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## Year in review in Intensive Care Medicine 2011: I. Nephrology, epidemiology, nutrition and therapeutics, neurology, ethical and legal issues, experimentals

Received: 14 December 2011  
Accepted: 14 December 2011  
Published online: 4 January 2012  
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ESICM 2012

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### Introduction

A number of articles have been published in the fields of neurology, nutrition, epidemiology, nephrology, and ethics,

together with interesting experimental investigations. This year, we wanted to integrate the works published in *Intensive Care Medicine* with the most relevant papers in these various fields published in other distinguished journals.

## Nephrology

Acute kidney injury continued to be hot topic in 2011. Early diagnosis remains an issue of increasing importance, with the aim being to install early preventive measures in critically ill patients. Several very promising biomarkers turned out to have serious limitations in specific disease states, e.g. NGAL in septic shock [1, 2]. Cystatin C is another biomarker that is presumed to allow the early detection of small declines in glomerular filtration rate (GFR), but may also reflect tubular damage if measured in the urine. Royakkers et al. [3] investigated both urine and serum cystatin c in a multicentre prospective observational trial including 151 patients, and could not detect any diagnostic value for urinary cystatin c, only a very moderate performance of serum cystatin c for the prediction of AKI (AUC 0.72), and a very poor one for predicting the requirement for renal replacement therapy RRT (renal replacement therapy) (AUC  $\leq$ 0.66). Serum cystatin C may also be futile as a biomarker for AKI (acute kidney injury) in the setting of renal obstruction [4].

Discrimination between transient and persistent AKI is of clinical relevance but currently often based on urinary indices which are not very reliable in critically ill patients. Darmon et al. [5] used a different approach by determining Doppler resistive indices in 51 patients. They found that a RI  $>0.795$  predicted persistent AKI with an OR of 1.85 (95% CI 1.2–2.85) upon applying logistic regression analysis. Considering the large influence of interobserver variability on this method, larger multicentre trials are required to prove the utility of this method in daily clinical practice.

The question of the optimal mean arterial pressure to optimise renal perfusion and renal function is still unresolved. Redfors et al. [6] approached this question in an elegant crossover study including 12 postcardiac surgery patients with norepinephrine-dependent vasodilatory shock. Increasing the target mean arterial pressure (MAP) from 60 to 75 mmHg resulted in significantly improved GFR (27%) and urinary output associated with increased oxygen delivery (13%) and reduced renal oxygen consumption. A further increase of MAP to 90 mmHg was ineffective or even detrimental for these parameters. The results indicate severely disturbed autoregulation of the kidney in vasodilatory shock and possible benefits from targeting a higher MAP of around 75 mmHg.

Three studies investigated the epidemiology of AKI of specific aetiologies. Hoste et al. [7] examined the incidence of contrast-media induced AKI (CI-AKI) in 787 predominantly surgical ( $\sim$ 75%) patients. As opposed to data obtained from non-critically ill patients, the authors found a near-threefold increased incidence, with rates of between 16 and 23% depending on the definition used. Contrast-induced AKI was associated with a significantly increased length of stay, higher requirements for renal

replacement therapy and mortality (1-year mortality 55.5 vs. 24% in patients without CI-AKI). Decreased renal function at the time of intervention, lower mean arterial pressure, vasoactive therapy, and administration of diuretics were found to be major risk factors for CI-AKI. This study, currently the largest of its kind, underlines the importance of nephrotoxic medication in this specifically vulnerable group of patients, and sets the stage for future randomised trials investigating effective preventive measures against CI-AKI.

Pettila et al. [8] and Nin et al. [9] reported the epidemiology of AKI associated with severe H1N1 infections in different parts of the world. They found incidence rates of AKI of between 34 and 51%, demonstrating the high frequency of this complication in patients suffering from H1N1 infection. The occurrence of AKI was associated with a significantly increased risk of hospital mortality. Nin et al. specifically addressed the question of early AKI versus late AKI (after ICU day 2), and found a worse outcome for the latter, indicating that a large proportion of early AKI occurring in the context of H1N1 infection is presumably due to pre-renal factors like dehydration or hypotension, which can be easily corrected, resulting in rapid renal recovery. However, as demonstrated in accompanying correspondence by Nin et al. [10], viral particles could also be found within renal tissue obtained from a few biopsies, which possibly contributed to AKI. These studies provide further insight into the pathophysiology of AKI in the setting of severe viral infections; it is most probably a mixture of pre-renal causes combined with endothelial damage and severe disturbance of the coagulation system caused by exaggerated inflammatory response and finally complicated by secondary bacterial infections. Direct renal effects of viral infiltration of the kidney, however, appear to be a very rare mechanism for AKI [11].

Sepsis is considered a well-established risk factor for AKI, with sepsis-associated AKI showing a very modest prognosis, substantiated by mortality rates of up to 75% [12]. On the other hand, AKI itself is considered a systemic disease associated with impaired immune function. Mehta et al. [13] investigated the frequency and the clinical consequences when sepsis developed as a complication of AKI in 618 critically ill patients from the multicentre PICARD study. They found that about 40% of the patients developed sepsis at a median of 5 days after AKI, with similar consequences for outcome as seen in sepsis-associated AKI itself. This study demonstrates the importance of preventing AKI as well as taking measures against infections in patients already suffering from AKI to avoid consecutive development of sepsis.

Another condition in which alterations in patients' immune response may significantly influence outcome is liver cirrhosis. Berry et al. [14] showed that a reduction in HLA-DR expression by monocytes to less than 40% of

admission values was highly correlated with increased 90-day mortality. The changes in HLA-DR expression were also associated with reduced Th1 response to antigenic stimulation and exaggerated secretion of the anti-inflammatory cytokines IL-10 and IFN- $\gamma$ .

## Epidemiology

Three epidemiologic studies investigated the outcomes of postsurgical patients admitted to the ICU. Analysing the data for 88,504 patients collected from several Austrian ICUs over a period of 11 years, Rhodes et al. [15] found that pre-existing morbidities such as chronic renal disease, respiratory or cardiac failure, cirrhosis, alcoholism, acute kidney injury or nonmetastatic cancer significantly impaired outcome. Independent from those risks, reason for admission, urgency of operation, age and SAPS II score turned out to be major factors associated with hospital mortality. An interesting observation was the fact that survival had improved over the investigated period of 11 years.

Another important risk factor for increased morbidity and mortality appears to be postoperative red blood cell transfusion, as shown by Mohnle et al. [16], who analysed a cohort of 945 patients with a low-to-moderate risk profile after coronary artery bypass grafting among 5,436 patients enrolled in an international multicentre trial. Patients receiving red blood cell transfusions had a higher likelihood of experiencing cardiac events or harvest site infections, and suffered from impaired composite morbidity outcome which included hospital mortality, renal failure, pneumonia and mediastinitis.

An increased body mass index may be protective in surgical intensive care unit patients. Hutagalung et al. [17, 18] analysed ICU and hospital mortality in 9,935 patients, and found that both overweight (BMI 25–29.9 kg/m<sup>2</sup>) and obese (BMI 30–39.9 kg/m<sup>2</sup>) patients showed a significantly lower 60-day hospital mortality than very obese and even normal weight patients. Interestingly, the improved survival prevailed despite a higher incidence of AKI in these specific weight groups, as already shown in another recent study [18].

