as compared to patients aged  $< 75$  years. In this analysis, ageing is independently associated with higher mortality rates in patients with circulatory failure, whatever the etiology. By 1 year after admission, most patients aged  $> 85$  years had died.

Assessment of the central venous-to-arterial carbon dioxide difference [ $P(v-a)CO_2$ ] seems to be helpful in assessing the adequacy of the cardiac index (CI) to oxygen demand when incremental doses of dobutamine are infused into patients with stable chronic heart failure. Whether such phenomena can be observed in stable septic shock patients is presently not known. Moreover, it has been demonstrated that  $P[v-a]CO_2$  can be substituted by the central venous-to-arterial  $CO_2$  difference ( $\Delta PCO_2$ ) in critically ill patients. Mallat et al. [8] tried to solve this conundrum by assessing the behavior of  $\Delta PCO_2$ , an index of the  $CO_2$  production ( $VCO_2$ )/CI ratio, in hemodynamically stable septic shock patients, but with ongoing signs of tissue hypoperfusion, given incremental doses of dobutamine. Twenty-two hemodynamically stable septic shock patients with no signs of global tissue hypoxia, with normal blood lactate levels, were enrolled in their prospective study. Despite a dose-related increase in CI and  $DO_2$ , dobutamine infusion did not result in a dose-dependent decrease in  $\Delta PCO_2$ , and  $VO_2$  and  $VCO_2$  showed a statistically significant increase in parallel with the increased doses of dobutamine. The authors concluded that the measurement of  $\Delta PCO_2$  may be a useful tool to assess the adequacy of oxygen supply to metabolic and oxygen demand.

Schmidt et al. [9] retrospectively evaluated the impact of fluid balance (FB) on day-90 mortality in a cohort of 115 adult patients treated with extracorporeal membrane oxygenation (ECMO) for refractory heart failure and 57 patients treated with ECMO for refractory respiratory failure. Early positive FB, especially at day 3, was found to be a robust and independent predictor of 90-day mortality, regardless of the primary diagnosis, acute kidney injury (AKI) or renal replacement therapy (RRT) use. In addition, these authors confirmed that AKI during ECMO is frequent and that those patients requiring continuous RRT are at greater risk of mortality. The conclusion drawn by the authors was that prospective studies of tight FB control over the first 5 days of ECMO are warranted.

## Cardiac arrest

Hypothermia remains a hot topic in cardiac arrest (CA) management. In a 7-day profile publication, Debaty et al. [10] report a randomized multicenter study of the impact of intra-arrest therapeutic hypothermia (IATH, 34 °C) in out-of-hospital cardiac arrest (OHCA) patients. In the control group (122 patients), cooling was performed as usual, i.e. as soon as possible after hospital admission, whereas in the interventional group (123 patients) patients received an infusion of cold saline with external cooling during cardiopulmonary resuscitation (CPR). Patients were included in the study whatever the initial rhythm, even though a large proportion of patients had a non-shockable rhythm. IATH did not have any significant effect on laboratory markers of inflammation and brain damage (neuron-specific enolase at 24 h) or on outcome, even though the target temperature was achieved earlier in the interventional group. No side effect of IATH was reported.

Severe neurological impairment secondary to hypoxic-ischemic brain injury is common after resuscitation from CA, and an early identification of patients with no chance of good neurological outcome will help avoid inappropriate treatment. Such prognostication is never straightforward and is further complicated by the use of mild therapeutic hypothermia. A recent Advisory Statement from the European Resuscitation Council and the European Society of Intensive Care Medicine (ESICM) provides evidence-based, expert consensus guidance on prognostication in comatose survivors of CA [11]. Following a GRADE-based systematic review, expert consensus was achieved using web-based Delphi methodology. The quality of evidence was low or very low for almost all of the 73 studies reviewed. A careful clinical neurological examination, with adequate time allowed to exclude confounding factors, remains the foundation for prognostication of the comatose patient after CA. The most robust predictors of poor prognosis are coma in patients with absent or extensor posturing at  $\geq 72$  h after CA (whether or not treated with MTH), bilateral absence of pupillary or corneal reflexes and bilateral absence of the N20 wave of somatosensory evoked potentials. Less robust predictors include status myoclonus, elevated neuron-specific enolase (NSE) at 48–72 h, non-reactive electroencephalography (EEG) patterns after rewarming and neuroimaging evidence of diffuse post-anoxic injury. Prognostication using multiple variables is preferable but often limited by the shortage of relevant investigations and expertise. If the results of prognostic tests produce conflicting results or prognostication remains uncertain, further clinical observation and re-evaluation is recommended.

