Intensive Care Med (2014) 40:147–159
DOI 10.1007/s00134-013-3184-5

Giuseppe Citerio
Jan Bakker
Matteo Bassetti
Dominique Benoit
Maurizio Cecconi
J. Randall Curtis
Glenn Hernandez
Margaret Herridge
Samir Jaber
Michael Joannidis
Laurent Papazian
Mark Peters
Pierre Singer
Martin Smith
Marcio Soares
Antoni Torres
Antoine Vieillard-Baron
Jean-François Timsit
Elie Azoulay

Year in review in Intensive Care Medicine 2013: I. Acute kidney injury, ultrasound, hemodynamics, cardiac arrest, transfusion, neurocritical care, and nutrition

Received: 27 November 2013
Accepted: 29 November 2013
Published online: 13 December 2013

G. Citerio (✉)
NeuroIntensive Care Unit, Department of Anaesthesia and Critical Care, Ospedale San Gerardo, Via Pergolesi 33,
20900 Monza, Italy
e-mail: g.citerio@hsgerardo.org
Tel.: +39-39-2334316
Fax: +39-39-2334340

J. Bakker
Erasmus University Medical Center, Rotterdam, The Netherlands

M. Bassetti
Azienda Ospedaliera Universitaria Santa Maria della Misericordia, Udine, Italy

D. Benoit
Ghent University Hospital, Ghent, Belgium

M. Cecconi
St George's Hospital, London, UK

J. R. Curtis
Harborview Medical Center, University of Washington, Seattle, USA

G. Hernandez
Pontificia Universidad Católica, Santiago de Chile, Chile

M. Herridge
University of Toronto, Toronto, Canada

S. Jaber
Saint Eloi University Hospital, Montpellier, France

M. Joannidis
Medical University, Innsbruck, Austria

L. Papazian
Hôpital Nord, Marseille, France

M. Peters
Great Ormond St Hospital, London, UK

P. Singer
Beilinson Hospital, Tel Aviv, Israel

M. Smith
University College London Hospitals, London, UK

M. Soares
D'Or Institute for Research and Education, Rio de Janeiro, Brazil

A. Torres
Hospital Clinic, University of Barcelona, Ciberes, IDIBAPS, Barcelona, Spain

A. Vieillard-Baron
Hôpital Ambroise Paré, Paris, France

J.-F. Timsit
Université Paris Diderot / APHP-Hopital Bichat - Réanimation Medicale et des maladies infectieuses, Paris, France

E. Azoulay
Hôpital Saint-Louis, Paris, France

Acute kidney injury

Despite significant advance of knowledge in the field, acute kidney injury (AKI) still remains a syndrome with significant morbidity and mortality. The commonness of this syndrome in critically ill patients has been highlighted by the prospective FINNAKI study [1] including 2,901 patients from 17 Finnish ICUs, which found an AKI incidence of nearly 40 %. Hypovolemia, diuretics, artificial colloids, and chronic kidney disease were identified as major independent risk facts for developing AKI in the ICU. The study also confirmed that reversibility of AKI highly depends on the AKI stage at presentation with a 30 % resolution on the following day for AKI stage 1 and 87 % AKI persistence in patients with stage 3. Severity of hypotension and postoperative ventricular function appeared to be the major determining factors for developing renal damage in children undergoing cardiac surgery [2].

The long-lasting quest for a generally accepted definition and classification of AKI appears to have finally reached its mission with the publication of the KDIGO Clinical Practice Guidelines AKI [3]. The widely accepted criteria based on small changes of serum creatinine of at least 0.3 mg/dl or a reduced urinary output of less than 0.5 ml/kg/h for at least 6 h were evaluated in a complete dataset of more than 17,000 critically ill patients treated at a tertiary hospital in Boston, USA [4]. Both mortality and requirement of renal replacement therapies (RRT) correlated with the magnitude of relative increase in serum creatinine serum as well as the duration of oliguria supporting the current conceptual approach to AKI. However, for better risk estimation and for the development and validation of preventive measures against AKI, more sensitive biomarkers are urgently needed [5]. Serum neutrophil gelatinase-associated lipocalin (NGAL) is one of the biomarkers which had been investigated in several settings and was found to predict occurrence of AKI up to 48 h before a significant increase in serum creatinine and also indicated requirement of RRT in critically ill patients [6]. However, its major limitation is the influence by systemic inflammation and its resulting increase in serum levels even in the absence of AKI [7]. Another setting where NGAL apparently failed to perform as an early predictor was contrast-induced AKI in critically ill patients as shown in a French study performed in an ICU of a university hospital [8]. Urinary NGAL was hoped to be a more reliable parameter for AKI in the setting of sepsis [9]. However, a prospective observational study by Glassford et al. [10] compared several commercial assays as well as specific ELISAs detecting various isoforms of urinary NGAL in 100 patients with systemic inflammation and lowest stage of AKI. The authors found a lack of specificity for AKI prediction and a very poor association with further RRT requirement. It turned out that urinary NGAL comprised monomeric forms (deriving from neutrophils and renal tubular cells), homodimeric NGAL (produced by neutrophils only), and heterodimeric NGAL (produced by renal tubular cells only). Heterodimeric NGAL cannot be assessed by currently available tests. Even more disappointing was the finding that correlation of any determination of urinary NGAL with serum NGAL was weak at best.

Transient limb ischemia as a strategy to protect against contrast-induced AKI drew attention but definitely requires more studies [11]. Probably the most important measure a practicing clinician can take to prevent AKI is to avoid any additional harm, especially application of nephrotoxic agents. In this context the use of hydroxyethyl starch (HES) has raised attention due to two large randomized controlled trials (RCT) showing increased requirement of RRT after the use of 6 % tetrastarch [12, 13]. A systematic review investigating the effect on 6 % tetrastarch showed a clearly increased risk of requiring treatment with RRT as well as increased mortality in critically ill patients [14]. The effect was even more pronounced in another meta-analysis concentrating on patients with severe sepsis and showing a relative risk (RR) of 1.42 (95 % CI 1.09–1.85) for RRT requirement and an RR of 1.13 (95 % CI 1.02–1.25) for 90-day mortality independent from HES origin (maize- vs. potato-derived tetrastarch) [15]. The fact that intravenously applied HES is eliminated primarily by the kidney and predominantly stored in this organ provides a sound pathophysiological rationale for potential renal toxicity of HES. Osmotic nephrosis characterized by pinocytosis and lysosomal storage of starch molecules histologically proven in the context of renal transplantation may be the presumed pathomechanism of AKI. These findings may contribute to substantially change fluid management in critically ill patients [16].

HES effects were also analyzed in a post hoc, subgroup analysis of all 798 patients with severe sepsis randomized to fluid resuscitation with HES 130/0.42 vs. Ringer's acetate. Intervention effects estimated as risk ratios were analyzed between the HES vs. Ringer's acetate groups to detect subgroup heterogeneity of the effects on 90-day mortality [17] and, in another paper, the degree and clinical importance of bleeding [18].

The increased 90-day mortality observed in patients with severe sepsis resuscitated with HES was independent of other variables and HES increased the risk of bleeding which was associated with increased risk of death. As the analyses were planned post hoc and their power is reduced, the results should be interpreted with caution.