The association of older age and outcome with prolonged ICU stay was investigated in a cohort of 11,395 cardiac surgery patients by Ettema et al. [19]. The authors were able to demonstrate that all three major currently applied prediction models for outcome—the Parsonnet model, the Huijskes model and the EuroSCORE—showed poor calibration with age >70 and decreasing discrimination, which was worst for age >80 (AUCs were 0.68, 0.69 and 0.64, respectively). Obviously, outcome and recovery in older patients is rather more dependent on their general condition than on the conventional parameters used for scoring systems.

## Predictors of mortality

Simple, widely available lab tests could represent useful markers and predictors of outcome in ICU patients, especially when a strong rationale supports their potential prognostic value. For instance, eosinophil count is tightly and readily regulated by cytokines and is related to the stimulation of the adrenal axis. Likewise, the presence of eosinopenia has already been reported as a marker of infection. In a large prospective study, Abidi et al. [20] evaluated the prognostic value of serial eosinophil count measured daily from ICU admission until the seventh day of stay in 200 patients. The absolute eosinophil count was lower over the entire ICU stay in nonsurvivors. Eosinopenia (<40 cells/mm<sup>3</sup>) was found to be an independent predictor of ICU mortality, with an area under the ROC curve of 0.82. These findings highlight the usefulness of the inexpensive and probably underused leukocyte formula in the ICU.

Similarly, the presence of hypoxic hepatitis—defined as the presence of a transient increase in serum aminotransferase activity of over 20 times the upper limit of the normal range in the absence of putative causes of liver necrosis (virus, drugs)—in patients with cardiocirculatory or respiratory failure was carefully scrutinised in a large cohort of 1,066 patients admitted to a medical ICU [21]. The mortality of the 118 patients who fulfilled the criteria of hypoxic hepatitis was indeed increased, especially in the subgroup of patients who required vasopressor therapy. After adjustment, the presence of hypoxic hepatitis was found to be a strong independent risk factor for mortality in patients receiving vasopressor therapy.

Another common finding is corticosteroid insufficiency related to critical illness, a condition associated with increased mortality. The diagnosis of this condition is challenging, as the usefulness of the ACTH test as well as the type of cortisol assay that should be used are still debated. Molenaar et al. [22] compared the values of total and free cortisol after an ACTH test. They found in a set of 112 patients (49 with sepsis) that the diagnosis of adrenal failure was not affected by the type of test used, as free and total cortisol measurements were closely related. These findings could have important implications for daily practice.

## Predictors of outcome of sepsis and physiopathological insights

The search for biomarkers of sepsis outcome is an intense field of clinical research. Several new potential markers were assessed and validated by different teams who published their reports in the journal in 2011. An early rise in circulating endothelial protein C was found to be associated with a high mortality [23]. This finding confirms the activation of coagulation at the initial stage of sepsis, and suggests a pathogenetic role for endothelial protein C in the pathway.

In another study [24], the concentration of cardiac troponin T detected by a high-sensitivity assay was found to be elevated in all patients with severe sepsis, and this level was correlated with other indices of poor outcome of sepsis, even though it was not found to be an independent predictor of survival. These findings further support the presence of myocardial injury in sepsis, in proportion to the severity of the sepsis, consistent with other data.

Likewise, the risk of acquisition of a second infection in patients with sepsis was found to be increased when the dendritic cell count was persistently low [25]. A selective depletion of circulating plasmacytoid and myeloid dendritic cells was demonstrated by these authors and by others early after the onset of sepsis. The study suggests that the persistence of low levels increases susceptibility to the development of a second infection, and opens up a large field for further research.

High-mobility group box 1 is a histone that plays a role in the coordination of inflammatory pathways. Barnay-Verdier et al. [26] demonstrated the presence of antibodies directed against high-mobility group box 1 in plasma samples from patients with sepsis. The presence of these antibodies could play a protective role, since the mortality was found to be lower in patients with the highest levels. Moreover, the emergence of these antibodies during the course of sepsis was detected more often in survivors than in nonsurvivors.

The pathogenesis of encephalopathy associated with sepsis could include mitochondrial dysfunction. Therefore, mutations and polymorphisms of mitochondrial DNA might affect the cerebral response to sepsis. In a well-defined cohort of Chinese patients with sepsis, Yang et al. [27] found that a haplogroup of mitochondrial DNA was a strong predictive factor for the development of septic encephalopathy. If confirmed in other populations, such findings pave the way for genomic research in the ICU.

In another exciting line of clinical research, the metabolic alterations of subcutaneous fat tissue were characterised by microdialysis [28]. These researchers found that tissue glycerol and glucose levels were higher during septic shock than during severe sepsis. In contrast, lactate, pyruvate and lactate-to-pyruvate ratios were similar in both conditions. These important findings are likely to change our understanding of the role of fat tissue in the metabolic response to sepsis.

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## Nutrition and therapeutics

In 2011, several important findings in the fields of metabolism and therapy were reported in the journal. These were new physiopathological insights based on commonly recorded data, or more sophisticated approaches using cutting-edge technologies. New therapeutic advances were presented as well.

Blood glucose concentration and glucose metabolism continuous to be a major topic of interest and is still controversial. During the last decade, neither the most cited study in *Intensive Care Medicine* [29] nor the largest interventional study published in *Intensive Care Medicine* [30] has been able to settle the issue of tight glucose control. During 2011, Mackenzie et al. [31] contributed with a systematic analysis of a local database containing blood glucose concentrations and outcomes using a metric methodology. In principle, three different measures that influenced outcomes in terms of mortality were identified out of the blood glucose concentrations; hyperglycaemia, hypoglycaemia, and glucose variability. Needless to say, the study did not include the possibility of differentiating the relative predictive values of the three measures, but as pointed out by Krinsley [32] in an accompanying editorial, future studies of blood glucose control cannot avoid including all three measures.

Meyfroidt et al. [33] from the working group who presented the initial report on tight glucose control, reported the advantage of an automatic predefined blood glucose threshold. The incidence of hypoglycaemia was reduced by 1/3, but the variability of blood glucose was not affected.

The difficulties involved in feeding critically ill patients by the enteral route are well recognised. Often it is gastric emptying that is the problem. Nguyen et al. [34] have investigated the absorption of fat and carbohydrates in the small intestine in relation to motility following surgical repair of abdominal aortic aneurysms. Motility was impaired as compared to controls. This resulted in reduced absorption of both fat and carbohydrate. Over time, it was demonstrated that the reduced fat absorption was more prolonged after the surgical procedure. This technique opens up interesting possibilities and seems suited for use in evaluations of other groups of critically ill patients, and perhaps to guide the composition of enteral formulations as suggested by the authors.

The optimal nutrition of critical ill patients is a really hot topic, in particular after the EPaNIC study favouring delayed parenteral nutrition [35]. The TICACOS study by Singer et al. [36] is a pilot study in mechanically ventilated patients ( $n = 112$ ) employing a bundle comprising supervised nutrition intervention including indirect calorimetry, as compared to a body weight guided protocol. The indirect calorimetry group received a higher intake of calories and protein, demonstrating the feasibility of indirect calorimetry. The fact that higher intake was also associated with a longer ICU stay is in total accord with the abovementioned EPaNIC study. As pointed out in an accompanying editorial, the use of indirect calorimetry should be recommended to individualise nutrition, extending follow-up beyond the doors of the hospital [37].

