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Year in review in Intensive Care Medicine 2010: I. Acute renal failure, outcome, risk assessment and ICU performance, sepsis, neuro intensive care and experimentals

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Acute renal injury

Acute renal failure (or acute kidney injury, AKI) is an important issue in critical care because, as was demonstrated in the past, the patients' prognosis is dependent on the disturbed renal function. In 2010, four interesting reviews were presented dealing with general, but also with some specific issues of AKI in critically ill patients: One of the utmost important topics in this context is the question if and how AKI may be prevented in patients at risk for

developing AKI. The working group within the European Society of Intensive Care Medicine (ESICM) consented on an expert opinion list of recommendations [1]. This work was based on a systematic literature search between 1966 and 2009. Several clinical conditions were elucidated, and optional endpoints were extracted. The studies were graded according to existing guidelines. The most important recommendations are prompt resuscitation of the circulation, the use of vasoactive drugs under strict haemodynamic monitoring and additional measures such as renal replacement therapies (RRT). The problem of hypoalbuminemia and its relation to AKI was part of a special paper presenting a meta-analysis of observational studies [2]. As a result of the lack of clear evidence in this context, the authors provide data from observational studies, with evidence that hypoalbuminemia is a significant independent risk factor both for AKI and for death following AKI development. They conclude that any recommendations regarding optional replacement of human albumin under these conditions are premature, and controlled studies are warranted to assess interventions aimed at correcting hypoalbuminemia. The outcome after AKI in patients with severe burns is the topic of another meta-analysis [3]. The authors describe the prevalence and outcome of this specific patient group, with a three- to six-fold higher mortality for AKI patients. In conclusion, this review clearly shows that AKI remains prevalent and is associated with increased mortality in patients with severe burn injury. Finally, another group of authors discussed the age-related changes, and examined the most frequent aetiologies for renal impairment in the elderly [4]. They conclude that this clinical entity will likely become more common, because of the aging of the population, especially highlighting the methods for prevention of AKI development or worsening in the elderly critically ill patient.

Biomarker research in AKI has gathered enormous momentum lately. New biomarkers are sought to aid the earlier diagnosis of AKI as well predicting outcome including requirement for RRT. A new biomarker, serum angiopoietin-2, already shown to be associated with increased mortality in sepsis, was also found to predict 28-day survival in a study including 117 critically ill patients requiring RRT [5]. During recent years neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a very promising early marker of AKI. Serum NGAL was evaluated recently in more than 300 patients showing the capability to predict AKI at least 24 h earlier than the risk, injury, failure, loss, and end-stage kidney (RIFLE) criteria in a mixed intensive care unit (ICU) population [6]. However, as already shown in children, NGAL released from neutrophils is significantly elevated in sepsis even in the absence of AKI. In line with these findings Bagshaw [7] showed significantly higher serum NGAL values in patients suffering from sepsis-associated AKI as compared with non-septic AKI. Furthermore, Martensson et al. [8], in a smaller study including only patients with sepsis, showed that serum NGAL was not reliable in predicting AKI in this specific patient group. Urinary NGAL, however, still appeared promising in this setting showing an increase between 12 and 24 h prior to detection of AKI by RIFLE. In the face of these studies an accompanying editorial [9] outlined that no single biomarker has yet reached the required specificity to be regarded as the “renal troponin”.

An increasing number of studies indicate that sepsis-associated AKI must be considered an entity of its own. Important insight into renal histopathologic changes was provided by post-mortem autopsies in 19 patients who had died from septic shock [10], which is currently the largest investigation in this field. The authors found specific changes, namely capillary leukocyte infiltration in glomeruli and capillaries as well as tubular cell apoptosis. These findings are distinctly different from the so-called acute tubular necrosis very frequently observed in AKI. Vasopressors are an important tool in preventing deterioration of renal function in septic shock. Earlier studies indicated that the choice of vasopressor is not that important [11]. On the contrary, a secondary analysis of the vasopressin and septic shock trial (VASST) showed that in the early stage RIFLE risk, vasopressin was more effective than norepinephrine in preventing progression to higher stages of RIFLE and even requirement for RRT [12]. Though still requiring a randomized controlled trial for validation these findings may change recommendations for preventing AKI [1].

Increased body mass index (BMI) was found to be a risk factor for developing AKI in the ICU [13]. This is in line with previous studies indicating increased risk of morbidity in obese critically ill patients [14]. Similar to this study obese patients with a BMI between 30 and 35 were found to exhibit the lowest mortality, substantiating the idea of modestly increased BMI constituting a survival factor for ICU patients and even influencing post ICU ward mortality.

Citrate anticoagulation has emerged as the preferred method of anticoagulation during the last few years [15] probably even being associated with superior survival [16]. Severe liver insufficiency as can be found in septic shock with multiple organ failure has often been reported to be a limitation for using citrate because of the danger of citrate accumulation due to impaired metabolism. Excellent tolerability of citrate anticoagulation has now been demonstrated in a study including 70 burn septic shock patients treated with continuous veno-venous haemodiafiltration (CVVHDF) [17]. The study showed excellent tolerability and higher efficacy for citrate in terms of circuit survival as compared with heparin anticoagulation in this very special group of patients.

Outcome and scores, ICU performance and risk assessment

Refusal of admission to patients is a serious decision with implications to patient survival. A multicentre, multinational

study investigated factors influencing triage decision [18]. Factors like availability of ventilator beds, severity of disease, Karnofsky score, absence of comorbidities, presence of haematological malignancies but not lower age per se positively influenced the probability of being admitted to an ICU. Interestingly surgical and trauma patients were more likely to be admitted than medical patients. As expected ICU admission increased survival substantially in patients with greater severity of disease.

Ward mortality after discharge is a nearly as important issue. It is well known that admission scores are very not suitable to predict mortality after discharge. The Sabadell score is a subjective score categorizing discharged patients into four groups based on physicians evaluation of the patients ranging from "expected good prognosis in the long term" (score 0) to "not expected to survive hospital stay" (score 3) [19]. This score was validated in a prospective multicentre trial in Spain showing very reliable prediction of hospital survival at ICU discharge [20].

The SAPS 3 project, which was endorsed by the ESICM and carried out by 299 ICUs worldwide, was aimed at providing a new model for improved risk adjustment in critically ill patients which is accessible cost-free to intensivists [21]. This score, already validated repeatedly, exhibits superior performance to previous severity scores. A large prospective cohort study undertaken in Thailand analysing more than 1,800 patients found excellent discrimination but poor calibration of SAPS 3 in a medical intensive care patient requiring first-level customization. A similar process has been required with other severity scores when adapting to local populations. Analysing the data of 28 Brazilian ICUs a customized equation of SAPS 3 for South American countries was found to be very accurate in predicting outcomes in critically ill cancer patients when compared with other scores like SAPS II, Mortality Probability Models III and Cancer Mortality Model [22]. Another investigation from Norway demonstrated satisfying inter-rater reliability for both SAPS 3 and SAPS II scores. Standardized mortality ratio, however, showed larger variability in SAPS 3. This finding is presumably due the heavier reliance of SAPS 3 on data coming from interpretation of charts, whereas SAPS 2 is more dependent on laboratory values [23].