Renal replacement therapies

Several studies have addressed important issues about RRT in 2013. Continuous renal replacement therapy (CRRT) remains the predominant treatment modality for AKI in critically ill patients throughout Europe as emerged from an international survey performed in 2010, which was answered by 273 intensivists from 50 countries [19]. Although this choice may be mainly driven by local availability of various modalities, as well as the profession in charge of providing RRT (i.e., intensivists or nephrologists), this may also have significant implications for patient outcome in terms of renal recovery. A sophisticated systematic review investigating intermittent and continuous modalities of RRT found higher rates of dialysis dependency in patients who were initially treated with intermittent forms of RRT [5]. However, the finding of a twofold increased risk of requiring dialysis for AKI survivors was mainly derived from observational studies and not substantiated by RCTs. Consequently al lot of research is still warranted to address this important question which has a significant impact on a patient's quality of life as well as health-care costs. The latter aspect was addressed in a Finnish study performing a 5-year cost utility analysis (CU) of RRT in AKI based on 410 patients treated in a mixed ICU [20]. Calculating an overall 5-year median CU of 271,116€/quality adjusted life year (QALY), the authors found significant variations in CU depending on age, survival time, and severity of disease. CU was significantly better for survivors with renal recovery (28,684€/QALY) than for those requiring chronic RRT afterwards (98,606 €/QALY). As known from many other interventions costs significantly increase with higher age because of a drastically decreasing gain of QALYs by RRT above the age of 75.

In 2010 the CRRT standard with regard to treatment dose appeared to be around 35 ml/kg/h with a tendency to higher doses in septic patients according to the survey mentioned above [19]. Of note the two large trials [21, 22] showing no benefit by applying higher doses than 25 ml/kg/h had already been published at that time. However, a nested cohort substudy including 115 patients of the RENAL trial indicated that continuous venovenous hemodiafiltration (CVVHDF) at higher intensities of 40 ml/kg/h may confer more rapid hemodynamic stabilization and weaning from vasopressors as compared to 25 ml/kg/h [23]. Consequently, higher intensity CRRT continued to be regarded as having some potential in certain situations, especially with the intention to achieve some blood purification from inflammatory mediators. At last, the question whether higher doses are of benefit in patients with septic shock was addressed by the IVOIRE study [24], a multicenter RCT comparing a dose of 70 ml/kg/h over 96 h to a "standard dose" of 35 ml/kg/h in patients with septic shock. The lack of any difference with regard to either the primary endpoint, i.e., 28-day mortality, or the secondary endpoints like change in hemodynamic profile, improvement in severity scores, ventilation days, duration of RRT, renal recovery, ICU or hospital stay, and 90-day mortality lead to the conclusion that HVHF cannot be recommended for treatment of AKI in septic shock. Despite its limitation of a premature study termination at 140 patients, the study still has an important impact as the largest RCT having addressed this important question.

Dynatremias in ICU

Recently several publications reported increased mortality with dysnatremias in critically ill patients. The study by Lindner et al. [25] concentrated on the question of whether hypernatremia affects the acid–base status of critically ill patients. A rise in serum sodium was found to be paralleled by metabolic alkalosis characterized by increased base excess due to sodium. The exact mechanism of this finding has to be further elucidated but the "old" contraction alkalosis due to free water deficit appears an attractive explanation.

Critical care ultrasonography

Volpicelli et al. [26] prospectively analyzed the diagnostic value and efficacy of point-of-care ultrasonography (POCUS) in the emergency department. POCUS is a basic and fast ultrasonic examination of the heart, lungs, abdomen, and peripheral veins. In a study of 108 hypotensive non-trauma patients, the authors suggested that such an approach could guide physicians in the diagnostic process and then in therapeutic management.

Baldi et al. [27] proposed another interesting application of ultrasonography in a pilot study. In 20 critically ill patients, they prospectively reported that lung ultrasonography could be used semiquantitatively to evaluate extravascular lung water (EVLW), using the "B-line score", i.e., briefly the number of B-lines detectable in an anteroposterior examination. There was an acceptable correlation with CT evaluation of EVLW. This suggests that intensivists can assess EVLW noninvasively at the bedside.

In 94 patients admitted to the ICU for shock or respiratory failure, Vieillard-Baron et al. [28] tested the hemodynamic monitoring capability and safety of a new single-use miniaturized transesophageal probe that can be left in place in patients for 72 h. In this multicenter and prospective study, they reported an acceptable image quality and the value of the recorded hemodynamic information in guiding treatment.

Echographic left ventricular function, stroke volume, and fluid responsiveness evaluation

Petzoldt et al. [29] studied the accuracy of the determination of stroke volume using transpulmonary thermodilution (TPTD) and calibrated (C) and uncalibrated (UC) arterial pulse contour (PC) methods in 18 patients undergoing transcatheter aortic valve implantation. The reference method used was transesophageal echocardiography (TEE). They found that TPTD remained accurate even in severe aortic stenosis, as did C-PC. In UC-PC, the trend was more accurate than a single measurement. Aortic insufficiency following the procedure is a significant limitation to the PC method, whether there is calibration or not. Scolletta et al. [30] reported that indices of left ventricular function derived from pulse wave analysis, compared with echocardiography, could be used to monitor cardiac function. They tested a new device called "most care", based on a high-frequency analysis of the arterial signal. It could allow intensivists to record d*P*/d*t* and a surrogate of left ventricular ejection fraction, as well as the arterial–ventricular coupling.

Finally, considering that patients with severe preeclampsia are often oliguric and at severe risk of acute pulmonary edema, Brun et al. [31] reported that passive leg raising (PLR) in this indication is useful in detecting fluid responsiveness. They found that PLR predicted fluid responsiveness well in this specific setting of pregnant patients, whereas only 52 % of the oliguric patients were actually responders to fluids.

Echography: training and quality

In a multicenter prospective study, Charron et al. [32] used a previously validated scoring system to determine how many TEE examinations trainees have to perform in order to be competent in evaluating hemodynamics in mechanically ventilated patients. Forty-one intensivists were included. The authors found that 25 TEE examinations in 6 months was the best compromise between sensitivity and specificity for competency, whereas 31 TEE examinations in 6 months had a specificity of 100 %.

Acute respiratory distress syndrome (ARDS) and right ventricular (RV) function: echographic evaluation

Several papers published in 2013 reiterated the importance of RV function evaluation by echocardiography in patients ventilated for ARDS. Lhéritier et al. [33] reported a multicenter prospective study including 200 patients with early moderate to severe ARDS, all submitted to protective ventilation. They reported three important results. First, the incidence of acute cor pulmonale (ACP) was 22.5 %. Second, a $PaCO_2$ greater than 60 mmHg was strongly and independently associated with ACP. Finally, TEE appeared much more efficient than transthoracic echocardiography. In the same issue of the journal, Boissier et al. [34] reported a prospective and observational study in 226 patients with moderate to severe ARDS using the Berlin definition, all submitted to protective ventilation. They also found three important results. First, the incidence of ACP was 22 %. Second, the driving pressure and the infectious cause of lung injury were strongly associated with the occurrence of ACP. And finally, ACP was an independent factor associated with ICU and hospital mortality (67 % in the group with ACP vs. 49 % in the group without ACP). On the basis of these two papers and previous ones published in the same field, Vieillard-Baron et al. [35] wrote a summary in the new section of the journal, "What's new", about ACP in ARDS. They proposed a new approach to ventilatory strategy called the "RV protective approach".

Management of hemodynamically unstable patients and monitoring cardiovascular physiology at bedside

The management of hemodynamically unstable patients requires a robust understanding of physiology in order to make decisions that can change therapy and improve patients' outcome. One of the seminal publications of a randomized trial of goal-directed perioperative therapy (GDT) was a study published in 1993 [36]; this study was revaluated critically and with an historical perspective by Boyd in the series "My paper 20 years later" [37]. In 2013, the new Surviving Sepsis Guidelines [38] have been published. A lot of importance is given to the time of interventions; for instance administration of antibiotics has to occur within 1 h of the recognition of septic shock and severe sepsis. Different targets are also set within the first 6 h and within 12 h of recognition of sepsis. For what concerns fluid managements, the guidelines still recommend targeting a central venous pressure (CVP) of 8–12 mmHg (or 12–15 mmHg in ventilated patients). The guidelines recognize the role of dynamic measures of fluid responsiveness. Crystalloids are the recommended fluid for initial resuscitation, while the guidelines recommend the avoidance of HES. An $ScVO_2$ of greater than 70 % and/or SvO_2 of greater than 65 % can be used to target resuscitation. Resuscitation can also be targeted to normalize lactate.