Another important part of nutrition is selenium supplementation, as most countries in Europe have a low natural abundance of selenium, and inflammatory states lower the plasma concentration further. Recent studies have

demonstrated a survival advantage of selenium supplementation [38]. Manzanares et al. [39] report a study with high selenium supplementation: 2.0 mg as a bolus followed by 1.6 mg/24 h for 10 days. The high dose of selenium resulted in stimulation of glutathione peroxidase and a lower incidence of hospital-acquired pneumonias. The clinical advantage in terms of morbidity in this comparatively small study ( $n = 35$ ) indicates that prompt restoration of selenium status early in the course of critical illness is important.

The muscle protein depletion seen during critical illness is present in all age groups. Tuvdendorj et al. [40] report quantitative measurements of skeletal muscle protein turnover, including separate measurements of the synthesis rate and the degradation rate in patients with extensive burn injuries. Muscle protein degradation was increased regardless of age, but the synthesis rate was higher in children, resulting in a significantly better protein net balance in children. This finding is in line with earlier clinical reports of separate studies in children and adults of protein turnover in critical illness, but this finding of Tuvdendorj et al. is original, as it has never before been demonstrated in a homogeneous patient population dichotomised for age. Still, the generalisability beyond burn injury remains to be demonstrated.

Modulating oxidative stress by increasing endogenous antioxidant defence mechanisms has already been intensively investigated. A new set of data was presented in the journal this year [41]. The administration of pharmacological doses of selenium for 14 days in 75 patients with systemic inflammation or sepsis allowed an increase in glutathione peroxidase activity as compared to 75 untreated patients. However, no change was found in mortality, even in subgroups of patients stratified by severity of disease or organ failures. The modalities and indications for antioxidant strategies should definitely be carefully scrutinised in the future. Paraquat intoxication is a prototypical example of oxidative stress associated with high mortality. In such cases, therapeutic options and antidotes are scarce. A new treatment algorithm (high-dose cyclophosphamide + high-dose methylprednisolone) has been assessed and compared to the previous treatment (cyclophosphamide + dexamethasone) in a very large cohort of 111 patients with paraquat poisoning [42]. Mortality was decreased from 92 to 66% in patients randomised to the new algorithm. These important results obviously bring a major contribution to the field of toxicology.

## Neurology

### Searching for markers of cerebral vasospasm

The occurrence of symptomatic cerebral vasospasm (SCV) after aneurysmal subarachnoid haemorrhage (aSAH) is a frequent clinical condition that is unfortunately associated with worsened morbidity and mortality [43, 44]. The ability

to predict patients at high risk for vasospasm would help in targeting early therapeutic efforts. So far, this has remained an unsatisfied plea [45]. In the ICU, clinical assessment by bedside evaluation is of limited usefulness due to sedation or clinical severity. Transcranial Doppler is a useful screening tool for middle cerebral artery vasospasm, with less utility in evaluating other intracranial vessels, and computed tomographic perfusion may help predict vasospasm when used early during the clinical course [46]. Due to the difficulties involved in identifying SCV, several early markers that could be used to provide therapies focused on early brain damage signs have been searched for, with the aims being to prevent but also reduce the intensity of later developing neurological complications [47]. Turck [48] used an awkward panel including four brain injury-related proteins, one cardiac marker and a clinical score, and demonstrated that this is a valuable albeit complex tool for identifying aSAH patients at risk of poor outcome.

Recently, pentraxin 3 (PTX3), a protein induced by proinflammatory signals produced by neutrophils, macrophages, myeloid dendritic and endothelial cells, has emerged as a key player in local inflammatory and ischaemic events, and it has been proposed as a valuable prognostic and diagnostic tool in many conditions, substantiating the evidence that PTX3 has useful features for a potential biomarker. In this context, Zanier [49] investigated the concentrations of PTX3 and its relation with SCV in the plasma and cerebrospinal fluid (CSF) of 38 aSAH patients. PTX3 was elevated in all SAH patients in both plasma and CSF. Early, acute peak CSF PTX3 was significantly higher in patients who later developed vasospasm [median 13.6 (range 2.3–51.9) ng/ml] compared to those who did not [3.2 (0.1–50.5) ng/ml,  $p = 0.03$ ]. The temporal pattern of CSF PTX3 in patients with vasospasm was triphasic, with a peak during the first 48 h after SAH, a subsequent decrease in the following 48–96 h, and a secondary significant increase with the occurrence of vasospasm. The measurement of CSF PTX3 can improve early diagnosis of this complication, and will be evaluated as a potential early biomarker in further researches. Even if we are improving in the identification of potential biomarkers to use as an early warning for CVS, this search is not yet concluded, and in the future we will probably ameliorate our comprehension in this exciting field.

### Barbiturate therapy for refractory ICP

High intracranial pressure (HICP) frequently complicates severe traumatic brain injury, aSAH and other neurological disorders. Raised intracranial pressure has been consistently associated with poor neurological outcome. Treggiari [50], in a systematic review of trauma patients, evaluated the management of raised ICP and related neurological outcomes. ICP refractory to therapy and the response to treatment are very good predictors of



neurological outcome compared to absolute ICP values. Relative to normal ICP, raised ICP was associated with a 3.5- to 6.9-fold increase in mortality. Raised but reducible ICP was associated with a 3- to 4-fold increase in the probability of death or poor neurological outcome. Refractory ICP pattern was associated with a dramatic increase in the relative risk of death (odds ratio >110). The same applies to aSAH patients [51].

Our efforts at controlling HICP encompass the use of first-line therapies (CSF withdrawal, sedation, osmotics, hyperventilation, CPP optimisation). If all of these fail and the patient is salvageable, we are obliged to use “second-tier” therapies, including barbiturates, hypothermia and decompressive craniectomy. High doses of barbiturates are still recommended to control HICP refractory after the failure of maximal standard medical and surgical therapy [52]. Along with many other severe side effects, the most important being haemodynamic instability and pulmonary complications, dyskalaemia has been described as a severe adverse effect in case reports [53, 54]. Thiopentone inhibits voltage-dependent potassium currents and inhibits phosphofructokinase, causing intracellular sequestration of potassium during its administration and an extracellular release when it is stopped. For this reason, the discontinuation of the drug must not be abrupt; it has to be slowly tapered. However, the real incidence and characteristics of dyskalaemia during and after barbiturate coma have not been well described. Ng et al. [55] performed a retrospective review of all 47 patients who received barbiturate therapy for refractory HICP during an 18-month period in a neurosurgical ICU. 89.4% of the barbiturate patients’ cohort developed hypokalaemia after the induction of barbiturate therapy. The median time to onset of hypokalaemia was 11 h and the time to nadir of serum potassium levels was 25 h. More importantly, 34% patients developed hyperkalaemia on weaning off barbiturate therapy. All patients who developed hyperkalaemia had previously been hypokalaemic. The mean potassium replaced during hypokalaemia was higher in patients who developed hyperkalaemia compared to those who did not. Therefore, hypokalaemia and hyperkalaemia are frequently associated with induction and cessation of barbiturate coma. Serum potassium levels must be monitored vigilantly. Patients who develop hypokalaemia and receive large potassium replacement may be at greater risk of hyperkalaemia on cessation. Hyperkalaemia at cessation has been described as cause of cardiac arrest in this population.