Two studies were concerned with organisation of ICUs. The ICUFUND survey investigated reimbursement practices [24] and demonstrated that ICU physicians definitely prefer separate funding from hospitals and that funding systems including nurse workload were considered superior. Obviously this parameter best reflects actual use of resources by patients. In addition to financial aspects, benchmarking is a very important issue, which still is far from being optimal (e.g. when using average standardized mortality ratio (SMR)). Moreno and co-workers [25] published a brilliant approach to characterize risk profiles for single ICUs. Instead of using a single average SMR the authors established an individualized profile by calculating deviation from an SMR of 1 based on SAPS II for each severity class (i.e. SAPS II score). This method provides a profile which depicts ICU performance for patients at each degree of severity of disease.

Implementing new therapeutic strategies in a complex environment such as an ICU is not that simple, especially when several categories of healthcare professionals are involved. For instance, glucose control is a procedure that requires a step-by-step implementation based on guidelines compatible with the local environment. Eslami et al. [26] compared various aspects of glucose control (efficiency/effectiveness, safety and protocol-related indicators) in three different Dutch ICUs which used different strategies for the implementation of glucose control. A common hallmark was an increased rate of hypoglycaemic events, but this did not stop the process of guideline implementation. The effectiveness of glucose control was variable, leading to substantial revision of each of the guidelines. The use of computer-based intensive insulin protocol is one of the future developments to improve the performance of glucose control. Campion et al. [27] reported their 38-month experience in two different ICUs and found that the manual transcription of blood glucose values was a significant source of error, resulting in inappropriate recommendations for the insulin infusion rate.

Clinical-decision support systems were used successfully to decrease the risk of drug–drug interactions, as shown by the comparison of a period where senior clinicians were helped by a dedicated computerised algorithm with usual care [28]. Patient safety was improved, as shown by a decrease in the incidence of QT interval prolongation and the incidence of hypokalaemia when the computer-based algorithm efficiently decreased the incidence of drug–drug interactions. In terms of safety and adequacy of management, the outcomes of patients with severe sepsis were compared according to the size of ICU [29]. The major finding of this Finnish study was a decreased mortality of surgical patients when they were managed in a large ICU, as compared with smaller units. In respect to safety, Bryland et al. [30] drew the attention towards the presence of harmful glucose degradation products in infusion fluids containing glucose, commonly used during surgery and in ICUs. Importantly, these glucose degradation products were also found in the serum of patients as well as signs of advanced end glycation products and attributable impairments of neutrophil function.

Regarding risk stratification, Hausfater et al. [31] reported the risk factors for mortality from the analysis of a large database of hyperthermic patients admitted in an emergency department in Paris during the 2003 heatwave. Nine independent predictive factors for mortality were

identified, allowing the development of a risk score and the definition of three categories of risk.

The consequences of dysnatraemia (hyper- or hypo-) present at ICU admission were carefully screened in a national Austrian registry of more than 150,000 patients [32]. Mild or severe dysnatraemia was found in 25% of the admissions, and associated with increased raw and risk-adjusted mortality ratio. The multiple logistic regression analysis showed indeed an independent mortality risk rising with increasing severity of hypo- and hypernatraemia.

The acquisition of paresis during an ICU stay is another frequent complication, which is still incompletely understood. In order to assess the influence of hormonal factors, Sharshar et al. [33] prospectively measured the plasma levels of pituitary and peripheral hormones in patients at risk of ICU-acquired paresis. In those patients with paresis, blood glucose concentration was increased and the hormonal pattern of hypogonadism was found in men.

Sepsis, mediators, genetic predisposition to sepsis

A multifaceted intervention promoted by the Surviving Sepsis Campaign (SSC) [34] study group to facilitate compliance with selected guideline recommendations for management of severe sepsis and septic shock in the ICU, emergency department (ED), and wards of individual hospitals and regional hospital networks was implemented voluntarily in the US, Europe and South America. Elements of the guidelines were "bundled" into two sets of targets to be completed within 6 h and within 24 h. An analysis was conducted on data submitted from January 2005 through March 2008.

Analysing data on the compliance with bundle targets and association with hospital mortality from 15,022 subjects at 165 sites the authors showed that the reduction in hospital mortality rates was associated with sustained, continuous quality improvement in sepsis care. Compliance with the entire resuscitation bundle increased linearly from 10.9% in the first site quarter to 31.3% by the end of 2 years ($P < 0.0001$). Compliance with the entire management bundle started at 18.4% in the first quarter and increased to 36.1% by the end of 2 years ($P = 0.008$). Compliance with all bundle elements increased significantly, except for inspiratory plateau pressure, which was high at baseline. Unadjusted hospital mortality decreased from 37 to 30.8% over 2 years ($P = 0.001$). The adjusted odds ratio for mortality improved the longer a site was in the campaign, resulting in an adjusted absolute drop of 0.8% per quarter and 5.4% over 2 years (95% CI, 2.5–8.4%).

Novel important findings in the areas of pathogenesis and biomarkers of sepsis were published in 2010 in *Intensive Care Medicine*.

Accurate and reliable biomarkers are still needed to aid an early diagnosis and monitoring of patients with sepsis. New approaches derived from a better understanding of some of the complex mechanisms of the septic response have been recently assessed. For instance, pentraxin-3 (PTX3) is a newly discovered inflammatory mediator produced by neutrophils, macrophages, myeloid dendritic and endothelial cells. Mauri et al. [35] evaluated the predictive value of PTX3 levels in a set of data from 90 patients with severe sepsis or septic shock. The main finding was that persisting high levels of PTX3 were associated with mortality, and with the severity of sepsis, including the magnitude of coagulation and fibrinolysis dysfunction.

Similarly, the release of soluble ST2, a negative regulator of the Toll-like receptors (TLR), can be assessed by plasma concentration of soluble ST2 receptor (sST2). Hoogerwerf et al. [36] indeed found that in a sample of 95 patients with severe sepsis admission values, persisting high levels of sST2 correlated with disease severity and mortality.

Inhibition of macrophage inhibitory factor (MIF), a thioredoxin-like protein, is a potential novel therapeutic strategy for sepsis. Connections between thioredoxin itself and MIF were confirmed by Leaver et al. [37] who found a significant correlation between the plasma levels of thioredoxin and MIF in patients with sepsis/systemic inflammatory response syndrome (SIRS). This finding obviously opens the way to further research to confirm this link and to understand its underlying mechanism.

Another intriguing aspect of the pathogenesis of sepsis is the activation of the haeme oxygenase-1 (HO-1) enzyme in monocytes, and the anti-inflammatory and anti-oxidant of this pathway. Takaki et al. [38] confirmed in septic patients a close correlation between the level of expression of HO-1, the activity of the enzyme and markers of oxidative stress.