Further evidence that dynamic indices of fluid responsiveness may be better than static parameters such as CVP comes from an elegant animal study on pigs by Trepte et al. [39]. In a model of severe acute pancreatitis they compared two resuscitation strategies, one in which hemodynamic management was guided by CVP (>12 mmHg) and mean arterial pressure (MAP) and one by stroke volume variation (SVV <10 %), MAP, and cardiac output (CO). Pigs managed with SVV and CO had a better survival (29.4 vs. 11.8 %, $p < 0.05$). Microcirculation was also improved in this group.

While noradrenaline is the recommended vasopressor in septic shock, vasopressin is currently being studied as a possible alternative. Vasopressin levels are known to be low in adult patients with septic shock. In pediatric patients, vasopressin levels have been shown to be elevated and to remain elevated for up to 72 h. Vasopressin levels may provide important information at the bedside;

however, measurement of vasopressin is problematic because of its short half-life and instability. Copeptin (a vasopressin precursor) has been recently investigated as a possible surrogate for vasopressin levels. Lee et al. [40] compared copeptin and vasopressin levels in a pediatric population with sepsis and septic shock and in a group of healthy children. While they found a difference in median vasopressin levels at baseline between the three groups, copeptin showed no differences between groups.

Often the physiology is monitored in front of our eyes and we do not see it. An elegant study by Monnet et al. [41] reminded us that the end tidal CO_2 can be used as a hemodynamic monitoring surrogate. The authors found that changes in end tidal CO_2 ($EtCO_2$) during a PLR test can give more information than arterial blood pressure in order to predict which patient can increase CO with subsequent fluid administration. In this study an increase in $EtCO_2$ of more than 5 % during a fluid challenge predicts an increase in CO of more than 15 % with fluid administration.

The study of venous return according to Guytonian theory has not been possible until recently. The understanding of venous return is important for the correct use of fluids and vasoactive drugs. Cecconi et al. [42] studied the effect of a fluid challenge on the venous return by looking at changes in mean systemic filling pressure analogue (Pmsa), CVP, and the gradient between the two. Patients were classified as responders or nonresponders depending on whether they had an increase in CO after fluid administration. The authors demonstrated that in postsurgical intensive care patients the Pmsa is increased in similar ways in responders and nonresponders, but the gradient between Pms and the CVP is increased only in responders.

Lakhal et al. [43] assessed whether invasive and noninvasive blood pressure (BP) monitoring (CO and the mean of four intra-arterial and oscillometric brachial cuff BP measurements) allows the identification of fluid challenge responders, i.e., patients that increased their CO. In 130 patients, the correlation between a fluid-induced increase in pulse pressure and fluid-induced increase in CO was weak and was similar for invasive and noninvasive measurements of BP. In deeply sedated population, a large increase in invasive pulse pressure (23 %) or even in noninvasive pulse pressure (35 %) reliably detected a response to fluid. In the absence of a marked increase in pulse pressure, a response to fluid was unlikely.

The ultimate goal of any hemodynamic intervention is the improvement of tissue perfusion. The carbon dioxide difference between the arterial and venous blood (pCO_2-gap) has been proposed as a marker of tissue perfusion. Van Beest et al. [44] showed that pCO_2gap could be reliably measured by taking central venous blood samples instead of mixed venous blood samples. They also found that a persistent high pCO_2gap at 24 h is associated with poor outcome. This study highlights even more the importance of this often forgotten parameter at the bedside.

Ruiz-Rodriguez et al. [45] used a very innovative approach in order to see if artificial neural networks can be used to monitor BP noninvasively and continuously using pulse oximeter data. They analyzed 7,715 time periods in 707 patients. They found that, when comparing the new method with invasive arterial measurements, the mean bias and SD values were -2.98 ± 19.35 mmHg for systolic BP, -3.38 ± 10.35 mmHg for mean, and -3.65 ± 8.69 mmHg for diastolic BP. Despite the limitations of this study in terms of clinical applications owing to the high SD, this study represents a starting point for the use of artificial neural networks in the analysis of available physiological data at the bedside.

Cardiac biomarkers

The search for an optimal biomarker in critical care is still open. Legrand et al. [46] summarized what has been discovered in terms of new biomarkers and in terms of new use of known biomarkers. That review highlights the fact that treating complex syndromes represents an important limit when using biomarkers in the ICU, and it also presents the latest discoveries in the field. The authors show very clearly the different aspects that one has to keep in mind when looking at this issue such as predefined endpoints, patient populations, positive and negative predictive values etc. Troponins have been shown to be a prognostic biomarker not only after coronary events but also in the context of critical illness. Several studies have investigated the prognostic value of troponins in sepsis. Bessiere et al. [47] presented a meta-analysis studying the relation between troponin elevation in sepsis and mortality. They found that troponin was elevated in 61 % of the cases (58–64 %). Elevated troponin was significantly associated with all-cause mortality. The area under the curve was 0.68. In practice elevated troponins identify septic patients at higher risk of mortality.

Transfusions and coagulation management

Transfusion of blood components is common after cardiac surgery; little data is available about the contribution of different blood products to survival. In a large study on 5,216 coronary artery bypass graft patients, Bjursten et al. [48] investigated the relationship between red blood cells, plasma, and platelets administration and long-term mortality (7.5 years follow-up). Red blood cell transfusion was not associated with increased mortality while plasma transfusion was associated with decreased long-term survival and platelet transfusion was associated with increased long-term survival.

Coagulation management is also still a matter of debate. Verheyden et al. [49] investigated the effect of the withdrawal of aprotinin in 2008 on cardiac surgery patients in the UK. The authors performed a propensity analysis of two large cohort of patients pre and post withdrawal. In total they studied 6,608 patients in whom they found that aprotinin withdrawal was associated with an increased risk of bleeding, a higher rate of emergency re-sternotomy, and a higher incidence of AKI. In a higher-risk group of patients ($n = 1{,}002$) they also found an increased risk of mortality at 30 days. Interestingly these findings are in contrast with previously published studies that led to the withdrawal of aprotinin.

There is great controversy surrounding red blood cell transfusion. Leal-Noval et al. [50] studied whether red blood cell transfusion in non-bleeding patients was associated with improved outcome in a retrospective, pair-matched cohort study. They found that non-transfused patients had lower hospital mortality, lower rate of ICU readmissions, lower rate of nosocomial infection, and a lower incidence of AKI in a matched cohort of 428 patients. Despite the limitation of a retrospective observational study, these results support the use of restrictive transfusion policies and highlight the need for RCTs in order to study transfusion strategies in ICU patients.

Lauzier et al. [51] explored the predictors of major bleeding and the association between bleeding and mortality in medical–surgical critically ill patients receiving heparin thromboprophylaxis in a large trial dataset. Patients with trauma, orthopedic surgery, or neurosurgery were excluded. Among 3,746 patients, bleeding occurred in 5.6 %. Time-dependent predictors were prolonged activated partial thromboplastin time, lower platelet count, therapeutic antiplatelet agents, renal replacement therapy, and recent surgery. The type of pharmacologic thromboprophylaxis was not associated with bleeding. Patients with bleeding had a higher risk of in-hospital death.

As major bleeding has modifiable risk factors and is associated with in-hospital mortality, strategies to mitigate these factors should be evaluated in critically ill patients.