## Cerebral monitoring

Not all monitors give you the same numbers! The physiological idea behind cerebral oxygen monitoring is that the PbrO<sub>2</sub> value accurately represents the balance between oxygen delivery and oxygen consumption in brain cells, and that changes in PbrO<sub>2</sub> will therefore reflect

pathophysiological alterations. These changes could then be used to guide treatments to prevent or mitigate hypoxic injury [56]. PbrO<sub>2</sub> has been frequently monitored using a Licox system (LX, Integra Neuroscience, Biot, France), the only available device until a couple of years ago. Recently, a different manufacturer (Raumedic, Munchberg, Germany) introduced a new probe, the Neurovent-PTO (NV). Dengler [57] compared the performance of the two systems in 11 comatose traumatic brain injury (TBI) or aSAH patients during dynamic changes in inspirational oxygen fraction and mean arterial pressure. PbrO<sub>2</sub> was recorded continuously in patients using the two probes which were placed side-by-side in the same cerebrovascular region. Once a steady baseline value was reached, FiO<sub>2</sub> was increased by 20% for 10 min. Once the baseline was again achieved, MAP was increased by 20 mmHg for 10 min. The PbrO<sub>2</sub> values of both probes differed significantly at all times. The LX probe reacted significantly faster to changes in FiO<sub>2</sub> and MAP. Limits of agreement ranged between -32.1 and 20.0 mmHg. Mean LX values were 6.1 mmHg lower than NV values. Even if the examined patient cohort was rather small, the data suggest that LX and NV probes measure different PbrO<sub>2</sub> values in routine monitoring as well as during phases of dynamic changes in FiO<sub>2</sub> and MAP. These data therefore do not support the view that both probes can be used interchangeably. The practical advice for the clinician is to be aware of the performance of the system they are using and to adapt treatment thresholds accordingly.

Lescot and co-workers [58] tested intracranial pressure monitors in a study on neurosurgical intensive care patients. They used the Pressio and the Codman devices and compared the results with direct intraventricular measurement. They found that both pressure monitors approximated intraventricular cerebrospinal fluid pressure with an accuracy of  $\pm 7$  mmHg, a result that may be acceptable under many clinical conditions.

In another study, the brain temperature was measured using two different magnetic resonance techniques [59]. Healthy volunteers were exposed to intranasal cooling, and brain temperature changes were measured and mapped using MR spectroscopic imaging and phase-mapping techniques. The decrease in brain temperature assessed by MR was  $-1.7^{\circ}\text{C}$  by spectroscopic imaging and  $-1.8^{\circ}\text{C}$  by phase mapping at the end of 1 h of nasal cooling. The rectal temperature fell by  $0.5^{\circ}\text{C}$ . Thus, the simple nasal cooling technique had a substantial effect on brain temperature.

## Ethical and legal issues

### End-of-life care in specific countries

During 2011 in *Intensive Care Medicine*, there were three articles that focused on end-of-life care in specific

countries. First, Solarino and colleagues conducted a national survey of Italian physicians following the high profile death of a 36-year-old woman who had been in a vegetative state for 17 years [60]. The Italian Supreme Court granted the woman's father his wish to discontinue nutrition and hydration. The authors of this paper emailed a questionnaire to 70,000 physicians working for the Italian Public Health System and University Medical Hospitals. 22,219 doctors responded, representing a response rate of 32%. Approximately three-quarters had experience in treating patients in a persistent vegetative state. Approximately 60% of them considered tube feeding to be a medical therapy, and 66% believed that withdrawing artificial nutrition and hydration could be appropriate if based on the patient's wishes. There was broad consensus among Italian physicians that a clear legislative position regarding the withdrawal of artificial nutrition and hydration is needed.

Second, Weng and colleagues [61] conducted an anonymous survey of the attitude of Chinese intensivists toward end-of-life care in the ICU. Although no list of Chinese intensivists exists, they used an innovative snowball method to identify 534 potential participants from 21 regions in China. The response rate was 59%. The authors found that approximately 60% of physicians reported admitting patients with very poor prognosis to the ICU, and only 19% reported giving complete information to the patients and their families. The use of do-not-resuscitate orders or the limitation of life-sustaining therapy in terminally ill patients was uncommon. Interestingly, the authors compared their results to studies using the same survey in Hong Kong and in Europe. Intensivists in China were equally likely to admit patients with poor prognosis to the ICU as those in Hong Kong and Europe, but were less likely to report withholding or withdrawing life support.

Finally, Kubler and colleagues [62] reported the results of a survey of intensivists attending a national intensive care congress in Poland. Of the 400 questionnaires distributed, 54% were returned. Almost all respondents (93%) reported that they had withheld life support, and 75% of the respondents reported that they had withdrawn life support. Older physicians and those who reported no religious affiliation were more likely to report withholding life support. Respondents from large hospitals (>400 beds) were also more likely to report foregoing life support in ICU patients. These results were similar to a study conducted in Western Europe using the same questionnaire.

#### Communication and collaboration in end-of-life care

A qualitative study by Lind and colleagues [63] studied family members' experiences of end-of-life decision-making in Norwegian ICUs, in order to ascertain the

degree to which the family felt informed and included in decision-making. The authors used a grounded theory method of qualitative analysis with interviews of 27 bereaved family members. This study found that family members wanted a more active role in decision-making, in order to be able to communicate the values and preferences of the patient. The authors also found that clinicians often used a "wait and see" strategy to address decision-making early in the ICU stay, which many family members experienced as unnecessarily delaying the family members' ability to come to terms with the severity of the patient's illness and to participate in decision-making. Family members also discussed the importance of communication with ICU nurses. The authors suggest that ICU clinicians need more training in the knowledge and skills of effective communication with families of critically ill patients.

Jensen and colleagues [64] conducted a survey of nurses and physicians in the ICU as well as physicians in primary care to examine communication and collaboration between ICU and primary care clinicians regarding decisions to forego life support in the ICU. The study was conducted in seven hospitals in Southern Denmark. Participants included 495 ICU nurses, 135 ICU physicians, and 146 primary physicians, with an overall response rate of 84%. Among primary care physicians, approximately 60% found their experience of collaboration to be satisfactory, compared to only 36% of ICU physicians and 27% of ICU nurses. ICU physicians and nurses were more likely than primary care physicians to perceive that decisions regarding withdrawal of life support were unnecessarily postponed due to communication between ICU and primary care clinicians. The authors suggest that multidisciplinary patient conferences, nurse involvement in the decision-making process, and guidelines for foregoing life support might improve communication and collaboration.

#### End-of-life care in paediatric ICUs

Cremer and colleagues [65] conducted a multicentre prospective observational study to assess the prevalence of questioning about the appropriateness of initiating or maintaining life support in 15 French-speaking paediatric ICUs, and to evaluate decision-making processes. Among the 5,602 children admitted, 410 died (7%) and 175 of those (43% of the deaths) died after foregoing life support. The utility of life support was questioned in 308 children (6%) with a prevalence of 13 per 100 patient-days. More than 30% of the children survived despite the appropriateness of life support being questioned, and 23% survived despite a decision to forego life support. The median clinician time spent on making and presenting decisions about the utility of life support was considerable at 11 h per child. On any given day in each paediatric

ICU, there was more than one child for whom a decision to forego life support was being considered, representing a significant amount of paediatric ICU clinicians' time, and suggesting that this is an important part of paediatric intensive care.