Various biomarkers have also been used to assess the severity of hypoxic brain injury and allow prognostication

after CA, but the optimal biomarker and cut-off values are uncertain and predictive abilities in the presence of MTH uncertain. The neuropeptide secretoneurin (SN) is specifically expressed in neuronal tissues and has multiple biological functions. It is upregulated by hypoxia and therefore has potential as a novel biomarker for hypoxic brain injury after CA. The prognostic value of SN was recently investigated in a prospective observational study of 134 patients admitted to an ICU after successful CPR following CA [12]. There was on average a sixfold increase in serum SN levels within the first 24 h after CPR, with significantly higher levels in patients with a poor neurological outcome compared to those with a good neurological outcome. SN predicted outcome earlier than NSE and is likely not influenced by MTH. It therefore has the potential to be a superior biomarker for early neurological prognostication after CA.

Exploring large datasets could help improve our understanding of the efficacy of various clinical interventions. Bougouin et al. [13] reported the very interesting results of a large population-based registry on sudden cardiac death in the greater Paris area, which is home to >10 % of the general French population. Of the 7,238 cases of OHCA included in the registry over a 2-year period, 15 % were related to an extracardiac etiology and 85 % (6,165) were of cardiac origin. Of these patients, only 1,332 (22 %) were ultimately admitted to hospital alive. Initial rhythm was shockable in 26 % of cases, 58 % underwent coronary angiography and almost the same proportion was treated by therapeutic hypothermia. This study demonstrates that prognosis clearly remains very poor, since only 4.5 % of the patients with OHCA of cardiac origin (7.5 % of patients who actually underwent attempted resuscitation and 21 % of patients admitted alive) were discharged alive. Factors associated with prognosis were bystander CPR and initial shockable rhythm (increased survival), age, longer response time, occurrence of cardiac arrest at home and epinephrine dose of >3 mg during resuscitation (decreased survival).

Al-Alwan et al. [14] reported the incidence and prognosis of CPR among patients already on mechanical ventilation using patient data in the Finnish medicare database between January 1994 and December 2005. Among the 471,962 patients who received in-hospital CPR during the period, 18.4 % survived. When CPR was performed in patients already ventilated, survival at hospital discharge was only 10.1 %, compared with 19.2 % in patients not already ventilated. At the 1-year follow-up, survival was 4.1 % in patients with CPR while ventilated. ICU staff and family members discussing the management of such patients should be aware of these results, which should, however, be interpreted with caution in the light of the paper discussed next.

Efendjev et al. [15] reported temporal trends in CA incidence and outcome in Finnish ICUs from 2003 to 2013 using patient data in a large nationwide ICU

database and TISS-76 (Therapeutic Intervention Scoring System 76) documentation. All patients who needed CPR while admitted to the ICU for any reason other than cardiac arrest (ICU-CA patients) were enrolled in this study. The crude incidence of ICU-CA was 29/1,000 admissions, which decreased over time. Most ICU-CAs occurred in non-operative cardiovascular patients, with the vast majority (89 %) occurring during the first 3 days in the ICU. Most patients (80 %) were ventilated. The 53.1 % in-hospital mortality decreased over the study period.

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### Ultrasonography in critically ill patients

The potential benefits from point-of-care ultrasound (US) and fair expectations about its utility in the ICU sometimes need to be reconsidered given the general paucity of the literature on the topic, mainly due to the relative novelty of many applications of US. Three articles published in *Intensive Care Medicine* last year (re)opened an interesting pro/con debate on the use of echography for the initial management of critically ill patients [16–18].

An important aspect of the clinical application(s) of each new technological development is training at the bedside. After a statement published in *Intensive Care Medicine* in 2011 [19], the same group of experts published the results of a round table [20] held in Paris in 2013 during the ESICM congress. The 2014 international statement reports detailed training standards for advanced critical care echocardiography which should form the basis of future European certification in advanced critical care echocardiography.

In a prospective single-center study, Nguyen et al. [21] determined the learning curve of 30 intensivists performing US-guided jugular central venous catheter placement after a training program which included 30 min of instruction and a 7-min-video to illustrate the procedure and the manipulation of the probe. The learning curve was evaluated using two scoring systems, with the first evaluating preparation (with sterile cover and manipulation of the probe) and the second evaluating technical skills (vessel identification, needle visualization, internal jugular puncture and guide insertion, among others). The authors also recorded the time required for the procedure. The findings demonstrated that he required skills were easily acquired after an average of six to eight procedures. Total time needed for catheter placement, from arrival of the US machine in the patient's room to dressing, was 21 min after eight procedures.

Volpicelli et al. [22] performed a single-center prospective study to determine the ability of lung ultrasonography (LUS) to approximately quantify pneumothorax volume, using the projection of the lung point on the chest; the results were compared with

measurements made using computed tomography (CT) scan (59 patients) and/or chest X-ray (94 patients). Trained operators performed LUS. A total of 124 spontaneously breathing patients with previously diagnosed pneumothorax were consecutively enrolled in the study. The authors reported that projection of the lung point on the chest appears to be a useful predictor of pneumothorax volume and that LUS can reliably classify the pneumothorax as small or large. Following publication of this paper, however, interesting items of correspondence were published in *Intensive Care Medicine* which shed light on the potential limitations of this approach [23, 24].