Cardiac arrest

Nolan [52] presented the most recent advances in the management of out of hospital cardiac arrest (OOHCA). Data shows that outcomes have improved over the last 10 years, probably as a result of better pre-hospital and in-hospital care for these patients. In this elegant review different topics are discussed such as CPR, advanced life support, and post-resuscitation care. An important point about the management of OOHCA is that with the advent of therapeutic hypothermia prognostication has to be delayed at least to 72 h after rewarming.

Therapeutic hypothermia (TH) has been established for many years as the standard post-resuscitation management method in OOHCA. External cooling is often used to achieve TH; however, often external cooling is not sufficient to achieve effective temperature management. Ricome et al. [53] investigated the incidence of external cooling failure and the factors associated with it. In a restrospective analysis on 594 patients, they found that failure was common, with 191 patients not able to achieve the target temperature within 12 h after cardiac arrest. Independent risk factors for external cooling failure were early coronary angiography intervention, a high body weight, a high temperature on ICU admission, and a long delay between collapse and the start of cooling. Hemodialysis and male gender were associated with cooling success. Vaahersalo et al. [54] evaluated post-resuscitation care, implementation of TH, and outcomes of ICU-treated OOHCA patients admitted to 21 ICUs. Among 548 patients included in the study, 311 had a shockable rhythm and 237 had a non-shockable rhythm. Compared to patients not receiving TH, the overall outcome was better in shockable rhythm patients, while non-shockable rhythms did not seem to benefit from TH.

Prognostication after cardiac arrest (CA) remains a key challenge for intensivists and has been complicated by the use of TH. The four recommended methods for predicting poor prognosis, i.e., clinical neurological examination (including pupillary response, corneal reflex, and motor response), myoclonic status epilepticus, somatosensory evoked potentials (SSEP), and serum levels of neuron-specific enolase, are based on studies conducted before the introduction of TH. Kamps et al. [55] conducted a meta-analysis designed to assess the sensitivity and false positive rate of clinical neurological examination and SSEPs to predict poor neurological outcome in adult patients treated with TH after cardiopulmonary resuscitation. The prognostic reliability of SSEPs and the pupillary response to light was maintained after treatment with TH, but this meta-analysis was unable to determine with certainty the true prognostic value of either. Absent motor responses and corneal reflexes at 72 h post-resuscitation were not sufficiently reliable to predict poor outcome after the use of TH.

Brain injury is well established as a cause of early mortality after OOHCA, but post-resuscitation shock also contributes to death. A large retrospective study by Lemiale et al. [56] described the incidence, risk factors, and relation to mortality of post-CA shock and brain injury. Post-CA shock occurred in 68 % of the patients. Death was caused in the ICU in 34.8 % from post-CA shock and in 65.2 % from neurological injury. Brain injury accounts for the majority of deaths, but post-CA shock affects more than two-thirds of OHCA patients. Age, raised blood lactate and creatinine values, and time before restoration of spontaneous circulation increased the risk of ICU mortality from both shock and brain injury.

Immediate treatment of arterial hypotension to maintain adequate tissue perfusion is therefore a cornerstone of CA victims. Along these lines, Beylin et al. [57] explored the relationship between early hemodynamic goals and outcomes in CA victims undergoing TH. In a cohort of 168 CA patients (45 % survivors, 35 % with good neurological outcome), survivors had higher MAPs at different time points than non-survivors. Increased requirement for vasoactive agents was associated with mortality at all time points.

Further prospective studies on hemodynamic optimization after CA need to be performed.

Couper et al. [58] conducted a systematic review and meta-analysis to evaluate whether debriefing improves the outcome of critical illness. Of 2,720 studies identified, 27 were finally considered. Debriefing was found to be efficient, especially in CA where meta-analysis found evidence that debriefing improved the outcome of the resuscitation process and the return of spontaneous circulation, but not survival or hospital discharge.

Neurocritical care

Neurocritical care has evolved substantially over the last two decades. Improved understanding of the pathophysiology of neurological injury and parallel advances in monitoring and imaging techniques have led to the implementation of evidence and consensus-based guidelines for a range of neurological conditions, and the introduction of individualized treatment strategies that have translated into improved outcomes. The evidence base for the treatment of acute brain injury (ABI) in particular continues to grow. Stocchetti [59] conducted a PubMed search of human studies of ABI published in 2012 and identified 2,058 references relating to acute ischemic stroke (AIS), 1,869 to traumatic brain injury (TBI), 1,072 to intracerebral hemorrhage (ICH), and 534 to subarachnoid hemorrhage (SAH).

Studies evaluating the effectiveness of care in specialist neurocritical care units are often confounded by secular trends because of the use of historical control periods. Large database research may help in identifying and quantifying these effects. Damian et al. [60] and colleagues used the large UK Intensive Care National Audit and Research Centre (ICNARC) database to assess mortality changes over time for patients with primary ICH, myasthenia gravis (MG), and Guillain–Barré syndrome (GBS) treated in an ICU, and also investigated whether the type of ICU in which the patients were treated affected mortality. An overall decline in mortality was observed between 1996 and 2009, and this was most marked (and statistically significant) for ICH. Hospital mortality for ICH was lower in patients treated in a neurocritical care unit compared to a general ICU, and this advantage persisted after adjustment for potential confounders including surgical intervention. Although the smaller reductions in MG and GBS mortality rates over time were not statistically significant, they were substantially higher than those previously reported. The high proportion of MG and GBS patients requiring ventilatory support in this study suggests that a high threshold for ICU admission compared to other studies might account for the higher reported mortality rates and also that earlier referral to ICU might improve outcome. Of concern is that a large proportion of the MG and GBS in-hospital deaths occurred after ICU discharge. Although premature ICU discharge might be a factor, the authors argue that this cannot fully explain their findings and question whether the quality of step-down facilities in the UK, where the vast majority of such patients are discharged to general medical wards rather than to rehabilitation facilities, is implicated.

Intracranial pressure control

Acute brain dysfunction, either related to a primary injury such as TBI, ICH, SAH, and AIS, or because of the secondary cerebral effects of systemic illness such as septic encephalopathy, is frequently encountered in ICU patients. One of the key challenges in all ABI types is the management of raised intracranial pressure (ICP). A higher burden of intracranial hypertension, both in degree and duration, is associated with worse outcome after TBI, and consensus guidelines recommend treatment of ICP of 20 mmHg or higher [61]. Osmotic therapy has been a cornerstone of the management of intracranial hypertension for decades but its use remains controversial. Mannitol is recommended by consensus guidelines [61], but has never been subject to a large randomized comparison and has well-known side effects. Hypertonic saline (HS) has many beneficial effects on the injured brain in addition to its osmotic action. Unlike mannitol it increases serum osmolality directly rather than by inducing an osmotic diuresis, thereby expanding intravascular volume and potentially augmenting cerebral blood flow. There are no large, randomized comparisons of HS with mannitol, or long-term functional outcome studies of HS. Against this background there remains an urgent need to clarify the optimal agent and osmolar load to lower elevated ICP and the role (if any) of hyperosmolar solutions in the routine fluid management after ABI. Whilst it is accepted that serum hypo-osmolality must be avoided, the routine maintenance of a hyperosmolar state as a means of preventing brain swelling remains controversial and its physiological rationale unclear. Two studies published in *Intensive Care Medicine* in 2013 address these issues. Following evidence that a hyperosmolar sodium lactate (SL) solution is effective in treating intracranial hypertension [62], Ichai et al. [63] conducted a double-blind RCT comparing the ICP effects of a continuous infusion of SL (Na^+ 504 mmol/l, K^+ 4.0 mmol/l, Ca^{2+} 1.36 mmol/l, Cl^- 6.74 mmol/l, and lactate 504.1 mmol/l) with isotonic saline in 60 patients with severe TBI. The infusions were begun within 12 h after the injury and continued at a rate of 0.5 ml/kg/h for 48 h. SL decreased the number of episodes of raised ICP by more than 50 % compared to controls (23 vs. 53 episodes respectively, $p < 0.05$), and the number of patients with at least one episode of ICP greater than 20 mmHg was also smaller in the SL group (36 vs. 66 %, $p < 0.05$). Fewer interventions were required to treat intracranial hypertension in the SL group (31 vs. 53, $p < 0.05$), although the nature of the interventions was similar in the two groups. The hyperosmolar solution used in this study contained HS and the authors accept that this might have been responsible for the observed effects on ICP. However, they also discussed two other possible explanations for their findings. Whilst glucose remains the primary energy source for the brain, lactate can also be an energy source during aerobic metabolism, especially during periods of increased energy requirements [64]. Under these circumstances, the administration of lactate might improve cerebral cellular bioenergetics and thereby reduce cellular swelling and ICP. This study did not measure metabolic variables so was unable to address this issue. Secondly, the lactate in the SL solution is rapidly metabolized in the cell but the high sodium concentration of SL (504 mmol/l) results in extracellular sodium accumulation. This leads to an efflux of negatively charged ions from the cell, primarily chloride, to maintain extracellular electrical neutrality. Chloride plays a key role in cell volume regulation and this chloride movement might be accompanied by water to maintain the osmotic equilibrium, in turn reducing or limiting cellular edema and ICP. Studies incorporating diffusion-weighted MRI should be conducted to test the hypothesis further.