Devictor and colleagues [66] conducted a multicenter prospective study, the Eurydice II study, in 45 paediatric ICUs in Europe. They identified decisions to forego life support in 166 children, representing 41% of the paediatric deaths. They found some regional variability, with more patients dying after CPR in Eastern and Central Europe than in Northern and Western Europe. The vast majority of decisions to forego life support were discussed by clinicians and families during a formal family meeting, after which the medical staff generally made the final decision. The decision was almost always documented in the medical record. The majority of parents were informed of the final decision and were at the bedside during their child's death. Decisions were made to forego life-sustaining treatment in 41% of children who died, which was higher than the 33% seen in Eurydice I conducted in 2002, 6–7 years earlier. Eurydice II found that a higher percentage of parents were now informed about the meeting and its conclusion as compared with the earlier Eurydice I. This study shows a trend towards the standardisation of paediatric end-of-life practices across European countries in the past decade, with increased communication with the parents of critically ill children.

#### Resource allocation and identification of organ donors

Kohn and colleagues [67] sent questionnaires to a national sample of US ICU clinicians, soliciting their preferences for allocating their last bed to a gravely ill patient with little chance of surviving versus a deceased or dying patient for whom aggressive management could help others through organ donation. The authors received completed surveys from 684 of 2,206 physicians (31%) and 438 of 988 nurses (44%). They found that physicians were more likely than nurses to adhere to the "rule of rescue" by allocating the last bed to the gravely ill patient (46 vs. 33%). The magnitude of the social benefit to be obtained through organ donor management (5 or 30 life-years added for transplant recipients) had small and inconsistent effects on clinicians' willingness to prioritise the donor. The most common reason for allocating the last bed to an identifiable patient was that clinicians perceived strong obligations to identifiable living patients.

The authors argue that this allegiance to the rule of rescue will be a major challenge for efforts to develop ethical and standardised ICU triage practices.

In order to identify a potential organ donor as early as possible and maximise the donor conversion rate, it is important to study this conversion rate. However, the

donor conversion rate is calculated with different assessment tools, making it difficult to compare across studies and centres. de Groot and colleagues [68] conducted a study to determine which assessment tool can be used for a realistic estimation of a potential organ donor pool, and how they compare to each other with regard to the donor conversion rate. They conducted a retrospective chart review of patients diagnosed with a subarachnoid haemorrhage, traumatic brain injury, or intracerebral haemorrhage, and applied three different assessment tools. In their cohort of patients, 179 out of 564 (32%) died. After applying three different assessment tools, the number of patients found to be brain dead, before exclusion due to medical reasons or age, ranged from 76 to 107 patients. The authors identified one tool that was the most practical for identifying patients with a realistic chance of becoming brain dead and therefore identifying the patients most likely to become a potential organ donor.

## Experimentals

### Acute lung injury and mechanical ventilation

Most previous studies have focused on the propagation of epithelial and endothelial injury in ALI/ARDS; the ability of bacteria to colonise host defense mechanisms are not well studied in this pathophysiologic process. Piccin and colleagues [69] examined the hypothesis that mechanical ventilation directly affects respiratory defense mechanisms (the mucociliary system). The authors used different modes of mechanical ventilation in rabbits, and demonstrated that mechanical ventilation using high volume and high pressure led to detrimental changes in the large proximal airway mucociliary system compared with lower tidal volume ventilation. Although a significant decrease in tracheal mucus secretion was noted across all ventilated groups, only animals ventilated with high pressures showed a significant reduction in ciliary beating frequency. The authors speculated that the mucociliary alterations occurred as a result of tissue hypoperfusion caused by mechanical ventilation with high pressures and high airway flows. An editorial [70] pointed out that the relevance of the observation is yet to be investigated in patients under mechanical ventilation. It is nevertheless important to understand the effects of changes in mucociliary clearance in the context of ventilator-induced lung injury that may alter host susceptibility to infections or prolonged intubations due to secretion retention.

Mechanical ventilation with high tidal volume increased the generation of reactive oxygen stress (ROS), cytokine responses, and the activation of mitogen-activated protein kinase (MAPK) and nuclear factor (NF)- $\kappa$ B associated with



lung injury [71]. In an isolated, perfused rat model, the administration of apocynin, a strong oxidative inhibitor known to block nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in neutrophils, macrophages, and endothelium [72–74], depressed oxidative stress, attenuated inflammatory responses, and reduced ventilator-induced lung injury (VILI) [71].

Resolution of the alveolar epithelial/capillary membrane damage that occurs during acute lung injury (ALI) requires a coordinated and effective tissue reconstruction program to re-establish a functional barrier [75]. Regeneration of alveolar epithelial cells and matrix turnover are controlled by regulatory pathways, while dysregulation of these pathways may result in amplification of the initial injury and disorderly repair, with sustained inflammation and development of pulmonary fibrosis [76, 77]. Since WNT/ $\beta$ -catenin signaling has been reported to be involved in epithelial cell injury [78], Villar et al. [79] demonstrated that this pathway is modulated early during ventilator-induced lung injury. This modulation may represent a promising therapeutic target for attenuating or preventing the pathological consequences of acute lung injury.

The mechanisms of ventilator-induced diaphragmatic damage (VIDD) are not fully elucidated [80]. Previous studies have shown that high tidal volume ventilation leads to the activation of serine/threonine kinase/protein kinase B (Akt) and c-Jun NH2-terminal kinase (JNKs) [81]. Activation of the phosphoinositide 3-OH kinase (PI3-K)/Akt pathway also results in the phosphorylation of the class O of forkhead box transcription factor (Foxo) proteins [82]. Li et al. demonstrated that a high tidal volume ventilation-induced diaphragmatic damage model was associated with the activation of JNK and Foxo4, and this process was dependent on the Akt and JNK pathways. These data help us to understand the effects of mechanical forces on the diaphragmatic injury, as well as suggest whether inhibiting the Akt and JNK pathways offers possible treatment options [83].

Previous studies have shown that high-dose corticosteroids or neuromuscular blocking agents (NMBA) [84] may affect diaphragm function [85]. Maes et al. [86] hypothesised that the combination of rocuronium (NMBA) and corticosteroids would result in a further deterioration of diaphragm function in a model of ventilator-induced diaphragm dysfunction (VIDD). They observed that the negative effect of rocuronium infusion with controlled mechanical ventilation was absent with the administration of a high dose of corticosteroid due to inhibition of the calpain and caspase-3 system.