In a single-center prospective study, Begot et al. [25] assessed the ability of resident novices in LUS to identify and quantify unoculated pleural effusion after a limited training program (1 h of instruction, 30 min of illustrative cases and 90 min of tutored hands-on focus on the identification and quantification of pleural effusions) and compared this ability with that of intensivists experienced in the field. Quantification was based on the maximal interpleural distance. Twelve residents examined 147 patients with suspected pleural effusion, leading to a mean of  $15 \pm 9$  evaluations per resident. Agreement between resident novices and experienced intensivists was considered as good to excellent for diagnosis in both lungs. Agreement was also excellent for interpleural space measurement.

Finally, based on the results of a single-center prospective study with 45 blunt trauma patients, Leblanc et al. [26] reported that the extent of lung contusion quantified by trained operators using a predefined LUS score is a good predictor of the occurrence of ARDS using the Berlin definition [27] in the following 3 days. The extent of lung contusion on LUS was also well correlated with CT scan measurements. In addition, the authors confirmed the performance of LUS for the diagnosis of other injuries in this context, such as pneumothorax and hemothorax.

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### Acute neurological illness in the ICU

The pathophysiology and management of several acute neurological disorders have been reviewed in *Intensive Care Medicine* in 2014. MacDonald et al. [28] recently reviewed the pathophysiology of aneurysmal subarachnoid hemorrhage (SAH). This review, which appears in the “Understanding the Disease” series highlights how early brain injury impacts on mortality. This injury is related to the immediate effects of aneurysm rupture, and the subsequent cellular, metabolic and inflammatory consequences that result in impaired neurovascular coupling, disruption of the blood–brain barrier, cerebral ischemia and cerebral edema. New insights into the

pathogenesis of delayed cerebral ischemia and the importance of early identification and effective treatment to minimize poor outcome are discussed. The importance of SAH-related systemic inflammatory response and cardiovascular and respiratory complications are also highlighted.

Increasing numbers of patients with acute ischemic stroke (AIS) are being admitted to the ICU for aggressive physiological optimization and management of post-stroke complications, including those related to thrombolytic therapy, as well as patients receiving recently released treatments. Although there are detailed European and US Guidance for the management of AIS, very little of this focuses on ICU management. A recent, structured narrative review provides key recommendations for the critical care management of AIS [29]. In addition to the four interventions supported by class I evidence (care by a multidisciplinary team in a stroke unit, intravenous tissue plasminogen activator within 4.5 h of thrombotic stroke onset, aspirin within 48 h of stroke onset and decompressive craniectomy for malignant middle cerebral artery infarction), the authors provide their own recommendations, based on the best available evidence, on airway and ventilation management, hemodynamic and fluid optimization, fever and glycemic control, management of anticoagulation, antiplatelet and thromboprophylaxis therapy and control of seizures.

Status epilepticus (SE) is the second most common life-threatening neurological emergency (after AIS) and carries a high risk of mortality and morbidity. In an article entitled “What’s new in status epilepticus”, Rossetti and Bleck [30] review contemporary management and novel therapies of SE. The crucial importance of rapid seizure control is emphasized, and the authors’ recommendations for three sequential—and escalating—lines of treatment are discussed in detail. The role of newer third-line therapies, such as ketamine, is debated.

Determining the line between life and death, whether diagnosed by cardiorespiratory or neurological criteria, is crucial. Indeed, death is pronounced not only because further treatment is inappropriate, but also because society requires confirmation of this event with certainty. Advances in medicine and technology have made it possible to support or replace failing organs in many circumstances, challenging commonly held notions of the biology of death and the dying process. Although >40 years have past since the concept of brain death was introduced into clinical practice, many of the controversies that surround it have not been settled, particularly with regard to the inevitable association between brain death and organ donation. Truog and Miller [31] debate these issues within the context of organ donation and the “dead donor rule”. It has been argued that brain death does not cohere with a biological or scientific understanding of death, although there is an intuitive

plausibility and scientific support that patients who are irreversibly comatose and apneic are dead.

There have been increasing calls for international standardization of the determination of death diagnosed by both cardiorespiratory and neurological criteria, and for agreement on precise terminology to improve clarity in discussions and debate about death. A recent report summarizes the first phase in the development of such international standards [32]. A single operational definition of death based on clear biomedical standards—rather than anatomically based terms such as “cardiac” or “brain” death—has been proposed. The Working Party recommended that death be defined as “the permanent loss of the capacity for consciousness and all brain stem functions as a consequence of permanent cessation of the circulation or catastrophic brain injury”. This recommendation fulfills the requirement for determining death using clinical criteria based on direct observation or examination of the patient after specified preconditions have been fulfilled and reinforced the exclusion of confounding factors. The next phase of this work, to include broader representation of international stakeholders, will develop clinical practice guidelines for the determination of death.