Ketones may also act as an energy source for the injured brain [65] and exogenous ketone supplementation has been shown to have beneficial effects on ATP levels and cerebral blood flow in animal models of TBI and stroke. Ketone supplementation is complicated by hyperosmolality and acid–base disturbance, and a formulation that allows a rapid increase in brain ketone levels whilst maintaining a target serum osmolality and minimizing acid–base disturbance is sought. White et al. recently investigated the effects of a novel, balanced sodium ketone solution, sodium D-3-hydroxybutyrate (BHB), on metabolic variables in a non-starved and non-brain injury rodent model [66]. Two formulations of BHB [40 mmol/l (BHB40) and 120 mmol/l (BHB120) in 3 % NaCl] were compared with a 3 % saline solution (control). All solutions contained equimolar concentrations of sodium (514 mmol/l), and the chloride concentration was 514, 474, and 394 mmol/l in the control, BHB40, and BHB120 groups, respectively. Infusion of the hyperosmolar BHB solution resulted in a progressive increase in cerebrospinal fluid (CSF) BHB levels at 1 and 6 h compared to baseline, related to the concentration of the BHB solution administered. CSF levels of BHB did not change in the control group. There were also significantly higher levels of BHB in brain tissue in the treatment compared to the control group, and this was also related to the amount of BHB administered. In this study, addition of BHB to HS did not lead to changes in acid–base balance or adversely affect the steady maintenance of a hyperosmolar state. Replication of these findings in animal models of brain injury is required prior to further investigate any potential neuroprotective effects of BHB in humans.

Pediatric traumatic brain injury

International consensus and evidence-based guidelines for the management of adult TBI are available [61], but evidence in pediatric TBI is relatively scarce. All major studies have excluded patients younger than 14–16 years, so there remains uncertainty about the optimal management of ICP and cerebral perfusion pressure in pediatric TBI. A retrospective review [67] of a prospectively collected database described the clinical characteristics, current practice of ICP monitoring and management, and the relationship between clinical and radiological variables and 6-month outcome in a cohort of 199 patients under the age of 19 years admitted to three Italian ICUs with TBI. ICP was monitored in 117 (59 %) cases overall and in 90 (70 %) of those with severe TBI. Data were available for detailed analysis of ICP in 104 patients. ICP exceeded 20 mmHg for more than 5 min in 87 (84 %), with a similar proportion of intracranial hypertension (86 %) in patients with severe TBI. Standard therapy was provided for intracranial hypertension, and 6-month outcome data were available for 196 cases. Overall, 21 % of patients died, 72 % had a favorable outcome (good recovery 63 %, moderate disability 9 %), 6 % severe disability, and one patient remained in a persistent vegetative state. Mortality was 21 %. In a multivariable logistic regression model, only the motor component of the Glasgow Coma Scale (GCS) at admission, pupil responses, and highest average 24-h ICP were independent predictors of outcome. Although pediatric TBI appears to be associated with a high incidence of intracranial hypertension, aggressive management on the ICU (applying both surgical and medical measures) may achieve a favorable outcome in many patients.

Nervous system infections

Bacterial meningitis is the most common form of meningitis, and associated with delayed cerebrovascular complications. Analysis of a nationwide prospective Dutch cohort study of 1,032 cases of CSF culture-positive community-acquired bacterial meningitis demonstrated a 1.1 % incidence (11 cases) of delayed cerebral thrombosis [68]. All of the 11 patients had an initial response to treatment but deteriorated after 7–42 days, and the final outcome was poor in all but one of them. *Streptococcus pneumoniae* was the causative organism in 10 of the 11 cases and dexamethasone was administered before or with the first dose of antibiotic in nine. Patients who developed cerebral thrombosis had higher complement C5a CSF concentrations on the initial diagnostic lumbar puncture compared to those without delayed thrombosis, suggesting a role of complement-mediated thrombosis through C5a. The overall beneficial effects of dexamethasone on mortality persist despite the devastating outcome of patients who develop delayed cerebral thrombosis, and the authors of this study therefore recommend no change in practice on the basis of their findings.

Intensive care unit-acquired weakness and delirium: increase your awareness

Intensive care unit-acquired weakness (ICU-AW) is a frequent and debilitating complication of critical illness that has a substantial impact on outcome. Therefore, it is important to be aware of it, promptly identify it, and utilize strategies that help to prevent muscle weakness in the ICU. A review of the possibility of prevention of ICU-AW has been recently published [69].

Autonomic dysfunction is another frequent neurological complication in the critically ill, and associated with increasing severity of critical illness and mortality. In an observational cohort study, Wieske investigated autonomic dysfunction in critically ill patients with and without ICU-AW [70]. Heart rate variability (HRV), measured daily for a maximum of 15 days, was used to identify autonomic dysfunction in 83 patients of whom 15 (18 %) had ICU-AW. Abnormal HRV was observed in all patients irrespective of the presence of ICU-AW but this study identified multiple confounders of HRV, including sedation, mechanical ventilation, norepinephrine, and heart rate, suggesting that HRV may not be a reliable indicator of autonomic dysfunction in the critically ill.

Delirium among critically ill patients has been described over the last decade, particularly its diagnostic criteria, risk factors, prevention and treatment strategies, and outcomes. The ICU environment and sedation add complexity to delirium identification in the ICU. Haenggi et al. [71] described how sedation per se can result in positive items of the more common delirium scales, and therefore in a diagnosis of delirium. Apparent prevalence of delirium is dependent on how a depressed level of consciousness after sedation stop is interpreted (delirium vs. persisting sedation). Moreover, the paper "The accurate recognition of delirium in the ICU: the emperor's new clothes?" [72] elegantly and critically revised the reasons for our inability to accurately identify delirium in the ICU, including sedation, and suggests a more inclusive definition of ICU delirium.