Other novel insights into the field of the cytokine-related pathways were also described. Single-nucleotide polymorphisms of nine cytokine genes (out of 13) were associated with ex vivo cytokine production by LPS-stimulated leukocytes or risk of development of sepsis in a cohort of trauma patients [39]. A relationship between IL-6, IL-10 and the responsiveness to an ACTH stimulation test were also reported by Kwon et al. [40], strongly confirming an interference between the inflammatory response and the neuro-endocrine pathway.

Another insight was described by Levy et al. [41] who demonstrated an increased muscular lactate concentration, with a consistent muscle-to-serum lactate gradient, in patients with severe sepsis. The muscular lactate was also correlated with plasma epinephrine concentration, suggesting a link with the activation of the Na^+K^+-ATPase muscular enzyme.

Once again, these findings stress the increasing complexity of the septic response and the involvement of

several pathways. These recent data will likely lead to the availability of more reliable biomarkers of sepsis and to a better understanding of the susceptibility to infection and the variability in the severity of sepsis.

There are many approaches to understand the pathophysiology of systemic infections and severe sepsis, one of which was the topic of a sound review of the RAGE axis, which stands for "receptor for advanced glycation end-products" and its ligands [42]. The RAGE-dependent mechanisms have been identified for a wide range of disorders such as systemic inflammation, acute lung injury and myocardial dysfunction. The numerous animal experiments are presented showing the beneficial effects of inhibiting these mechanisms. The authors conclude that also in humans, the potential for using these pathways for evaluating novel therapeutic approaches does exist. Other pathways such as TLR-dependent mechanisms were presented in another review [43], elucidating the role in bacterial infection and sepsis, but also for non-septic inflammatory response. The authors give insight into pathophysiology of TLR-2 and -4 contributing to organ dysfunction and critical illness. In addition, optional therapeutic consequences are part of this overview. A similar issue was covered in a paper on soluble mediators causing ventilator-induced lung injury and multi-organ failure [44]. Cytokines, coagulation factors, hormones, lipid-derived mediators, and oxidants are described based on a broad literature search, thus covering the roles of these mediators in the pathophysiology, and trying to describe "candidate mediators".

A decreased level of mitochondial DNA (mtDNA) has been reported in blood from septic patients. Pyle et al. [45] collected blood from 147 patients with severe sepsis and in 83 healthy control subjects. They confirmed a marked diminution of mtDNA in septic patients compared with healthy controls. In a subgroup of 13 patients, they showed that this apparent decrease was due to an increase of circulating neutrophils (containing less mtDNA compared with other leukocyte types). However, septic monocytes also had a decreased mtDNA content and correlated with disease severity (APACHE II score).

Several papers published in *Intensive Care Medicine* in 2010 concentrated on the central role of microcirculatory failure in organ dysfunction and sepsis. The physiological functions of the vascular endothelium were described as a highly dynamic cell layer controlling coagulation state, permeability, growth state and vascular tone [46]. Most of these functions have been discovered as key mechanisms involved in pathogenesis of microcirculatory failure in severe sepsis. The resulting "hyporesponsiveness", a major problem during vasopressor therapy in septic shock, was the topic of another review discussing basic physiology, but also providing clinical data on the relation between vasoactive drugs and organ perfusion [47]. In addition, a brief outline was presented demonstrating current therapeutic strategies and possible future approaches. As a logical consequence, this leads to the striking role of new techniques for better diagnosis and monitoring of microcirculation, which was described in another paper [48]. A sound review of the current literature on methods used to evaluate the microcirculation in humans is the major part of this manuscript. The techniques currently available for the clinician to assess patients with severe sepsis and septic shock are discussed, with special regard to microvideoscopic techniques, as well as laser Doppler and near-infrared spectroscopy techniques. Finally, the therapeutic approaches for improvement of microcirculatory failure were elucidated, with special attention paid to recent developments that have enabled direct in vivo observation of the microcirculation and concepts that have originated from it [49]. A Medline search was conducted by analysing eighty original papers evaluating the specific relationship between perfusion and vasoactive drugs, demonstrating a wide range in interindividual effects.

Neuro intensive care

Non-invasive monitoring: NIRS, TCD and BIS

Three mainstays of the medical treatment of patients with traumatic brain injury (TBI) are to control raised intracranial pressure (ICP) and to maintain cerebral perfusion pressure (CPP) and cerebral oxygenation within normal ranges. Consequently, monitoring of these parameters in neurocritical care is important; however, it requires invasive systems. A more ideal approach would be non-invasive measurements of cerebral oxygenation. In this regard, near-infrared spectroscopy (NIRS) offers hope [50]. Basically, in NIRS, light generated at specific wavelengths is transmitted through the scalp into the brain, and changes in the light attenuation at the receiving end are converted via a computer algorithm into changes in chromophore concentration. NIRS captures an average of the arterial, capillary and venous compartments. Translation of NIRS systems and methods into the clinical field requires an understanding of the physiologic basis of the measured NIRS signals, and unfortunately some uncertainly still remains. Leal-Noval [51] compared in a prospective, observational study in 22 stable patients with severe traumatic brain injury (TBI) the relationship between the standard invasive brain tissue oxygen pressure ($PbrO_2$), measured with a Licox system, and non-invasive regional transcranial oxygen saturation (rSO_2).

$PbrO_2$ is the partial pressure of oxygen in the extracellular fluid of the brain and reflects the availability of oxygen for oxidative energy production. It represents the balance between oxygen delivery and consumption, and is influenced by changes in capillary perfusion. $PbrO_2$ measurement contributes to the prevention of delayed

cerebral damage after TBI and other acute neurological conditions. Normal $PbrO_2$ values based on Licox technology are around 25–30 mmHg, based on animal research. This was confirmed in patients with normal ICP and CPP. The likelihood of death increased with increasing duration of time at or below a $PbrO_2$ of 15 mmHg. The continuous monitoring of $PbrO_2$ is now accepted as being safe and feasible. Initial concerns regarding the invasiveness of these intraparenchymal sensors and the risk of haemorrhage and infection have proved negligible. Nevertheless the possibility of obtaining comparable information with non-invasive, less expensive, economically and biologically, systems remains attractive.

Leal-Noval [51] monitored each patient during a 16-h period allowing a total of 41,809 paired records variables to be analysed and compared. Although a relationship between rSO_2 and $PbrO_2$ was confirmed, the authors reported low accuracy for detecting episodes of moderate cerebral hypoxia, defined as a $PbrO_2 \leq 15$ mmHg. Higher sensitivity and specificity was found at a lower cutoff value, i.e. $PbrO_2 \leq 12$ mmHg, representing more severe cerebral hypoxia.