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## Neuromonitoring

Some patients are admitted to an ICU for the management of an acute neurological insult, such as traumatic, hemorrhagic or ischemic brain injury, whereas many others develop brain dysfunction as a consequence of their underlying critical illness. Monitoring the brain and neurological function, therefore, is of major relevance in the critical care setting. Fundamental to neurological monitoring is serial clinical assessment of neurological status. A pragmatic approach to the neurological examination of critically ill patients was recently published by an Expert Panel of the ESICM [33]. This Consensus Statement highlights the importance of conducting a full clinical neurological examination in all ICU patients, stressing that this should include the assessment of consciousness and cognition and the examination of brain stem and motor function. Daily sedation holds to allow the assessment of neurological function are recommended in all patients except those with reduced intracranial compliance. The Guidance highlights the importance of the Glasgow coma score (GCS) as a standardized, internationally recognized method for evaluating a patient’s global neurological status. In association with the identification and documentation of localizing signs, such as pupil responses and limb weaknesses, the GCS remains the mainstay of clinical assessment 40 years since its first description. The main limitations of the GCS are that

verbal responses are not assessable in intubated patients, and brainstem function is not directly considered. The Guidance recommends that four scores, which have been designed and validated to overcome these issues, can be used to differentiate yet further patients with a GCS of 3, although there is limited evidence that this approach has greater inter-rater reliability or prognostic value than the GCS alone.

Clinical assessment is limited in sedated patients and those with decreased conscious level, and various devices are available for neurological monitoring in such circumstances. Techniques which provide global or regional monitoring of cerebral perfusion, oxygenation and metabolic status are used in brain-injured patients to provide early warning of impending cerebral hypoxia/ischemia and metabolic distress. In 2014 the Neurocritical Care Society and ESICM published comprehensive and consensus-based Expert Guidance on multimodality neuromonitoring [34]. A systematic literature review of specific physiological processes that are relevant to the management of critically ill neurological patients was undertaken and used to formulate recommendations for individual monitoring techniques. Multimodal monitoring only has value when monitored outputs of brain physiology are interpreted by skilled clinicians and used to direct individualized therapeutic options.

Many neuromonitors are invasive and available only in specialist neurocritical care units. Interest in the development of non-invasive techniques that can be used more widely has been growing, and non-invasive assessment of intracranial pressure (ICP) is one such technique. Sekhon et al. [35] investigated the relationship between the measurement of optic nerve sheath diameter (ONSD) by CT and the directly measured ICP in a retrospective cohort study of 57 patients with severe traumatic brain injury (TBI). ONSD was highly discriminatory for the prediction of intracranial hypertension (ICP  $\geq 20$  vs.  $<20$  mmHg), and more powerfully predictive of increased ICP than any other CT finding.

The value of EEG in the diagnosis and management of clinical and non-convulsive seizures (NCSz) in patients with primary neurological conditions is well established, but it is now clear that all critically ill patients are at risk for the development of NCSz. In a retrospective study, Kurtz et al. [36] reviewed 154 surgical ICU patients without primary neurological disease who underwent continuous EEG monitoring because of altered mental state. NCSz were identified in 16 % of these patients and periodic epileptiform discharges in 29 %. One-third of the patients with NCSz had non-convulsive status epilepticus (NCSE), and all of these cases were septic. NCSz were independently associated with poor outcome. There is clearly an urgent need for large prospective studies to determine not only the exact prevalence and clinical impact of NCSz in critical care, but also to investigate whether treatment will improve outcome. In the

meantime, it is recommended that EEG monitoring be undertaken to exclude NCSz and NCSE in any patient with an unexplained or persisting altered consciousness.

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### ICU-acquired weakness

Critical illness polyneuropathy and myopathy (CIPNM) are neuromuscular disorders that develop after admission to an ICU and result in ICU-acquired weakness (ICUAW), with adverse effects on both short- and long-term outcomes, including delayed weaning from mechanical ventilation, increased ICU and hospital length of stay and increased mortality and long-term disability. The mechanisms of ICUAW are multiple and not yet fully elucidated, but a disturbed balance of myosin heavy chain (MyHC) has been implicated in the pathogenesis of the myopathy. To investigate this hypothesis further, Wollersheim et al. [37] measured MyHC synthesis and degradation in skeletal muscle in 29 critically ill patients at high risk of developing ICUAW. Open biopsy of the vastus lateralis muscle for analysis of mRNA, protein content and cellular ultrastructure by electron microscopy was performed at a median time of 5 days after ICU admission. A second biopsy was performed in the 22 patients who were still in the ICU at a median time of 15 days after admission. Time-dependent changes in myofiber architecture and MyHC synthesis and degradation were correlated with Medical Research Council (MRC)-rated muscle strength. Control biopsies were obtained from aged-matched healthy patients undergoing elective hip replacement surgery. ICU-acquired muscle wasting was characterized by early (day 5) disrupted myofiber ultrastructure and later (day 15) atrophy of slow- and fast-twitch myofibers. A decrease (compared to controls) in MyHC mRNA and protein expression was present at day 5 and persisted at day 15. This study supports the hypothesis that decreased synthesis and increased degradation of MyHC contributes to ICUAW and suggests that its pathogenesis is initiated very early after the onset of critical illness.