Seizures

Clinical seizures, non-convulsive seizures, convulsive and non-convulsive status, and cortical spreading depolarizations are more common in all brain injury types than previously believed, and independently associated with mortality and poor outcome. In 2013, the Neurointensive Care Section of the European Society of Intensive Care Medicine published recommendations for the use of electroencephalography (EEG) monitoring in critical ill patients [73, 74]. These were developed by a multidisciplinary group of experts following a systematic review of relevant literature, and classification of the evidence using the GRADE system. The group recommended that EEG monitoring should be used in generalized convulsive status epilepticus, and to rule out non-convulsive seizures in brain-injured and comatose patients with unexpected or unexplained altered consciousness. They also recommended that EEG be considered in comatose SAH patients to detect ischemia, and to improve prognostication after CA. EEG and continuous EEG (cEEG) monitoring is limited by its attenuation by sedative agents and is a resource-intense technology, requiring skilled personnel for interpretation. Its widespread rollout has therefore been limited. Telemedicine may increase the adoption of cEEG by allowing interpretation away from the bedside and there is also a drive towards the development of automated seizure detection software. RCTs investigating the effects of cEEG-guided treatment are urgently required.

Nutrition and intestinal failure

Clinical symptoms of intestinal failure include gastroparesis, vomiting, diarrhea, and constipation as well as intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS). Several papers have recently attempted to better characterize them. In a large prospective, multicenter, worldwide study, Blaser et al. [75] showed that severely ill mechanically ventilated ICU patients frequently have GI symptoms and IAH. Absent bowel sounds, GI bleeding, bowel distension, and an increasing number of coincident GI symptoms were associated with 28-day mortality. However, an attempt by the authors to improve the accuracy of the SOFA score with a valid GI dysfunction score was not successful and other parameters linked to intestinal failure need therefore to be explored. One of the symptoms, gastric emptying, is difficult to assess using gastric volume residue. Nguyen et al. [76] compared the measurement of gastric emptying after liquid nutrients using scintigraphy with the [^{13}C]octanoate breath test. The study showed that delayed gastric emptying was present in 27/33 patients. Gastric emptying curves were determined and showed that the best correlation between breath test and scintigraphy was at 120 min after meal absorption. The test was shown to be very useful but mainly for research purposes. The modest accuracy in predicting gastric emptying in an individual coupled with relatively wide confidence intervals makes the test less useful in the clinical setting.

IAH and ACS are common in the ICU and frequently associated with poor outcomes. The World Society of the Abdominal Compartment Syndrome updated the definition and clinical practice guidelines [77] on these syndromes using the GRADE approach. Consensus management statements included intra-abdominal pressure (IAP) measurements in patients at risk, protocolized IAP monitoring and management, decompressive laparotomy for overt abdominal compartment syndrome, and negative pressure wound therapy. The article is rich of supplementary material and useful practical flow charts.

Sim et al. [78] assessed the superior mesenteric artery (SMA) blood flow and glucose absorption in critically ill elderly patients. Using Doppler ultrasonography before and after a glucose meal, the authors found that in SMA flow was stimulated less by nutrients in elderly patients compared to healthy elderly volunteers and glucose absorption was reduced in the critically ill patients. This suggests that in elderly ICU patients, the SMA blood flow is less increased by glucose administration.

Another reason for a decreased intake in nutrients was investigated in 41 patients who had 121 planned procedures over a mean ICU stay of 18.7 days [79]. Enteral nutrition (EN) was stopped prior to 89 % of the 121 procedures. The cumulative duration for stopping of EN was 30.8 h or 7.9 % of the mean total ICU stay. In 31 % of the cessation episodes, EN was stopped without an order and in 23 % of episodes it was not necessary according to the institutional guidelines. On the basis of these findings, the study showed how EN delivery could be improved. When enteral feeding is not achievable, parenteral nutrition is indicated. Manzanares et al. [80] systematically compared the use of alternative intravenous lipid emulsions to the use of soya-based lipid emulsions. Twelve RCTs were analyzed and statistically aggregated. No significant advantage was found in terms of length of stay or infection rate when lipid emulsions enriched in medium chain fatty acids, omega-3 fatty acids or omega-3 fatty acids were compared to n-6 fatty acid lipid emulsions. However, more studies are needed to define the best lipid mixture to administer to ICU patients.

Glucose control, electrolytes, and vitamins

In an excellent "What's new in glucose control", Van den Berghe [81] summarized more than 500 papers published in 2012. Tight or looser control remains the heart of the debate and various points were stressed including the many confounders, which may lead to pitfalls. These include the type and accuracy of the instrument used to measure blood glucose concentrations, level of experience of the nurses, and the method in which insulin is infused. Hypoglycemia is of main concern in the tight glucose control approach but several recent studies in newborns, children, and neurosurgical patients did not detect any harm and even improved certain areas of cognition. Nevertheless, the Surviving Sepsis Guidelines [38] recommend maintaining glucose levels below 180 mg/dl and these recommendations appear to be well implemented. In a retrospective, observational study of 1,763 children in a large pediatric ICU in Birmingham, a survival advantage was found in children who showed a reduction in blood glucose on day 1 relative to the admission blood glucose value [82]. This result remained statistically significant after adjusting for severity of illness.

Osmolality is a measure of solute concentration defined as the number of osmotically active particles per kilogram of water. Numerous formulae are used to calculate osmolality using sodium, chloride, glucose, and urea serum/plasma osmotically active constituents. In a study comparing the 36 available formulae including the recent Zander formula, Fazekas et al. [83] compared measured osmolality from 236 patients with calculated osmolality. Mean differences of up to 35 mOsmol/kg H_2O were observed in most of the equations. However, the Zander formula had a negligible mean difference of 0.5 mOsmol/kg H_2O and the closest limits of agreement ranging from −6.5 to 7.5 mOsmol/kg H_2O. This formula could replace separate measurements of osmolality in many cases according to the authors. Another important study [84] explored the incidence of renal phosphate loss in ICU-related hypophosphatemia. Hypophosphatemia (below 0.6 mmol/l) occurred in 24 % of all the 290 patients in the first week of admission in a general

ICU, mainly in the first 3 days. In most of the cases (80 %), it was associated with increased renal phosphate loss and hypocalcemia due to a shift into the intracellular compartment. The most commonly known phosphaturic factors such as PTH, PTH-rP, FGF-23, and calcitonin did not play a major role. Another prospective cohort study [85] determined the prevalence of hypoviatminoses D in adult ICU patients and found that insufficiency was present in 54 % and deficiency (25-OH–D < 25 nmol/l) in 24 %. This low vitamin D status persisted during the ICU stay and was associated with worse disease severity and fewer hospital-free days.

Conflicts of interest None.