These observations cast further doubts on the potential applicability of NIRS in TBI. Whether NIRS has added value or even any value in TBI cannot be directly answered on the basis of this study. Of concern is that 45% of the original sample size of 56 patients were excluded for reasons specific to TBI or the technology: frontal haematoma, wounds on either the scalp or forehead, or deficient NIRS signal. Subcutaneous swelling or wounds on scalp and forehead are common in TBI patients. Intracranial lesions and/or recent surgery would further prohibit use of the technique. Uncertainty also exists regarding how traumatic subarachnoid haemorrhage may confound the signal. A technique that, in TBI, may not be applicable in nearly half of patients would seem of limited value. These factors, specific to TBI, set this disease aside with regard to the applicability of NIRS from other more controlled conditions such as extracranial vascular surgery. The study by Leal-Noval strengthens the opinion that NIRS technology may have potential but is not yet ready for routine clinical use in TBI.

Two studies explored application of an another frequently used non-invasive method, transcranial Doppler (TCD), in evaluating autoregulatory status in intracerebral haemorrhage (ICH) [52] and in detecting traumatic carotid dissection [53].

TCD ultrasonography is a non-invasive technique that allows one to observe velocity, direction and properties of blood flow in the cerebral arteries by means of a pulsed ultrasonic beam. TCD can be used to evaluate the state of cerebral autoregulation, or the ability of the cerebral vascular bed to undergo constriction or dilatation in response to various modifications of the cerebral perfusion pressure (CPP), to keep the cerebral blood flow (CBF) constant. The test essentially consists of assessing the changes of the flow velocity in mean cerebral artery (MCA) during changes in CPP, given that changes in MCA velocity reliably correlate with changes in cerebral blood flow.

ICH is a medical emergency, and delays in treatment result in worse outcome. Initial management should focus on urgent stabilization of cardiorespiratory variables and treatment of intracranial complications. Blood pressure management in ICH intracerebral haemorrhage is a cornerstone of the medical treatment and relies on functioning cerebral autoregulation. The association of high blood pressure (BP) and haematoma expansion is controversial. High blood pressure in patients with ICH may cause increased bleeding and haematoma growth. Several guidelines on ICH management advocate appropriate blood pressure control. Nevertheless, targets for treatment remain controversial.

The risks of a sudden therapeutic reduction in BP after ischaemic stroke are well known and are more evident in patients with disrupted autoregulation.

Reinhard [52] evaluated the time course of autoregulation in 26 patients with spontaneous ICH, studied on days 1, 3 and 5 after cerebral ictus. Autoregulation was non-invasively measured from spontaneous fluctuations of blood pressure and middle cerebral artery flow velocity, assessed by transcranial Doppler, using the correlation coefficient index Mx [54]. Mean values of ABP and CBFV were averaged over 3 s. From every 20 such segments (i.e. 60-s periods) separate Pearson's correlation coefficients between ABP and CBFV were calculated. The resulting 1-min correlation coefficients were then averaged to form the autoregulatory index Mx. This index was calculated for MCA sides ipsilateral and contralateral to the ICH. From the same signals, non-invasive cerebral perfusion pressure was calculated. Results were compared with 55 healthy controls and related with clinical and radiological factors and 3-month outcome utilizing the modified Rankin scale. Average Mx values of all patients did not differ across days or from controls. Higher Mx, i.e. poorer autoregulation, on day 5 was significantly related with more severe cases: lower Glasgow coma score (GCS), ventricular haemorrhage and lower non-invasive cerebral perfusion pressure. Increasing ipsilateral Mx between days 3 and 5 was related with lower Glasgow coma score and ventricular haemorrhage. In a multivariate analysis controlling for other haemodynamic factors, higher ipsilateral Mx on day 5 ($P = 0.013$) was a significant predictor for poor 90-day outcome.

Therefore, cerebral autoregulation is primarily preserved in acute ICH, but a secondary decline, mainly ipsilateral, to the ICH can occur in more severe cases.

Cerebral autoregulation still provokes debate, particularly in the context of clinical management of neurocritical care patients. This study by Reinhard [52]

demonstrated that autoregulation could be tested routinely and that it could be disturbed in more severe cases.

The missing link we have to explore in the future is if the evaluation of autoregulatory status could be helpful in selecting a more adequate pressure range during the ICU stay. We are still not able to respond to this crucial question.

Another application of TCD has been explored by Bouzat [53], i.e. the detection of traumatic internal carotid artery dissection using transcranial Doppler in head-injured patients. Traumatic dissections of cervical arteries are a rare injury. This complication is frequently missed after multiple injuries or minor neck trauma. Early diagnosis of traumatic internal carotid artery dissection (TICAD) is essential for initiating appropriate treatment that encompasses blood pressure control, avoiding hypo- and hypertension, and early, i.e. before the appearance of cerebral ischaemic symptoms, anticoagulant treatment. Early appropriate treatment could improve outcome in TICAD.

Bouzat searched for criteria, from TCD measurements on admission, that could be associated with subsequent TICAD diagnosis in a retrospective cohort study of 11 TBI patients with TICAD and absent or mild brain lesions on initial CT scan, 22 TBI controls with comparable brain CT scan lesions (controls 1), and 22 TBI controls with more severe brain CT scan lesions (controls 2) on admission.

TCD measurements were obtained on admission from both MCA. All patients had subsequent CT angiography to diagnose TICAD. A greater than 25% asymmetry in the systolic blood flow velocity between the two MCA was found in 9/11 patients with TICAD versus 0/22 in controls 1 and 5/22 in controls 2 ($P < 0.01$). The combination of this asymmetry with an ipsilateral pulsatility index ≤ 0.80 was found in 9/11 patients with TICAD versus none in the two groups of controls ($P < 0.01$). These results suggest that significant asymmetry in the systolic blood flow velocity between the MCAs and a reduced ipsilateral pulsatility index could be criteria from TCD measurements associated with the occurrence of TICAD in head-injured patients. To be universally accepted and incorporated in screening protocols for TICAD in TBI patients these results, even if encouraging, need to be prospectively validated. If a suspicion of post-traumatic TICAD is present, this non-invasive method could help in the selection of patients to study with a CT angiography (CTA). CTA has an established role in the diagnosis of internal carotid artery dissection, and the increased use and availability of high-resolution multi-detector scanners has fast replaced angiography and possibly MRA as the diagnostic modality of choice.

Another non-invasive monitoring system, bispectral index (BIS), has been tested in comatose survivors of cardiac arrest (CA) treated with therapeutic hypothermia (TH). TH improves outcome in comatose survivors of cardiac arrest and is an accepted standard of treatment nowadays. Unfortunately, TH also alters the predictive value of the classical neurologic prognostication [55] in patients with postanoxic coma and new paradigms have to be identified.