Although often suspected clinically, the definitive diagnosis of ICUAW relies on a structured clinical evaluation demonstrating decreased muscle strength assessed using the MRC scale, on nerve conduction studies (NCS) and on needle electromyography (EMG). Manual testing of muscle strength requires an awake, cooperative patient, and a comprehensive electrophysiological examination is both time-consuming and physically uncomfortable for awake patients. Moss and colleagues demonstrated that a simplified approach to the electrophysiological assessment of CIPNM, using a combination of unilateral peroneal (motor) and sural (sensory) NCS, has 100 % sensitivity and high specificity for the diagnosis of CIPNM [38]. These findings suggest that patients with normal peroneal and sural NCS are very unlikely to have CIPNM

and that further testing with EMG is unlikely to alter that conclusion. However, if these NCS are abnormal, the diagnosis of CIPNM should be explored further with comprehensive electrophysiological investigations. This more streamlined approach to the diagnosis of CIPNM may facilitate routine diagnostic testing and monitoring of weakness in critically ill patients.

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### Lactate and the injured brain

Lactate has previously been considered to be a harmful waste product of the cerebral anaerobic metabolism of glucose, but it is now known to have possible beneficial effects in the brain. Increased lactate after TBI may be the consequence of increased cerebral glycolysis rather than hypoxia/ischemia. Lactate can be “shuttled” from lactate-producing cells (astrocytes) to lactate-consuming cells (neurons) as an adaptive response to limit substrate reduction and maximize energy production. There is also experimental evidence that lactate is neuroprotective after acute brain injury. In a recent prospective study, multimodal brain monitoring was used to investigate the metabolic and hemodynamic effects of exogenous administration of hypertonic sodium lactate in 15 patients with severe TBI [39]. Lactate administration resulted in a statistically significant increase in cerebral microdialysis-monitored concentrations of lactate, pyruvate and glucose, with a concomitant reduction in glutamate and ICP. Taken together these data suggest that exogenous lactate can be utilized as a preferential and efficient energy source by the injured human brain, with resultant sparing of cerebral glucose.

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### Nutrition in the critically ill patient

Singer et al. [40] expressed their vision regarding nutrition in a “What’s New in Intensive Care” article. These authors pointed out the increasing body of evidence demonstrating the benefits of early enteral feeding and raised concerns regarding overfeeding and the use of predictive equations to target nutritional requirements. Hickmann et al. [41] explored changes in resting energy expenditure (REE) during sepsis and exercise, and they too described the poor accuracy of the more frequently used predictive equations, as well as demonstrating a strong correlation between measured REE and C-reactive protein levels. Thus, in their study, REE was increased in the presence of active exercise was present, while passive exercise was not associated with an increased REE. These findings are helpful since passive exercise is more often used than active exercise to prevent muscle loss in critically ill patients.

Regarding specific nutrients, Singer et al. [40] recommended that glutamine should be administered intravenously (IV glutamine) to patients requiring parenteral nutrition except if they suffer from organ failures involving liver or kidneys. They also suggested that supplemental n-3 fatty acids (10 g/day of omega-3 fatty acids) be continuously administered enterally in patients suffering from ARDS as this has been associated with improvement in the PaO<sub>2</sub>/FIO<sub>2</sub> ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) and a decrease in the length of ventilation. Nevertheless, when administered in larger doses and as a bolus, the results were not confirmed. Perez-Barcena et al. [42] studied the effects of IV glutamine in a trauma population. These authors did not find a clinical advantage to this treatment, possibly related to the fact that the dose administered did increase plasma levels above normal values in 39 % of the treated group who started with very low plasma levels at baseline. This study reinforces the hypothesis that administration of specific nutrients should be guided by adequate levels to ensure clinical efficacy. Identical conclusions were reached by Nie et al. [43] regarding the administration of eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) in critically ill patients suffering from ARDS. This meta-analysis of a mix of studies with continuous/bolus enteral administration of various doses of mainly EPA, but also DHA and/or GLA, did not show any advantage in terms of mortality or length of ventilation or ICU stay. However, improvement in the PaO<sub>2</sub>/FIO<sub>2</sub> ratio at days 4 and 7 were found, suggesting some pharmacological effects. Continuous enteral administration appeared to be superior to high-dose bolus administration.