It has been suggested that the airway pressure used in the mechanical ventilation of patients with ALI/ARDS should be in-between the low and upper inflection points of the pressure–volume ( $P$ – $V$ ) curve. During constant inspiratory flow, analysis of the airway pressure–time profile ( $P$ – $t$ ) can replace the static  $P$ – $V$  curve [87]. From

the mathematical point of view, the airway pressure can be described as a function of inspiratory time by the following equation: airway pressure =  $at^b + c$ , where the coefficient  $b$ , called the stress index, describes the shape of the  $P$ – $t$  curve during a tidal breath. If  $b < 1$ , it means that the compliance increases, suggesting tidal recruitment; if  $b = 1$ , it suggests that the compliance does not change, while if  $b > 1$ , it indicates compliance decreases, suggesting tidal overinflation [88]. Formenti et al. [89] tested the predictive ability of the stress index compared with quantitative lung CT scan in paralysed, mechanically ventilated pigs. The tests were conducted at PEEP values of 1 and 10 cm H<sub>2</sub>O in the absence and presence of pleural effusion by fluid instillation in pleural space. The investigators demonstrated a dissociation between the stress index, which suggested lung overinflation, and the CT scan, which showed lung recruitment. This observation suggests that the ability of the stress index to predict lung recruitment and overdistension was significantly reduced in the pathophysiological conditions. However, the authors did not measure the transpulmonary pressure in their study. An editorial [90] suggests that computation of the stress index as usually obtained from the airway pressure curve should be replaced by analysis of the transpulmonary pressure curve profile. In the heterogeneous airspace environment of ALI/ARDS, a reliable tool at the bedside to set desirable PEEP and VT is critical [91]. Traditional methods of monitoring lung mechanics using the pressure–volume curve, static compliance and the stress index have shown drawbacks, especially when the compliance of the chest wall is altered. Computed tomography (CT) scan is a powerful tool for mapping the distribution of the gas volume, but it is yet to be a part of bedside technology. The forced oscillation technique (FOT) may offer several potential advantages over traditional methods because it applies very small volume displacement, it minimises artifacts resulting from non-linearity of the respiratory system, and it does not require deep sedation and muscle paralysis. Using FOT in a surfactant depletion model of ALL, Dellaca and colleagues [92] performed incremental and decremental PEEP trials, and measured both conventional and FOT-derived respiratory system compliance at each step of PEEP changes. CT scan analysis was performed as a gold standard for monitoring lung compartments at end expiration. FOT was able to detect the minimal PEEP value needed to keep the lung open, and this was in good agreement with CT scan analysis with respect to sensitivity and specificity, suggesting that FOT may have potential value in defining adequate levels of PEEP to prevent/reduce the occurrence of de-recruitment. However, the validation of FOT to detect the extent of recruitment/de-recruitment and hyperinflation remains to be determined in more complicated clinical situations [93]. Variable ventilation is a new mode delivering volume-controlled ventilation with variation of the tidal

volume around an average value. Pillow et al. [94] found that variable ventilation increased dynamic compliance but not static compliance or oxygenation in preterm lambs. They also found decreased PaCO<sub>2</sub> and concluded that variable ventilation was more efficient than conventional ventilation. The authors speculated that the lack of improvement in oxygenation between the groups was due to right to left shunt. However, one may argue that the pulmonary vascular resistance might have decreased with the observed improvement in compliance and reduced CO<sub>2</sub> levels, thus resulting in better pulmonary blood flow and oxygenation. Further investigations are needed to address the effects of variable ventilation in physiological and pathological conditions.

The gradient between end-tidal partial pressure of CO<sub>2</sub> (PETCO<sub>2</sub>) and arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) (PET-aCO<sub>2</sub>) in mechanically ventilated patients presents a wide range of variation [95]. The reduction of the PET-aCO<sub>2</sub> gradient can be achieved in spontaneously breathing healthy humans using an end-inspiratory rebreathing technique, which equilibrates end-tidal, alveolar, arterial and venous PCO<sub>2</sub>. Based on the aforementioned, Fierstra et al. [96] investigated whether this method would reduce the PET-aCO<sub>2</sub> gradient in a ventilated animal model. This technique led to a reduction in the PET-aCO<sub>2</sub> gradient, while the precision of PETCO<sub>2</sub> as a surrogate for PaCO<sub>2</sub> was independent of the PaCO<sub>2</sub>, PaO<sub>2</sub>, and SaO<sub>2</sub> as well as the extent of lung disease. Therefore, the end-inspiratory rebreathing technique may allow precise, noninvasive monitoring of PaCO<sub>2</sub> in ventilated patients, but further studies are required to identify the limitations of the method.

### Monitoring of airway systems

Bohr's dead space (VD<sub>Bohr</sub>) measurement is commonly calculated using end-tidal CO<sub>2</sub> instead of the true alveolar partial pressure of CO<sub>2</sub> (PACO<sub>2</sub>). Tusman et al. [97] compared the measurement of VD<sub>Bohr</sub> using PACO<sub>2</sub> derived from either volumetric capnography or the standard alveolar air formula. The authors concluded that VD<sub>Bohr</sub> can be calculated with accuracy using volumetric capnography. In a correspondence letter, Graf [98] expressed concerns about using Bohr's formula for measuring physiological dead space. The measurement may refer to airway (VD<sub>aw</sub>) but not alveolar (VD<sub>alv</sub>) fraction. The letter also argued that using CO<sub>2</sub> as a tracer of overall ventilatory efficiency still requires the measurement of VCO<sub>2</sub>, expired minute ventilation and PaCO<sub>2</sub>. The value of PaCO<sub>2</sub> may be increased by shunt and/or V/Q inequalities, leading to physiological dead space overestimation. This is an interesting topic, and more studies and discussion are encouraged to clarify this issue. Despite all of the technical advances of recent years, auscultation provides both useful physiological

information and close patient–physician interaction. Today, there are automated systems that are available to detect, analyse, and interpret lung sounds. Image-based techniques of lung sound analysis such as vibration response imaging have been introduced and tested clinically. However, studies are warranted to determine their potential role in clinical practice. Vena et al. [99] report an analysis of the spectral characteristics of lung sounds. They observed significant correlation between intratidal recruitment measured with dynamic CT and the degree of crackles in the sound analysis, suggesting that air passage through atelectasis as well as poorly aerated areas is crucial for generating lung crackle sounds. They concluded that the computer-based analysis of crackle sounds is more sensitive for differentiating between small differences in healthy and injured conditions, especially at higher positive end-expiratory pressure (PEEP) levels, compared to conventional clinical auscultation. This simple and noninvasive technique of computer-based lung sound analysis may help intensivists monitor mechanical ventilation and diagnostic or therapeutic procedures such as recruitment manoeuvres in real time at the bedside. Yet the validation of the technique, and the variation of frequent measurements and interpretation of complex respiratory signals to optimise ventilator settings or to detect alveolar recruitment, especially in injured lungs, remain to be further investigated at the bedside [100]. Endotracheal tubes at high volume and low-pressure cuffs may fail to protect the lower airway from leakage of potentially contaminated secretions below the longitudinal folds. Ouanes et al. [101] studied the effects of PEEP levels, inspiratory effort intensity, peak pressures, tracheal tube cuff materials and sizes on the leakage of fluids past the cuff in an *in vitro* model of tracheal intubation and mechanical ventilation. The authors observed that leakage occurred more frequently at lower levels of PEEP, higher inspiratory efforts were associated with higher leakage, and polyurethane cuffs performed better than polyvinylchloride cuffs. In theory, most aspiration during mechanical ventilation occurs when tracheal pressure falls below hydrostatic pressure. Thus, the most important dependent variables are PEEP, inspiratory efforts and duty cycles. More studies are required to examine the effects of mechanical ventilation on leakage across the cuff.