The optimal approach to the prognostic evaluation of a patient treated with targeted temperature management has not been fully resolved. This is an issue of crucial importance, because it is ethically justifiable to limit care or withdraw support only when a poor prognosis is reasonably certain. Monitoring with electroencephalography (EEG) has been recommended and both human and animal data suggest that EEG and somatosensory-evoked potentials correlate with neurological outcomes if recorded after HT. Recent reviews have identified the need for simpler EEG technology that non-neurologists can routinely perform and interpret. BIS is a processed EEG monitoring tool that evaluates the electrical brain activity, ranging from zero, equivalent to a fully suppressed isoelectric EEG, to 100 in the awake patient. An accompanying variable, the suppression ratio (SR), estimates the percentage of each 1-min epoch that is isoelectric, also ranging from 0–100%.

On this track, Seder [56] evaluated the BIS and SR as very early predictors of neurological outcome during therapeutic hypothermia after CA in 97 patients after the first dose of neuromuscular blockade. BIS1 and SR1 were defined as the sustained plateau values in the 5–10 min after the first dose of neuromuscular blockade by observing the trend line from the BIS monitor. Outcomes evaluation (cerebral performance category, CPC) at discharge, was blinded. Good neurological outcome has been defined as a CPC 1-2 (GO) and poor outcome as a CPC 3-5 (PO). Receiver-operator characteristic curves and a multiple logistic regression model were constructed for GO and PO. The BIS1 was higher in patients with GO (37 [28–41] vs. 7 [3–15], $P < 0.001$). BIS1 < 22 predicted PO with a likelihood ratio (LR) of 14.2 and an area under the curve (AUC) of 0.91 (95% CI 0.85–0.98, $P < 0.001$). SR1 ≥ 48 predicted PO with a LR of 12.7 and an AUC of 0.90 (95% CI 0.83–0.98, $P < 0.001$). Both BIS1 (ΔAUC 0.16, $P = 0.006$) and SR1 (ΔAUC 0.16, $P = 0.005$) predicted outcomes better than the time to return of spontaneous circulation.

In this single-centre cohort utilizing moderate sedation, bispectral index and suppression ratio recorded immediately after the first dose of neuromuscular blockade were accurate and very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. According to these data and other research in the field, updated practical guidelines for prediction of outcome in comatose survivors after cardiopulmonary resuscitation are more than expected.

Delirium and sedation

Delirium is increasingly recognized as a major adverse event occurring postoperatively in surgical patients. Once

the diagnosis has been established, the main goal of delirium therapy is to identify important, potentially life-threatening, treatable, organic causes responsible for this syndrome.

Nevertheless it is difficult to substantiate the clinical diagnosis of postoperative delirium with objective parameters in ICUs. The purpose of a study of the Heidelberg group [57] was to analyse whether BIS index, cortisol and interleukin-6 were different in delirious patients as compared with non-delirious ones after cardiac surgery.

On the first postoperative day, delirium was analysed in 114 patients by using the confusion assessment method for ICU (CAM-ICU). Bilateral BIS data were determined. Immediately thereafter plasma samples were drawn to analyse patients' blood characteristics. The current ICU medication, haemodynamic characteristics, SOFA and APACHE II scores, and artificial ventilation were noted. Delirium was detected at 19.1 ± 4.8 h after the end of surgery in 28% of the patients. Delirious patients were significantly older than non-delirious ones and were artificially ventilated 4.7-fold more often during the testing. Interestingly, in delirious patients, plasma cortisol and interleukin-6 levels were higher ($P = 0.01$). The mean BIS index was significantly lower in delirious patients (72.6 (69.6–89.1); median [interquartile range (IQR), 25th–75th percentiles] than in non-delirious patients, 84.8 (76.8–89.9). BIS EEG raw data analysis detected significant lower relative alpha and higher theta power. A significant correlation was found between plasma cortisol levels and BIS index. The authors demonstrated that early postoperative delirium after cardiac surgery was characterized by increased stress levels and inflammatory reaction. BIS index measurements showed lower cortical activity in delirious patients with a low sensitivity (27%) and high specificity (96%).

Anxiolytics are often required in ICU for sedative comfort and patient safety. Yet sedative regimens typically incur consequences of reduced consciousness, impaired cognition and the risk of delirium. Recent emphasis has been towards reducing the depth of sedation, which has been instrumental in reducing mortality and overall ICU length of stay. Such principles are introduced in guidelines for "cooperative" patient sedation [58]. Additional benefits of a more awake patient include conservation of patient autonomy and early recognition of evolving neurological deterioration.

Commonly used ICU sedatives such as potent narcotics and benzodiazepines have been demonstrated to incite cognitive dysfunction and delirium. Dexmedetomidine (DEX) is an alpha2-agonist that appears to offer sedation without alteration in level of arousal or incurring a high incidence of delirium. Mirski [59] hypothesized that optimal titration of this agent may also have modest impact on cognitive function. At the Johns Hopkins, Mirski conducted a prospective, randomized, double-blinded study comparing DEX and propofol (PRO), a sedative-hypnotic often used for continuous ICU sedation, using an ICU-validated cognitive assessment tool, i.e. the validated 100-point Hopkins ACE adapted cognitive exam (ACE) cognitive battery. The aim of the study was to evaluate which sedative regimen offered the least decrement in intellectual capacity on awake and intubated brain-injured (BI, $n = 18$) and non-BI (12) ICU patients. Each patient received fentanyl/PRO and fentanyl/DEX titrated to a calm, awake state using a crossover design. Cognitive testing was performed at each study period using the ACE cognitive battery.

Sedation with PRO diminished adjusted ACE scores by a mean of −12.4 (95% CI −8.3 to −16.5, $P < 0.001$), whereas DEX improved ACE scores (6.8, 95% CI 1.2–12.4, $P < 0.018$). The difference in the change of ACE score between DEX versus PRO, the primary endpoint, was 19.2 (95% CI 12.3–26.1 $P < 0.001$) in favour of an improved ACE score on DEX. Patients with BI required less sedative, but effects of PRO and DEX on cognition were not changed. No serious adverse events occurred. Modest bradycardia was noted post hoc with DEX (−7.7 bpm, $P < 0.01$).

ICU patients may be offered sedation without necessarily compromising arousal or cognition. DEX seems a promising drug for obtaining this aim. Alleviation of anxiety and agitation can singly and effectively improve mental engagement and performance if overt forebrain dysfunction is avoided. Higher ACE scores with DEX may be a consequence of the intellect-sparing yet calming effect of this drug.