While studies of tight glucose control in patients have failed to be reproducible on a large scale, hyperglycemia remains of concern. Deane et al. [44] observed acute hyperglycemia in 1,000 critically ill patients and found that the risk of death increased by 20 % for each increase in acute glycemia of 1 mmol/l for patients with diabetes and a glycosylated hemoglobin (HbA1C) of <7 % before admission. This association was lost in diabetics patients with HbA1C >7 % who were poorly controlled. These findings are helpful to understand some discrepancies in the current literature. Daviaud et al. [45] studied patients undergoing an OHCA and resuscitation who were admitted to a large CA center in France. Patients with a relatively higher level of blood glucose level at admission had a worse outcome, and the increase in the median blood glucose level over the first 48 h was found to be an independent predictor of poor outcome [odds ratio (OR) 0.43, 95 % confidence interval (CI) 0.24–0.78, *p* < 0.006]. The authors suggested testing a strategy combining both control of glycemia and minimization of glucose variability to improve post-resuscitation care.

Finally, the routine measurement of gastric residue volume has recently been challenged [40]. Hamada et al.

[46] discuss an innovative way of measuring the gastric residual volume using ultrasonography which they showed to be accurate when compared to CT volumetric assessment of gastric content. These authors found a good correlation in many cases and suggested that this technique could be easily used at the bedside to assess patients at risk of large gastric residuals and aspiration, as well as to evaluate how the enteral nutrition is tolerated. Krag et al. [47] attempted to find evidence for stress ulcer prophylaxis using H<sub>2</sub> blockers in 12 trials and proton-pump inhibitors (PPIs) in two studies, mostly intravenously (19 out of 20 trials included). Although no difference in ICU mortality was observed, there was a significant decrease in gastrointestinal bleeding when compared to the control. However, this finding could not be confirmed in an analysis of trials with adequate random sequence generation, allocation concealment and blinding (*n* = 1), raising questions on the quality of the studies. No difference in nosocomial pneumonia was observed. Interestingly, enteral feeding alone was not associated with an increased incidence of ventilator-associated pneumonia, suggesting that enteral feeding may be sufficient to prevent upper gastrointestinal bleeding.

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### Acute kidney injury

After 10 years in development, publication of the widely accepted Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI has resulted in standardization of the diagnosis and staging of AKI [48]. However, validation of this classification is still missing in the pediatric population. Applying the KDIGO criteria on 3,009 patients from the University of Michigan Pediatric Critical Care Database, Selewski and co-workers [49] demonstrated an incidence of AKI of 24.5 %, with the majority of patients reaching AKI stage 3. This is currently among the largest pediatric cohort investigated for this syndrome, with the patient cohort comprising newborns and children aged up to 14 years. As has already demonstrated for adult patients, these authors found that AKI stage in their pediatric patients was significantly associated with increased length of stay, requirement of mechanical ventilation and mortality (OR 3.4, 95 % CI 2.0–6.0).

Sepsis is known as the major cause of AKI in critically ill patients [50], and recent research has provided new insights into the poorly understood pathophysiology of this entity. It would appear that reduced renal blood flow or renal ischemia is not a major component of a reduced glomerular filtration rate (GFR) in sepsis. Renal inflammatory and immunologic mechanisms appear to result in tubular cell injury, most likely mediated by damage or pathogen-associated molecular patterns [pathogen-



associated molecular pattern molecules (PAMPs) and damage/danger-associated molecular pattern molecules (DAMPs)] which are filtered at the glomerulum and recognized by renal tubular cells via several receptors, such as toll-like receptor 4. The resulting overexpression of NF- $\kappa$ B and subsequent release of tumor necrosis factors and other cytokines lead to reduced sodium reabsorption, activation of tubulo-glomerular feedback and further tubular cell injury. Eventually all these factors contribute to a loss of GFR and septic AKI [51]. Furthermore, a retrospective analysis of a large international multicenter database including 4,493 patients with septic shock found the development of AKI, which occurred in roughly 73 % of these patients, did not depend on the causal pathogen [52]. Although pulmonary infections were by far the leading cause of septic shock, a multivariate analysis fully adjusted for age, comorbidities and severity of disease showed that major risk factor appears to be the site infection, with urinary tract infection carrying the highest risk of AKI (OR 2.35, 95 % CI 1.78–3.09) followed by gastrointestinal and blood stream infections (each with an average OR of 1.5).