### Lung and distal organ interactions

It is becoming increasingly apparent that lung and brain represent an integrated physiological ensemble such that insults involving one will compromise the other and vice versa [102]. Severe neurological injury is associated with concurrent lung injury in clinical settings. Recent studies have shown that acute lung injury may be responsible for brain injury and poor neurocognitive

outcomes. However, the underlying biological mechanisms are yet to be elucidated. Heuer et al. [103] evaluated the independent and combined effects of sustained acute intracranial hypertension (AICH) and ARDS on lung injury and brain damage in a porcine model. They observed that markers of lung injury were augmented with AICH and rose further with concurrent AICH/ARDS. These observations shed valuable light on the complex process of signaling, involving neural, inflammatory, immunological, and neuroendocrine pathways. The fundamental physiological mechanisms still need to be addressed in future studies investigating whether the brain injury was due to increased capillary permeability, and whether the brain edema was vasogenic or cytotoxic. Given the significant epidemiologic and mechanistic overlap between sepsis and ALI/ARDS, it seems plausible that some of the known effects of sepsis on the brain may be relevant to brain dysfunction encountered in ALI/ARDS [102].

The brain is one of the first organs affected during sepsis development; however, the mechanisms associated with septic encephalopathy are not well known [104]. Comim et al. hypothesised that during sepsis, brain cytokines and chemokines may lead to alterations in the blood–brain barrier (BBB) permeability, resulting in an increase in the flux of inflammatory cells and toxic mediators into the brain, thus contributing to injury. They demonstrated that the brain's production of cytokines and chemokines was an early event during sepsis, and seemed to participate in both central nervous system dysfunction and BBB permeability alterations [105].

Studies are needed to demonstrate these links to enable the development of specific therapeutic strategies.

Since there is increasing interest in the use of both pulse pressure variation (PPV) and stroke volume variation (SVV) to predict preload responsiveness and drive resuscitation protocols, Mesguida et al. [106] evaluated the impact of increasing tidal volume, decreased chest wall compliance, and left ventricular contractility during intermittent positive-pressure ventilation (IPPV) on the relation between PPV and left ventricular stroke volume variation and intrathoracic blood volume changes in dogs. This study provides a systematic examination of the changes in the right and left heart pressure and stroke volumes during the ventilator cycle. The author's major conclusion is that there is tight coupling between pulse pressure and left ventricular SVV. The authors have also added some important new information that shows the effect of changes in chest wall compliance, tidal volume and left ventricular function on the measurements. It is noteworthy that a proper quantitative analysis would require integrating the area under the stroke volume curves of all the stroke volumes in inspiration and expiration. What the author is really showing is that there are transient differences between the right and left side peak stroke volumes that must be associated with gains or

losses of pulmonary vascular volume to fulfil the conservation of mass.

### Biomarkers, treatment of hypoxia and sepsis

Reliable biomarkers of sepsis are needed for early diagnosis and guidance of appropriate treatment.

Pentraxin 3 (PTX3) is expressed in a variety of cells, including inflammatory (e.g. macrophages, neutrophils, dendritic cells), endothelial, and epithelial cells. Additionally, the PTX3 level is well correlated with the severity of lung injury and multiple organ failure, and may serve as a biomarker for ALI/ARDS [107]. In order to analyse the role of PTX3 in an LPS-induced ALI model, PTX3 knock-out (PTX3-KO) mice were used, and more severe lung tissue injuries, neutrophil infiltration, cell death, activation of the coagulation cascade, and inflammatory responses were observed, indicating that PTX3 plays a protective role in the pathogenesis of ALI [108].

Izquierdo-Garcia et al. [109] conducted a study in rats where lung tissue, lung lavage fluids and serum samples were profiled from caecal ligation and puncture-induced sepsis and control groups using NMR and high-resolution magic angle spinning detection. Predictive PLS-DA models were constructed based on the NMR spectra of the three types of biological samples and employed to diagnose sepsis in other samples. The authors further reported that the predictive power obtained by combining the three types of samples was 100%. An advantage of employing metabolomics for potential diagnosis is the utilisation of biofluids and/or easily accessible tissues. Because lung tissue collection is invasive, while sepsis often appears in critically ill patients, the use of lung tissue for metabolomic analysis is not practical at the bedside. Moreover, bacteria play a key role in sepsis, particularly in conditions like peritonitis-associated sepsis. However, bacterium-related information was absent from their study. Therefore, the diagnostic value of the clinical treatment provided by this study is limited. Future studies may need to include urine samples for metabolomic analysis in order to understand bacterium-specific metabolites.

Several mechanisms have been proposed to explain vascular dysfunction induced by sepsis [110]. Experimental studies have shown that selective and nonselective inhibitors of vascular potassium ( $K^+$ ) channels increase arterial pressure or reverse shock-induced vascular hyporeactivity [111]. However, while the use of channel inhibitors remains an attractive option to counteract systemic vasodilation, it may also impair microcirculatory adaptation to shock [112]. Collin et al. [113] demonstrated that vascular  $K^+$  channels are activated and overexpressed, while their inhibition restores arterial pressure and vascular reactivity, and decreases lactate

concentration, thus offering potential therapeutic perspectives for septic shock.

In the search for treatments for critical illnesses, levosimendan has been found to be an interesting candidate, as it is a potent stimulator of vascular ATP-dependent potassium channels ( $K^+$ -ATP channels), inducing systemic vasodilation and reducing afterload. Schwarte et al. [114] examined the effect of levosimendan on cardiac output and tissue perfusion in the presence of hypoxia in a canine model. They found that when levosimendan was infused before hypoxia was induced, myocardial contractility, stroke volume and cardiac output were preserved in spite of the hypoxic insult. The novelty of this study is the examination of the antagonising effect of glibenclamide on the action of levosimendan. When given alone, glibenclamide caused a rise in systemic vascular resistance, suggesting that glibenclamide was acting to block  $K^+$ -ATP channels. When levosimendan was administered in the presence of glibenclamide, levosimendan caused a significant rise in cardiac output by improving myocardial contractility. This is indicative of levosimendan acting through a calcium-sensitising effect rather than on  $K^+$ -ATP channels. In a separate study, Revermann et al. [115] reported that the administration of levosimendan and nicorandil (a  $K^+$ -channel opener) attenuated the increased pulmonary vascular medial wall thickness in a model of pulmonary hypertension induced by monocrotaline challenge. Levosimendan significantly diminished the proliferation of pulmonary arterial smooth muscle cells, and this effect was attenuated by glibenclamide. In cell culture, levosimendan had a direct inhibitory effect on the platelet-derived growth factor induced proliferation of pulmonary arterial smooth muscle cells. These findings of levosimendan exerting inotropic, vasodilatory and anti-inflammatory properties under experimental conditions are exciting, but the real promise for levosimendan as a therapeutic candidate to support critical illness remains to be elucidated. Further *in vitro* and animal studies are required to understand the vasodilatory action of levosimendan, and the consequent effects—positive or negative—on end-organ perfusion [116]. Acute kidney injury is a common complication in patients with sepsis.