CNS complications in ICU

Admission of patients with malignancies to ICUs remains a very controversial issue. Neurological complications are common life-threatening events in patients with malignancies. Central nervous system (CNS) involvement requiring admission to the ICU has been reported in up to 20% of critically ill patients with malignancies. However, there are no studies specifically designed to determine the causes and outcomes of neurological events in this population. The information on CNS involvement in critically ill patients with cancer are scanty. Legriel [60] conducted a retrospective study of 100 consecutive critically ill cancer patients admitted to an ICU with central neurological events over a 7-year period. The study objective was to obtain information on the nature and outcomes of neurological events in critically ill cancer patients hospitalized in the ICU. These patients were managed by using standardized diagnostic and therapeutic strategies. Presenting manifestations were coma (56%), epilepsy (48%), focal signs (35%), encephalopathy (31%) and meningitis (7%). Cerebral imaging was abnormal in 61 patients, lumbar puncture in 17 and electroencephalography

in 6. Neurosurgical biopsy was performed on four patients. The main aetiologies included drug toxicity in 28, malignant brain infiltration in 21 patients and cerebrovascular disease in 20. Mechanical ventilation was needed for 60 patients. Anticancer chemotherapy was administered during the ICU stay in 15 patients. ICU and hospital mortalities were 28 and 45%, respectively. By multivariate analysis, independent positive predictors of hospital mortality were poor performance status [odds ratio (OR) 2.94, 95% CI, 1.01–8.55, $P = 0.047$), focal signs at presentation (OR 3.52, 95% CI, 1.14–10.88, $P = 0.029$), abnormal lumbar puncture (OR 5.49, 95% CI 1.09–27.66, $P = 0.038$) and need for vasoactive drugs (OR 6.47, 95% CI 1.32–31.66, $P = 0.021$). Remission of the malignancy (OR 0.20, 95% CI 0.04–0.88, $P = 0.033$) and GCS score at admission (OR 0.81/point, 95% CI, 0.70–0.95, $P = 0.009$) were negative predictors of hospital mortality.

Central neurological events are mainly related to malignant brain infiltration and drug-related toxicity. Despite advanced severity, a standardized intensive management strategy yields a 55% hospital survival rate.

As concluded in the accompanying editorial [61] these data should encourage the intensivist to evaluate opening the doors of the ICU to patients with malignancies and neurological complications, enabling them to receive optimal care.

Neuromuscular abnormalities are common in ICU patients and can have an impact on patients' ICU stay. Brunello [62] evaluated the incidence of clinically diagnosed ICU-acquired paresis (ICUAP) and its impact on outcome. Forty-two patients with SIRS on mechanical ventilation for at least 48 h were prospectively studied. Diagnosis of ICUAP was clinically defined as symmetric limb muscle weakness in at least two muscle groups at ICU discharge without other explanation. The threshold Medical Research Council (MRC) score was set at 35 (of 50) points. Using this score, full muscle strength results in 5 points (M5) per tested muscle. A clinical diagnosis of ICUAP was made when weakness ($\leq$M3) was diffuse, bilateral, involving upper and lower extremities, and resulted in a greater than 30% reduction in MRC score (<35 points), independent of presence or absence of sensitivity disturbance or reduced tendon reflexes. Activities in daily living were scored by using the Barthel index 28 and 180 days after ICU discharge. ICUAP was diagnosed in 13 of the 39 patients (33%). Multivariate regression analysis yielded five ICUAP-predicting variables ($P < 0.05$): SAPS II at ICU admission, treatment with steroids, muscle relaxants or norepinephrine, and days with sepsis. Patients with ICUAP had lower admission SAPS II scores [37 $\pm$ 13 vs. 49 $\pm$ 15 ($P = 0.018$)], lower Barthel index at 28 days and lower survival at 180 days after ICU discharge (38 vs. 77%, $P = 0.033$) than patients without ICUAP. Daily TISS-28 scores were similar but cumulative TISS-28 scores were higher in patients with ICUAP (664 $\pm$ 275) than in patients without ICUAP (417 $\pm$ 236; $P = 0.008$). The only independent risk factor for death before day 180 was the presence of ICUAP. A clinical diagnosis of ICUAP was frequently established by Brunello in this patient group. Despite lower SAPS II scores, these patients needed more resources and had high mortality and prolonged recovery periods after ICU discharge.

In order to better evaluate muscular weakness in ICU, Fan [63] evaluated inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. The goal of the paper was to determine inter-rater reliability of trained examiners performing standardized strength assessments using manual muscle testing (MMT). The authors report on 19 trainees undergoing quality assurance within a multi-site prospective cohort study. Inter-rater reliability was evaluated for specially trained evaluators ("trainees") and a reference rater, performing MMT using both simulated and actual patients recovering from critical illness. Across 26 muscle groups tested by 19 trainee–reference rater pairs, the median (interquartile range) per cent agreement and intraclass correlation coefficient (ICC; 95% CI) were 96% (91, 98%) and 0.98 (0.95, 1.00), respectively. Across all 19 pairs, the ICC (95% CI) for the overall composite MMT score was 0.99 (0.98–1.00). When limited to actual patients, the ICC was 1.00 (95% CI 0.99–1.00). The agreement (kappa; 95% CI) in detecting clinically significant weakness was 0.88 (0.44–1.00). MMT has excellent inter-rater reliability in trained examiners and is a reliable method of comprehensively assessing muscle strength.

Outcome prediction in SAH

Mortality due to aneurysmal subarachnoid haemorrhage (aSAH) fell by about 50% over the last 2 decades, due mainly to improved outcomes in cases surviving to reach hospital, without a substantial increase in the proportion of survivors with more severe disability [64]. The major cause of poor outcome in aSAH patients is related to neurologic injury caused by the haemorrhage itself and the neurologic sequelae that follow. An accurate early anticipation of long-term irreversible brain damage during the acute phase of patients with aSAH remains difficult.

For exploring the possibility to develop a multiparametric prognostic panel to facilitate early outcome prediction following aSAH, Turck [65] tested a combination of clinical scores together with brain injury-related biomarkers (H-FABP, NDKA, UFD1 and S100beta). Over the past few years, a large number of biomarkers, present in the blood and CSF, have raised interest in the detection of aSAH patients with poor clinical outcome. Nevertheless, the majority of these markers displayed either low sensitivity or specificity to anticipate the

detection of patients with poor outcome. Turck et al. [66, 67] tested post-mortem CSF as a model of massive brain insult. In these studies, heart-fatty acid binding protein (H-FABP), nucleotide diphosphate kinase A (NDKA) and ubiquitin fusion degradation protein 1 (UFD-1) were over-expressed in post-mortem compared to ante-mortem CSF and were validated as potential brain damaged biomarkers. Turck et al. [65] hypothesized that such a plasmatic marker may provide quantitative information reflecting the prediction of aSAH patient outcome. At hospital admission, S100b, H-FABP, troponin I, NDKA and UFD-1 protein blood concentrations were determined in patients with spontaneous aSAH. In addition to specific clinical parameters, their potential predictive power to detect poor 6-month outcome following aSAH evacuation was also tested.

Blood samples of 141 aSAH patients from two separated cohorts (sets of 28 and 113 patients) were prospectively enrolled and analysed with 14 months of delay. Patients were admitted within 48 h following aSAH onset. A venous blood sample was withdrawn within 12 h after admission. H-FABP, NDKA, UFD-1, S100beta and troponin I levels were determined by using classical immunoassays. The World Federation of Neurological Surgeons (WFNS) score at admission and the Glasgow outcome score (GOS) at 6 months were evaluated.