Prevention of AKI in both sepsis and non-sepsis-associated critical illness primarily depends on avoiding additional harm to the kidney [48, 53]. A previously underestimated risk factor may be the type of fluid used during volume resuscitation. Recent large randomized trials on fluid resuscitation in patients with sepsis [54, 55] as well as in other critically ill patients [56] revealed that hydroxethylstarch (HES) carries a significant risk for AKI as well as the requirement for RRT. There even appears to be a sign of increased mortality [57, 58], which initially led the European Medicines Agency (EMA) to recommend suspension of the licensing for HES in all indications. This recommendation was subsequently partly withdrawn, to allow the use of starches in severe hemorrhage in trauma and during surgery at the discretion of the treating physician. This decision is questioned in depth by six experts of the EMA in a commentary published in “What’s New in Intensive Care?” [59], who stress that continuing the use of HES means exposing a large number of patients to significant risk with potentially detrimental consequences. This commentary is supported by a systematic review investigating tissue deposition of HES [60]. Extracting data from 37 human (total 635 patients) and 11 animal studies, the authors demonstrated a significant accumulation of HES in several tissues, most predominantly in kidneys but also in relevant amounts in liver, bone marrow and skin. Additional sites of HES deposition were lymph nodes, spleen, lung pancreas, intestine, muscle, trophoblast and placental stroma. Interestingly, reports of (sometimes long-lasting) pruritus mainly originate from studies where HES has been applied for hemodilution as treatment of acute hearing loss. HES uptake by the kidney could be observed as early as 30 min after infusion. Storage in organs was

cumulative and increased with increases in the amount of HES administered; in some cases HES accumulation was long-lasting, persisting more than 8 and 10 years in skin and kidney, respectively. Remarkably, in 15 % of patients HES storage and associated symptoms occurred already at low doses of 0.4 g/kg body weight. An accompanying editorial, however, addressed the issue of benefit versus harm in an extremely valid manner. Colloids, at least theoretically, should enable faster and more effective intravascular volume expansion than colloids, with less risk of volume overload as long as the glycocalix is not significantly damaged. Thus, in early volume resuscitation and hemodynamic instability which is not sufficiently treatable with crystalloids, colloids may be the only alternative to stabilize patients [61].

The issue of crystalloid administration also requires intense scrutiny in the light of recent experimental findings. The most frequently used crystalloid fluid is a 0.9 % sodium chloride solution (or “normal” saline). This solution is far from being physiological, and its high chloride content of 154 mmol/l has been found to induce metabolic acidosis and vasoconstriction in the kidney, reducing the GFR in healthy volunteers [62]. A recent observational, before–after study showed that switching from normal saline to more balanced solutions with chloride contents of <110 mmol/l resulted in less AKI and fewer requirements for RRT [63]. This aspect was further investigated by a retrospective analysis of nearly 110,000 patients with systemic inflammatory response syndrome (SIRS) treated with crystalloids [64]. The authors of this study looked at mortality associated with chloride administration (quantified as millimolar chloride per liter of volume administration) and found that patients receiving >500 mmol chloride had a significantly increased mortality compared those receiving 100–200 mmol chloride (>10 vs. 3.5 %, respectively). However, the effect was also dependent on the total volume administered, and no negative effects of chloride could be shown for patients receiving <1,500 ml of fluids over a 72-h period. A multivariate analysis adjusted for fluid volume and severity of disease characterized by the Acute Physiology Score showed an increased risk of mortality (OR 1.094, 95 % CI 1.062–1.127) with increasing volume adjusted for a chloride load of >105 mmol/l. An accompanying editorial [65], however, highlighted that although these studies provide a signal of possible harm by normal saline, treating physicians have to consider that the effect appears to be dose dependent and that a randomized controlled trial proving this assumption, although still absent, is ongoing and the results expected soon. Until these results are available, physicians continuing the use of normal saline may be reassured by 150 years of clinical experience in its use and the fact that more 7,000 ICU patients have received 0.9 % saline in randomized controlled trials.

The issue of volume overload was also investigated in the very specific cohort of 172 patients requiring ECMO for either refractory heart failure ( $n = 115$ ) or refractory respiratory failure ( $n = 57$ ); about 60 % were also treated with RRT. Positive fluid balance on day 3 of the ECMO treatment turned out to be the most important predictor for mortality in this vulnerable cohort. Future interventional studies with the aim to limit positive fluid balance will have to show whether modifying this risk factor really does improve outcome.

Renal recovery after AKI is a recently emerging issue with significant implications for all healthcare systems [66]. Available data indicate that between 10 and 65 % of critically patients requiring RRT who survive to discharge may remain on chronic dialysis [67], although the largest randomized trials on RRT show renal recovery rates at 60 days of between 7 and 25 % [68]. However, even those patients who experienced AKI and never required RRT and showed recovery may develop chronic kidney disease later on and potentially end up on dialysis years after discharge from hospital. This population currently remains largely undetected [69]. A major problem may be the use of estimated GFR (eGFR), which is mainly based on serum creatinine levels. eGFR appears to overestimate renal function in patients staying in the ICU for a longer time. Such overestimation was nicely demonstrated in a secondary analysis of the EPANIC trial, involving 757 patients, which showed that a reduction in creatinine production was positively correlated with the length of stay in the ICU, likely due to muscle loss [70]. In this population, the discrepancy between measured creatinine clearance and eGFR became apparent in patients staying in the ICU for  $>7$  days, was more pronounced after AKI, but was also apparent in the group who did not experience AKI. These results clearly indicate that without performing a proper creatinine clearance test,  $>50$  % of patients with reduced renal function will be missed and probably not followed up for renal function.