References

1. Nisula S, Kaukonen K-M, Vaara ST et al (2013) Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 39:420–428. doi: 10.1007/s00134-012-2796-5
2. Morgan CJ, Gill PJ, Lam S, Joffe AR (2013) Peri-operative interventions, but not inflammatory mediators, increase risk of acute kidney injury after cardiac surgery: a prospective cohort study. Intensive Care Med 39:934–941. doi: 10.1007/s00134-013-2849-4
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guidelines AKI. http://kdigo.org/home/guidelines/acute-kidney-injury/. Accessed 27 Nov 2013
4. Mandelbaum T, Lee J, Scott DJ et al (2013) Empirical relationships among oliguria, creatinine, mortality, and renal replacement therapy in the critically ill. Intensive Care Med 39:414–419. doi: 10.1007/s00134-012-2767-x
5. Schneider AG, Bellomo R, Bagshaw SM et al (2013) Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 39:987–997. doi: 10.1007/s00134-013-2864-5
6. Cruz DN, Cal M, Garzotto F et al (2009) Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 36:444–451. doi: 10.1007/s00134-009-1711-1
7. Mårtensson J, Bell M, Oldner A et al (2010) Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med 36:1333–1340. doi: 10.1007/s00134-010-1887-4
8. Valette X, Savary B, Nowoczyn M et al (2013) Accuracy of plasma neutrophil gelatinase-associated lipocalin in the early diagnosis of contrast-induced acute kidney injury in critical illness. Intensive Care Med 39:857–865. doi: 10.1007/s00134-013-2826-y
9. Bagshaw SM, Bennett M, Haase M et al (2009) Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med 36:452–461. doi: 10.1007/s00134-009-1724-9
10. Glassford NJ, Schneider AG, Xu S et al (2013) The nature and discriminatory value of urinary neutrophil gelatinase-associated lipocalin in critically ill patients at risk of acute kidney injury. Intensive Care Med 39:1714–1724. doi: 10.1007/s00134-013-3040-7
11. Schneider AG, Bellomo R (2013) Acute kidney injury: new studies. Intensive Care Med 39:569–571. doi: 10.1007/s00134-013-2860-9
12. Myburgh JA, Finfer S, Bellomo R et al (2012) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 367:1901–1911. doi: 10.1056/NEJMoa1209759
13. Perner A, Haase N, Guttormsen AB et al (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134. doi: 10.1056/NEJMoa1204242
14. Gattas DJ, Dan A, Myburgh J et al (2013) Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 39:558–568. doi: 10.1007/s00134-013-2840-0
15. Patel A, Waheed U, Brett SJ (2013) Randomised trials of 6% tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis. Intensive Care Med 39:811–822. doi: 10.1007/s00134-013-2863-6
16. Myburgh J, McIntyre L (2013) New insights into fluid resuscitation. Intensive Care Med 39:998–1001. doi: 10.1007/s00134-013-2890-3
17. Mueller RG, Haase N, Wetterslev J, Perner A (2013) Effects of hydroxyethyl starch in subgroups of patients with severe sepsis: exploratory post hoc analyses of a randomised trial. Intensive Care Med 39:1963–1971. doi: 10.1007/s00134-013-3090-x
18. Haase N, Wetterslev J, Winkel P, Perner A (2013) Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial. Intensive Care Med 39:2126–2134. doi: 10.1007/s00134-013-3111-9
19. Legrand M, Darmon M, Joannidis M, Payen D (2013) Management of renal replacement therapy in ICU patients: an international survey. Intensive Care Med 39:101–108. doi: 10.1007/s00134-012-2706-x
20. Laukkanen A, Emaus L, Pettila V, Kaukonen K-M (2013) Five-year cost-utility analysis of acute renal replacement therapy: a societal perspective. Intensive Care Med 39:406–413. doi: 10.1007/s00134-012-2760-4
21. The VA/NIH Acute Renal Failure Trial Network (2008) Intensity of renal support in critically Ill patients with acute kidney injury. N Engl J Med 359:7–20. doi: 10.1056/NEJMoa0802639
22. The RENAL Replacement Therapy Study Investigators (2009) Intensity of continuous renal-replacement therapy in critically Ill patients. N Engl J Med 361:1627–1638. doi: 10.1056/NEJMoa0902413
23. Bellomo R, Lipcsey M, Calzavacca P et al (2013) Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis. Intensive Care Med 39:429–436. doi: 10.1007/s00134-012-2800-0
24. Joannes-Boyau O, Honore PM, Perez P et al (2013) High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med 39:1535–1546. doi: 10.1007/s00134-013-2967-z

25. Lindner G, Schwarz C, Gruessing H et al (2013) Rising serum sodium levels are associated with a concurrent development of metabolic alkalosis in critically ill patients. Intensive Care Med 39:399–405. doi: 10.1007/s00134-012-2753-3
26. Volpicelli G, Lamorte A, Tullio M et al (2013) Point-of-care multiorgan ultrasonography for the evaluation of undifferentiated hypotension in the emergency department. Intensive Care Med 39:1290–1298. doi: 10.1007/s00134-013-2919-7
27. Baldi G, Gargani L, Abramo A et al (2013) Lung water assessment by lung ultrasonography in intensive care: a pilot study. Intensive Care Med 39:74–84. doi: 10.1007/s00134-012-2694-x
28. Vieillard-Baron A, Slama M, Mayo P et al (2013) A pilot study on safety and clinical utility of a single-use 72-hour indwelling transesophageal echocardiography probe. Intensive Care Med 39:629–635. doi: 10.1007/s00134-012-2797-4
29. Petzoldt M, Riedel C, Braeunig J et al (2013) Stroke volume determination using transcardiopulmonary thermodilution and arterial pulse contour analysis in severe aortic valve disease. Intensive Care Med 39:601–611. doi: 10.1007/s00134-012-2786-7
30. Scolletta S, Bodson L, Donadello K et al (2013) Assessment of left ventricular function by pulse wave analysis in critically ill patients. Intensive Care Med 39:1025–1033. doi: 10.1007/s00134-013-2861-8
31. Brun C, Zieleskiewicz L, Textoris J et al (2013) Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. Intensive Care Med 39:593–600. doi: 10.1007/s00134-012-2770-2
32. Charron C, Vignon P, Prat G et al (2013) Number of supervised studies required to reach competence in advanced critical care transesophageal echocardiography. Intensive Care Med 39:1019–1024. doi: 10.1007/s00134-013-2838-7
33. Lheritier G, Legras A, Caille A et al (2013) Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. Intensive Care Med 39:1734–1742. doi: 10.1007/s00134-013-3017-6
34. Boissier F, Katsahian S, Razazi K et al (2013) Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. Intensive Care Med 39:1725–1733. doi: 10.1007/s00134-013-2941-9
35. Vieillard-Baron A, Price LC, Matthay MA (2013) Acute cor pulmonale in ARDS. Intensive Care Med 39:1836–1838. doi: 10.1007/s00134-013-3045-2
36. Boyd O, Grounds RM, Bennett ED (1993) A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 270:2699–2707
37. Boyd O, Grounds RM (2013) Our study 20 years on: a randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. Intensive Care Med 39:2107–2114. doi: 10.1007/s00134-013-3098-2
38. Dellinger RP, Levy MM, Rhodes A et al (2013) Surviving sepsis campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. Intensive Care Med 39:165–228. doi: 10.1007/s00134-012-2769-8
39. Trepte CJC, Bachmann KA, Stork JH et al (2013) The impact of early goal-directed fluid management on survival in an experimental model of severe acute pancreatitis. Intensive Care Med 39:717–726. doi: 10.1007/s00134-012-2775-x
40. Lee JH, Chan YH, Lai OF, Puthucheary J (2013) Vasopressin and copeptin levels in children with sepsis and septic shock. Intensive Care Med 39:747–753. doi:10.1007/s00134-013-2825-z
41. Monnet X, Bataille A, Magalhaes E et al (2013) End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. Intensive Care Med 39:93–100. doi: 10.1007/s00134-012-2693-y
42. Cecconi M, Aya HD, Geisen M et al (2013) Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med 39:1299–1305. doi: 10.1007/s00134-013-2928-6
43. Lakhal K, Ehrmann S, Perrotin D et al (2013) Fluid challenge: tracking changes in cardiac output with blood pressure monitoring (invasive or non-invasive). Intensive Care Med 39:1953–1962. doi: 10.1007/s00134-013-3086-6
44. Van Beest PA, Lont MC, Holman ND et al (2013) Central venous-arterial pCO(2) difference as a tool in resuscitation of septic patients. Intensive Care Med 39:1034–1039. doi: 10.1007/s00134-013-2888-x
45. Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Ribas V et al (2013) Innovative continuous non-invasive cuffless blood pressure monitoring based on photoplethysmography technology. Intensive Care Med 39:1618–1625. doi: 10.1007/s00134-013-2964-2
46. Legrand M, Januzzi JL, Mebazaa A (2013) Critical research on biomarkers: what's new? Intensive Care Med 39:1824–1828. doi: 10.1007/s00134-013-3008-7
47. Bessiere F, Khenifer S, Dubourg J et al (2013) Prognostic value of troponins in sepsis: a meta-analysis. Intensive Care Med 39:1181–1189. doi: 10.1007/s00134-013-2902-3
48. Bjursten H, Dardashti A, Ederoth P et al (2013) Increased long-term mortality with plasma transfusion after coronary artery bypass surgery. Intensive Care Med 39:437–444. doi: 10.1007/s00134-012-2723-9
49. Walkden GJ, Verheyden V, Goudie R, Murphy GJ (2013) Increased perioperative mortality following aprotinin withdrawal: a real-world analysis of blood management strategies in adult cardiac surgery. Intensive Care Med 39:1808–1817. doi: 10.1007/s00134-013-3020-y
50. Leal-Noval SR, Munoz-Gomez M, Jimenez-Sanchez M et al (2013) Red blood cell transfusion in non-bleeding critically ill patients with moderate anemia: is there a benefit? Intensive Care Med 39:445–453. doi: 10.1007/s00134-012-2757-z
51. Lauzier F, Arnold DM, Rabbat C et al (2013) Risk factors and impact of major bleeding in critically ill patients receiving heparin thromboprophylaxis. Intensive Care Med 39:2135–2143. doi: 10.1007/s00134-013-3044-3
52. Nolan JP (2013) What's new in the management of cardiac arrest? Intensive Care Med 39:1211–1213. doi: 10.1007/s00134-013-2917-9
53. Ricome S, Dumas F, Mongardon N et al (2013) Predictors of external cooling failure after cardiac arrest. Intensive Care Med 39:620–628. doi: 10.1007/s00134-012-2794-7
54. Vaahersalo J, Hiltunen P, Tiainen M et al (2013) Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med 39:826–837. doi: 10.1007/s00134-013-2868-1
55. Kamps MJA, Horn J, Oddo M et al (2013) Prognostication of neurologic outcome in cardiac arrest patients after mild therapeutic hypothermia: a meta-analysis of the current literature. Intensive Care Med 39:1671–1682. doi: 10.1007/s00134-013-3004-y