In the two cohorts, blood concentration of H-FABP, S100beta and troponin I at admission significantly predicted unfavourable outcome (GOS 1-2-3). A multivariate analysis identified a six-parameter panel, including WFNS, H-FABP, S100beta, troponin I, NDKA and UFD-1; when at least three of these parameters were simultaneously above cutoff values, prediction of unfavourable outcome reached around 70% sensitivity in both cohorts for 100% specificity.

The use of this panel, including four brain injury-related proteins, one cardiac marker and a clinical score, could be a valuable tool to identify aSAH patients at risk of poor outcome. Although the results of the present study are encouraging, additional studies are needed to establish the validity of this approach.

Experimentals

Mechanical ventilation, biomarkers of acute lung injury, and ischaemia reperfusion

A number of excellent studies published in 2009–2010 examined the mechanisms of ventilator-induced lung injury (VILI) and investigated the effects of different ventilatory strategies and pharmacological interventions in protecting the lung from VILI.

VILI is associated with biotrauma involving inflammatory cascade activation. An elegant study by Fanelli et al. [68] showed that pulmonary-derived phosphoinositide 3-kinase gamma (PI3 K) may play a central role contributing to VILI. In an isolated and perfused lung model, the investigators observed that PI3 K gene knockout mice had better preserved lung structure compared with wild-type mice in response to a given mechanical stress. The lung in PI3 K knockout mice showed a reduction in phosphorylation of protein kinase B (Akt), endothelial nitric oxide synthase (eNOS), production of nitrate and nitrotyrosine, and cAMP hydrolysis. These findings were further confirmed by using a PI3 K kinase inhibitor in combination with an inhibitor of cAMP hydrolysis in wild-type mice, suggesting PI3 K as a possible therapeutic target in the context of VILI.

The acute respiratory distress syndrome (ARDS) associated with transfusions, named transfusion-related acute lung injury (TRALI), may be largely overlooked as it often goes unrecognized. In particular, ARDS patients may be at high risk to develop TRALI under treatment with mechanical ventilation. This speculation is supported by a recent study by Vlaar et al. [69]. The investigators showed that within 2 h after administration of MHC-I antibodies, mice ventilated with low tidal volume develop TRALI which deteriorated with high tidal volume ventilation. In addition to biotrauma, it is suggested that maldistribution of tidal volume may have led to VILI. Thus an optimal PEEP level may be required to keep better regional volume distribution. For this purpose, electrical impedance tomography (EIT) was recently tested to identify regional tidal volume and compliance. In saline lavage-induced lung injury model in neonatal piglet, Dargaville et al. [70] measured global and regional tidal volume and compliance over a broad range of PEEP levels. They demonstrated that a PEEP level can be identified by EIT to achieve better distribution of regional tidal volume after lung recruitment. This suggests that EIT may be a useful tool to help select optimal PEEP in keeping the lung open. Beside the dedicated technique, researchers also search for simple techniques evaluating pulmonary oxygenation or gas exchange. Rees et al. [71] proposed a mathematical model to calculate oxygenation data upon changing the inspired oxygen fraction. They compared the results with those obtained using the multiple inert gas elimination technique as a reference to describe inert gas data from heterogeneous lung damage. They found that the simple mathematical model and the multiple inert gas elimination technique are comparable in simulating partial oxygen tension values, and the comparability and accuracy were similar over different ventilator settings. This observation may provide an alternate approach to estimate gas exchange in certain clinical situations.

From the therapeutic point of view, different patterns of mechanical ventilation may have an important impact on the outcome of lung injury. An interesting study by

Saddy et al. [72] compared the effects of different assisted ventilation modes in rats where initial lung injury was induced by administration of paraquat. The investigators reported that assisted ventilation modes led to better lung function and less inflammation and injury as compared with pressure-controlled ventilation. Henzler et al. [73] further investigated the effects of spontaneous breathing during mechanical ventilation on haemodynamics and lung injury in a pig model of intra-abdominal hypertension. When the animals were ventilated with biphasic positive airway pressure in the presence of unsynchronized spontaneous breathing, no improvement in haemodynamics but a greater degree of lung damage were observed. These results alert one against the use unsupported spontaneous breaths during mechanical ventilation with biphasic positive airway pressure during severe intra-abdominal hypertension.

Therapeutic interventions may have a place in reducing VILI. In a mouse model of VILI induced by high tidal volume ventilation, Peltekova et al. [74] reported that hypercapnia attenuated lung inflammation and injury in a dose–response and time-dependent manner. In particular, hypercapnia suppressed the expression of prostanoid-generating enzyme (COX-2) at both gene and protein levels. However, hypercapnia elevated the levels of nitrotyrosine in lung tissue, suggesting an increased oxidative stress. The results confirm the potential beneficial and detrimental effects of using hypercapnia. These effects must be taken into account when the hypercapnia approach is applied in the context of VILI. However, the study did not address whether the permissive hypercapnia is involved in hypermetabolism during mechanical stress. Because mechanical ventilation is delivered on a 24-h basis, inadequate adjustment leading to excessive work of breathing may result in hypermetabolism. Aslami et al. [75] tested the hypothesis that suspended animation is protective in VILI by reducing metabolism. In mechanically ventilated rats, VILI was induced by high pressure ventilation in the presence and absence of sodium hydrosulfide (NaSH, H_2S donor) infusion. The authors reported that NaSH dose-dependently reduced body temperature, heart rate, expired CO_2, and pulmonary inflammation. The anti-inflammatory effect was not observed in animals subjected to hypothermiato to a similar extent as seen with administration of H_2S. This study suggests that NaSH induces a hypometabolic state and reduces pulmonary inflammation, which is independent of body temperature. Further research is required to confirm the findings and to understand the mechanisms by which NaSH exerts anti-inflammatory effects in VILI.

Critically ill patients with acute lung injury are often complicated with multiple sources of insult. However, it is unclear whether the biological features of acute lung injury are similar or not in response to different initial insults. López-Aguilar et al. [76] randomly divided rats into three groups of acute lung injury models by using either high tidal volume ventilation, massive brain injury or endotoxin injection for 3 h. Despite the lack of evidence of significant alternation in lung function and structural changes, lung and systemic inflammatory responses such as production of cytokines and extracellular matrix proteins take place in all three models. Furthermore, the early lung inflammatory responses are similar in both direct and indirect lung injury models. However, because the cytokines and extracellular matrix proteins are not lung specific, it is difficult to separate the possible systemic inflammatory effects from local effects in the lung. Indeed, reliable biomarkers are very important for clinicians in bedside management, both as a diagnostic tool and as a follow-up of antibiotic therapy in patients with sepsis. Long pentraxin-3 (PTX3) is a soluble pathogen pattern recognition receptor for innate immunity. Studies by He et al. [77] and by Mauri et al. [35] were designed to test the validity of PTX3 as a biomarker in a mouse model of endotoxemia and in patients with sepsis. In the human study, the investigators reported that the PTX3 levels remained elevated during the first 5 days after the diagnosis of sepsis, and thus it appeared to be a reliable prognostic marker; PTX3 levels had a better discriminative power for survival than those of C reactive protein, IL-6 and TNF-α. In the animal study, endotoxemia was introduced by intratracheal instillation of LPS in mice. After 24 h, PTX3 protein in the bronchoalveolar lavage fluid was increased in parallel with the severity of lung injury. Importantly, this study demonstrated that the expression of PTX3 reflected an effective therapeutic intervention following the use of tissue factor inhibitor, which supports that PTX3 is a biomarker for acute lung injury. Although the study results are exciting, the use of PTX3 as a biomarker for heterogeneous and multi-organ syndromes, such as sepsis and ARDS, is yet to be established at bedside. An editorial by Zhang et al. [78] accompanied the article. It is suggested that PTX3 should be considered as a research tool in the field of intensive care medicine.