Hyponatremia, defined by a serum sodium concentration of  $<135$  mmol/l, is present in 15–20 % of emergency admissions to hospital and occurs in up to 20 % of critically ill patients. Symptomatology may vary from subtle to life threatening. Despite this, the management of patients remains problematic. Against this background, the ESICM, the European Society of Endocrinology (ESE) and the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA), represented by its new guidance body, the European Renal Best Practice (ERBP), have developed a Clinical Practice Guideline on the diagnostic approach and treatment of hyponatremia as a joint venture of three societies which represent specialists with a natural interest in hyponatremia. A major focus was placed on the treatment of acute hyponatremia, a life-threatening condition characterized by coma, seizure, vomiting or severe

cardio-respiratory stress that requires urgent therapy by the administration of hypertonic (3 %) saline [71].

Finally, the way in which intensive care medicine is practiced is heavily influenced by the working circumstances of the critical care specialist and even more by the region in which the ICU is found. Joynt and Tat [72] present a quick overview of the most important ten diseases a critical care specialist has to know when practicing in Hong Kong. Of course severe acute respiratory syndrome (SARS) is on top of the list but the effects of traditional Chinese medicine toxicity should not be underestimated.

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## Miscellaneous

Taccone et al. published a “What’s New in Intensive Care?” paper on fever control in the ICU [73] in which they reminded readers of the high prevalence of elevated body temperature in critically ill patients and reviewed and discussed the question of whether fever should actually be treated. On the one hand, for patients with infection, there is a relationship between early fever and decreased mortality, suggesting a potential protective effect of fever. On the other hand, this effect seems not to persist at high temperature and in other conditions, such as in acute lung injury where fever appears to be deleterious. However, evidence-based medical data for or against treating fever are currently lacking, and results have even been contradictory. More studies are expected: the Heat study in critically ill patients with known or suspected infection, the FACE II study in unselected critically ill patients with fever and the CASS study in septic shock patients.

Evaluation of the clinical result of practice in the ICU is very important. In a large observational cohort study, Galland et al. [74] evaluated the determinants of long- and short-term survival in critical illness. A total of 33,324 initial ICU admissions were analyzed, showing mortality rates within 30 and 90 days of 15.9 and 19.5 %, respectively. The authors observed two phases of survival related to critical illness: (1) short-term mortality, which was mainly determined by the acute illness, but its effect decayed relatively rapidly; (2) mortality beyond 3 months, among those who survived to that point, was mainly determined by age and comorbidity. Recognition of these findings is relevant to discussions with patients and surrogates about achievable goals of care.

In a retrospective cohort study, Gantner et al. [75] reported that after-hours discharge remains an important independent predictor of hospital mortality and readmission to the ICU. These authors used the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) for patients admitted to

Australian and New Zealand ICUs between January 2005 and December 2012. Among the 710,535 patients analyzed, 15.4 % were discharged after hours (6 pm–6 am), and these patients had a higher mortality than the others (6.4 vs. 3.6 %, respectively). An interesting editorial by Guidet and Bion [76], entitled “Night thoughts”, accompanies the paper.

Ghassemi et al. [77] from the Massachusetts Institute of Technology proposed an original approach to optimize unfractionated heparin (UFH) dosing, after having emphasized that activated partial thromboplastin time (aPTT) at 6 h after UFH infusion is frequently in the sub- or supra-therapeutic range based on the usual guidelines. Using the Multi-parameter Intelligent Monitoring in Intensive Care II (MIMIC II) database, they analyzed 1,511 patients admitted to the ICU at the Beth Israel Deaconess Medical Center who received heparin during their ICU stay. These authors reported that race, ICU type, gender, heparin dose, age and Sequential Organ Failure Assessment score were associated with such inappropriate aPTT. Using a complex statistical analysis, they finally proposed a model, which has yet to be

formally validated, to predict the optimal dose of UFH needed to achieve the target aPTT.

Data analysis and presentation are the foundations of scientific research and dissemination, and appropriate statistical methods are crucial. *Intensive Care Medicine* frequently involves statistical reviewers at an early stage of its review process to filter studies with suboptimal design and those applying inappropriate or insufficiently reported statistical methods. Poole et al. [78] use two examples, namely, diagnostic test and meta-analysis interpretation, to illustrate common statistical pitfalls. They note that even when statistical analyses are appropriate and correct, authors have a tendency to overemphasize their results and that this risks translation into clinical practice of treatments for which the benefits and risks have not been fully verified. Poole and colleagues also note the important ethical role that statistical reviewers play in minimizing this risk, but it is clear that we all (authors, reviewers, journal editors and readers) share this responsibility.

**Conflicts of interest** None.

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