56. Lemiale V, Dumas F, Mongardon N et al (2013) Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med 39:1972–1980. doi: 10.1007/s00134-013-3043-4
57. Beylin ME, Perman SM, Abella BS et al (2013) Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Intensive Care Med 39:1981–1988. doi: 10.1007/s00134-013-3075-9
58. Couper K, Salman B, Soar J et al (2013) Debriefing to improve outcomes from critical illness: a systematic review and meta-analysis. Intensive Care Med 39:1513–1523. doi: 10.1007/s00134-013-2951-7
59. Stocchetti N (2013) What is new in neurocritical care: 2012. Intensive Care Med 39:387–388. doi: 10.1007/s00134-013-2843-x
60. Damian MS, Ben-Shlomo Y, Howard R et al (2013) The effect of secular trends and specialist neurocritical care on mortality for patients with intracerebral haemorrhage, myasthenia gravis and Guillain-Barré, syndrome admitted to critical care. Intensive Care Med 39:1405–1412. doi: 10.1007/s00134-013-2960-6
61. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons et al (2007) Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. J Neurotrauma 24 Suppl 1:S37–S44. doi: 10.1089/neu.2007.9990
62. Ichai C, Armando G, Orban J-C et al (2009) Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med 35:471–479. doi: 10.1007/s00134-008-1283-5
63. Ichai C, Payen J-F, Orban J-C et al (2013) Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive Care Med 39:1413–1422. doi: 10.1007/s00134-013-2978-9
64. Bélanger M, Allaman I, Magistretti PJ (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 14:724–738. doi:10.1016/j.cmet.2011.08.016
65. Prins ML (2008) Cerebral metabolic adaptation and ketone metabolism after brain injury. J Cereb Blood Flow Metab 28:1–16. doi:10.1038/sj.jcbfm.9600543
66. White H, Venkatesh B, Jones M et al (2013) Effect of a hypertonic balanced ketone solution on plasma, CSF and brain beta-hydroxybutyrate levels and acid-base status. Intensive Care Med 39:727–733. doi: 10.1007/s00134-012-2790-y
67. Sigurta A, Zanaboni C, Canavesi K et al (2013) Intensive care for pediatric traumatic brain injury. Intensive Care Med 39:129–136. doi: 10.1007/s00134-012-2748-0
68. Lucas MJ, Brouwer MC, van de Beek D (2013) Delayed cerebral thrombosis in bacterial meningitis: a prospective cohort study. Intensive Care Med 39:866–871. doi: 10.1007/s00134-012-2792-9
69. Eikermann M, Latronico N (2013) What is new in prevention of muscle weakness in critically ill patients? Intensive Care Med 39:2200–2203. doi: 10.1007/s00134-013-3132-4
70. Wieske L, Yin DRPPCP, Verhamme C et al (2013) Autonomic dysfunction in ICU-acquired weakness: a prospective observational pilot study. Intensive Care Med 39:1610–1617. doi: 10.1007/s00134-013-2991-z
71. Haenggi M, Blum S, Brechbuehl R et al (2013) Effect of sedation level on the prevalence of delirium when assessed with CAM-ICU and ICDSC. Intensive Care Med 39:2171–2179. doi: 10.1007/s00134-013-3034-5
72. CABAL Investigators group, Devlin JW, Fraser GL et al (2013) The accurate recognition of delirium in the ICU: the emperor's new clothes? Intensive Care Med 39:2196–2199. doi: 10.1007/s00134-013-3105-7
73. Claassen J, Taccone FS, Horn P et al (2013) Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med 39:1337–1351. doi: 10.1007/s00134-013-2938-4
74. Claassen J, Mayer SA, Kowalski RG et al (2004) Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 62:1743–1748
75. Blaser AR, Poeze M, Malbrain MLNG et al (2013) Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study. Intensive Care Med 39:899–909. doi: 10.1007/s00134-013-2831-1
76. Nguyen NQ, Bryant LK, Burgstad CM et al (2013) Gastric emptying measurement of liquid nutrients using the C-13-octanoate breath test in critically ill patients: a comparison with scintigraphy. Intensive Care Med 39:1238–1246. doi: 10.1007/s00134-013-2881-4
77. Kirkpatrick AW, Roberts DJ, De Waele J et al (2013) Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 39:1190–1206. doi: 10.1007/s00134-013-2906-z
78. Sim JA, Horowitz M, Summers MJ et al (2013) Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years. Intensive Care Med 39:258–266. doi: 10.1007/s00134-012-2719-5
79. Passier RHA, Davies AR, Ridley E et al (2013) Periprocedural cessation of nutrition in the intensive care unit: opportunities for improvement. Intensive Care Med 39:1221–1226. doi: 10.1007/s00134-013-2934-8
80. Manzanares W, Dhaliwal R, Jurewitsch B et al (2013) Alternative lipid emulsions in the critically ill: a systematic review of the evidence. Intensive Care Med 39:1683–1694. doi: 10.1007/s00134-013-2999-4
81. Van den Berghe G (2013) What's new in glucose control in the ICU? Intensive Care Med 39:823–825. doi: 10.1007/s00134-013-2874-3
82. Nayak PP, Davies P, Narendran P et al (2013) Early change in blood glucose concentration is an indicator of mortality in critically ill children. Intensive Care Med 39:123–128. doi: 10.1007/s00134-012-2738-2
83. Fazekas AS, Funk G-C, Klobassa DS et al (2013) Evaluation of 36 formulas for calculating plasma osmolality. Intensive Care Med 39:302–308. doi: 10.1007/s00134-012-2691-0
84. Bech A, Blans M, Telting D, de Boer H (2013) Incidence and aetiology of renal phosphate loss in patients with hypophosphatemia in the intensive care unit. Intensive Care Med 39:1785–1791. doi: 10.1007/s00134-013-2970-4
85. Nair P, Lee P, Reynolds C et al (2013) Significant perturbation of vitamin D-parathyroid-calcium axis and adverse clinical outcomes in critically ill patients. Intensive Care Med 39:267–274. doi:10.1007/s00134-012-2713-y