A couple of studies examined the hypoperfusion status and the effects of treatment in distal organ during ischaemia/reperfusion. Acute renal failure is a frequent complication contributing to high morbidity and mortality in critically ill patients. Although the pathophysiology of acute renal failure is not fully understood, there is general agreement that renal hypoperfusion is an important factor in the pathogenesis of acute renal failure. Saotome et al. [79] conducted a study of a ewe model with various degrees of renal hypoperfusion. They observed that 25, 50 or 75% impairment of renal blood flow for 30 min was not associated with renal failure. During 2 h of 80% hypoperfusion, renal dysfunction took place that was reversed by restoration of normal renal blood flow. The authors concluded that “unlike total ischemia, severe hypoperfusion alone is insufficient to induce subsequent persistent acute kidney injury”. An excellent editorial by

Drs. Groesdonk and Heringlake [80] accompanied the article. They noted that this information is not really new, but rarely recognized in the current literature. The editorial further pointed out that the study did not determine the humoral responses to renal hypoperfusion, but such analyses may provide important insights into mechanisms by which isolated renal low flow behaves differently from the established models of combined systemic and renal hypoperfusion. Another study focused on inflammatory responses during ischaemia and reperfusion. In an intestinal ischaemia/reperfusion injury model induced by clamping both the superior mesenteric artery and the celiac trunk in mice, Crisafulli et al. [81] observed that the administration of olprinone, a specific phosphodiesterase-III inhibitor, resulted in up-regulation of cAMP and decreased injury in ileum tissue. The protective effects were associated with decreased inflammatory responses, suggesting an important signaling pathway during ischaemia and reperfusion shock. These findings need to be confirmed at multiple organs in different models for future study.

Experimental models of infections and sepsis

Anthrax has received much attention in relation to its possible use in bioterrorism. In a study published by Cui et al. [82], the authors investigated the effects of cell walls from *Bacillus anthracis* in comparison with those from *Staphylococcus aureus* and bacterial endotoxin (LPS). They showed that injection of high doses *B. anthracis* cell walls to rats was lethal, and that lower doses induced a marked inflammatory reaction, similar to that observed with other types of bacterial agonists. Without finding a clear explanation for this, they observed that non-lethal injections of *B. anthracis* cell walls or LPS protected rats again a subsequent infusion of the highly lethal *B. anthracis* toxin.

Newborns deprived of oxygen often develop pulmonary hypertension and multiple organ dysfunction, including cardiac failure. Joynt et al. [83] described a hypoxia/reoxygenation neonatal swine model, and studied the effects of epinephrine vs. dobutamine versus milrinone in the resuscitation of the piglets. Whereas all drugs improved cardiac output, only epinephrine and dobutamine increased mean arterial pressure (MAP). Milrinone just maintained MAP in comparison with control piglets who underwent severe hypotension and shock. No significant effect of the drugs was observed on the pulmonary arterial pressures. Oxygen delivery was increased in carotid and intestinal arteries with the three drugs, whereas only milrinone seemed to increase renal blood flow. The authors conclude that the three inotropes improve cardiac output, and oxygen delivery to tissues, with a small advantage in favour of milrinone owing to its renal effect.

It has been proposed that mechanical ventilation per se may influence innate immune defences of the lung. Villar et al. [84] induced sepsis in rats by performing cecal ligation and puncture, and randomized the rats to be ventilated with high versus low levels of lung stretch, or kept them spontaneously breathing. They found that a protective ventilation strategy attenuated TLR4 activation and decreased lung inflammation. In contrast, the injurious ventilation protocol increased lung TLR4 and IRAK3 levels, as well as lung and systemic inflammatory cytokine levels. This study emphasizes the intimate relationship between ventilation-induced lung inflammation and lung responses to bacterial agonists.

Renal impairment following colloid infusion has been a concern in many animal and human studies. Schick et al. [85] tested three fluid loading solutions in a model of rats rendered septic by cecal ligation and puncture. All the groups showed some alteration of renal function. The less deleterious was a crystalloid isotonic balanced solution. Kidney from septic rats resuscitated with either hydroxyethylstarch or gelatin showed marked impairment of renal function and histologic renal tubular abnormalities. This study adds to the concerns of using colloids as fluid replacement therapy in sepsis.

Adrenal dysfunction is a hallmark of patients with severe septic shock. However little is known about the histological changes in adrenals from septic patients or animals. Polito et al. [86] observed lipid depletion in the zona fasciculata from adrenals obtained in patients who died from septic shock. They observed similar abnormalities (as well as inflammation, necrosis and haemorrhage) in adrenals from rodents rendered septic with endotoxin or by cecal ligation and puncture. These histological findings may explain the adrenal dysfunction observed during severe sepsis syndromes.

Microvascular dysfunction with slower or stoppage of blood flow in capillaries has been reported in many organs in animal models of sepsis and in patients with septic shock, and certainly participates in tissue hypoperfusion. The intimate mechanisms of this capillary dysfunction remain poorly understood in vivo. Using a fecal peritonitis model in mice, Secor et al. [87] investigated the role of intravascular coagulation and platelet adhesion as a possible mechanism for capillary obstruction. They found that treatments with platelet depletion, P-selectin blockade (blockade of platelet adhesion), antithrombin, and ascorbate as antioxidant prevented blood cells sludging in microvessels. Studies with eNOS-deficient mice also implicated NO in the prevention of the platelet aggregation and stoppage of blood in the microcirculation. This study highlights the critical importance of platelet aggregation in the microvasculature as a pathogenic role for organ dysfunction during severe sepsis syndromes.

Both anti- and pro-inflammatory effects of β-agonists have been reported. Tsao et al. [88] investigated the effects of a β2-agonist, terbutaline, in a cecal ligation and

puncture model in rats. They found that terbutaline prevented systemic hypotension, reduced hepatic and renal dysfunction, decreased plasma IL-1β, NO production and tissue levels of reactive oxygen species, as well neutrophil recruitment to the lung and liver. In addition, terbutaline significantly improved survival rates in this rat model. The authors postulate that the protective effect of terbutaline may be related to a decreased inflammation via the activation of the β2 receptor.

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