The primary resuscitation strategy for these patients is fluid resuscitation to improve organ perfusion and oxygenation and thereby prevent distal organ failure. Legrand et al. [117] examined the effects of fluid resuscitation on renal perfusion in relation to renal microcirculatory function in endotoxemic rats. The authors observed that infusion of endotoxin resulted in altered microvascular perfusion and oxygenation distributions. Early fluid resuscitation greatly improved renal perfusion compared to late resuscitation, but it did not influence oxygenation distribution. Serum cytokine levels decreased in the

resuscitated groups, no matter whether early or late resuscitation was involved. Although the results are interesting, one has to keep in mind that the study was conducted at 300 min after endotoxin administration, and it is unknown whether this time frame is long enough to fully assess the therapeutic value of immediate versus delayed resuscitation in clinical situations. There are several issues that need to be addressed in future studies. For example, the volume and rate of fluid administration could simply have altered the disposition of endotoxin in the kidney. It is unclear how dramatic differences in aortic and renal artery flow and microvascular flow between endotoxin alone and endotoxin with fluid resuscitation had no impact on microvascular oxygen tension. Since the human erythropoietin fusion protein (EPO) gene was cloned over 25 years ago, several variants of the EPO molecule have been developed to improve its pharmacokinetic and pharmacodynamic characteristics and to separate its haemopoietic and neuroprotective properties [118]. For example, carbamylated erythropoietin fusion protein (cEPO-FC) contains two recombinant human EPO (rhEPO) molecules connected by the Fc region of human IgG<sub>1</sub>, and is thought to improve the cytoprotective effects while reducing side effects including hypertension and thrombosis. Simon et al. [119] report that pretreatment with a cEPO-FC is as effective as rhEPO in ameliorating spinal cord injury in a porcine model of acute spinal cord ischaemia and reperfusion. This study assessed short-term outcomes, including motor-evoked potentials and histological damage. Future studies will need to focus on the longer-term neurological outcomes and demonstrate an absence of systemic toxicity, including thrombosis. It is noteworthy that clinical studies raised the possibility that rhEPO could improve some clinical outcomes, including neuronal recovery, but rhEPO failed to show any clinical benefit with respect to the Barthel index, modified Rankin scale and mortality rate in patients with stroke [120, 121]. Thus, further experimental and clinical research is needed to determine if derivatives of rhEPO such as cEPO-FC can improve long-term neurological outcome without having potential adverse effects such as hypertension, thrombosis and mortality. Reactive oxygen species are produced by activated neutrophils during the inflammatory response to stimuli such as endotoxins, can directly or indirectly injure host cells, and have been implicated in the pathogenesis of ALI/ARDS. Hassett et al. [122] described the result of pulmonary overexpression of superoxide dismutase in the response to endotoxin administration in animals. Endotoxin produced a severe lung injury compared to a sham injury. Their results support the conclusion that superoxide dismutase plays an important role in lung injury in terms of neutrophil infiltration, cytokine responses, lung edema and histology. However, the delivery technique for the superoxide



dismutase transgene—using adeno-associated virus—remains controversial. The conclusion that gene therapy may be appropriate for ALI is a bit premature and need further studies.

Sepsis affects both oxygen delivery to tissues, through cardiac and macro- and microcirculatory alterations [123], and oxygen consumption, through effects on mitochondrial respiration [124]. Dyson et al. reported that the early fall in tissue oxygenation was associated with both macro- and microcirculatory impairment, the latter persisting despite restoration of the macrocirculation. However, by 24 h, this impairment had largely recovered, even though the animal predicted to have a poor prognosis were then manifesting clinical and biochemical signs of organ dysfunction, suggesting that cellular abnormalities were enhanced at this later stage [125]. Therefore, the utility of tissue PO<sub>2</sub> monitoring to highlight the local oxygen supply–demand balance, and dynamic O<sub>2</sub> challenge testing to assess microcirculatory function, merits further investigation.

The benefits of stress-dose steroid therapy and recombinant activated protein C (APC) in septic shock remain controversial [126]. Bouazza et al. [127] hypothesised that the combination of APC and steroids would be beneficial compared with their individual use in resuscitated septic shock induced by caecal ligation and puncture. They observed that either APC or dexamethasone improved arterial contractility and endothelial dysfunction resulting from septic shock; however, their combination increased survival, thus recommending the re-evaluation of the combined use of APC and steroids. The conclusion of the PROWESS-SHOCK study (still unpublished) that led to the retraction of the APC from the market has eliminated this molecule from clinical use.

Sepsis is associated with massive discharges of catecholamine and consequent persistent stimulation of the  $\beta$ -adrenergic receptor [128]. Selective  $\beta$ <sub>1</sub>-adrenergic blockers might present a new therapeutic capability against sepsis [129], although the exact mechanism remains to be elucidated. Mori et al. [130] observed that esmolol, a selective  $\beta$ <sub>1</sub>-blocker, improved outcome in a rat model of sepsis by preventing gut barrier dysfunction and thereby bacterial translocation.

Modulating the adrenergic system may be a new approach to the treatment of sepsis [131]. In rats with peritonitis,  $\beta$ <sub>1</sub>-blockade decreased proinflammatory cytokines and improved cardiac function and haemodynamics [129]. However, so far, no study has evaluated the haemodynamic tolerance of esmolol—a selective ultrashort-acting  $\beta$ <sub>1</sub>-blocker—in large animals with endotoxemic shock. Therefore, Aboab et al. [132] observed that selective  $\beta$ <sub>1</sub>-blockade was well tolerated in endotoxemic pigs treated with a continuous infusion of esmolol, and prevented sepsis-induced cardiac

dysfunction, confirming findings reported in small animals.

Oxidative stress has an important role in the development of the systemic inflammatory response [133]. Honokiol, a low molecular weight natural product, is an effective antioxidant and also presents anti-inflammatory and antitumor properties [134]. However, the precise mechanism of action of honokiol on septic acute lung injury remains unclear. Weng et al. [135] observed that honokiol administered after the onset of sepsis reduced acute lung injury and prolonged survival via the amelioration of oxidative stress in endotoxemic mice.

Tumor necrosis factor (TNF)- $\alpha$  has been implicated in the pathogenesis of septic shock. TNF inhibitors resulted in increased survival in experimental sepsis [136]; however, no anti-TNF agent modified survival in clinical sepsis trials [137]. Fluid therapy may itself have anti-inflammatory effects [138], but is rarely employed in preclinical sepsis models. Therefore, Qiu et al. [139] analysed whether the combination of TNFsr and fluids would be beneficial. They reported that the individual survival benefits of TNFsr and fluids were not additive in a rat sepsis model.

Multiple organ dysfunction syndrome (MODS) is defined as the progressive deterioration of function that occurs in several organs or systems in patients with septic shock. Zymosan-induced generalised inflammation reproduces the characteristics of human MODS, and has been used to evaluate new therapies [140]. Rinaldi et al. investigated the effects of hyperbaric oxygen (HBO) exposure on the expression of Toll-like receptors (TLR) 2 and 4, on their signal transduction, and on organ dysfunction during zymosan-induced MODS. They reported that the anti-inflammatory effect of HBO is associated with the inhibition of TLR signaling, and suggest that HBO therapy is effective at reducing systemic inflammation and associated organ dysfunction in this model [141].

Reactive oxygen species (ROS) are believed to be involved in electrical shock (ES) related myocardial injury [142], ischaemia/reperfusion injury, reperfusion arrhythmia, and cardiogenic shock. Ascorbic acid, a potent water-soluble antioxidant, has been found to attenuate oxidative damage, myocardial injury, and arrhythmia during reperfusion [143]. However, so far, no in vivo study has evaluated whether ascorbic acid administration benefits defibrillation and resuscitation. Therefore, Tsai et al. [144], in a rat model of ventricular fibrillation and electrical shock, observed that the intravenous administration of ascorbic acid at the start of cardiopulmonary resuscitation reduced lipid peroxidation and myocardial necrosis, diminished mitochondrial damage, facilitated resuscitation, and improved outcome.

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