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Delirium in the ICU and distress after discharge

Delirium is associated with prolonged intensive care unit (ICU) stay: its early recognition, treatment and prevention are becoming increasingly important. Scales and evaluation tools for delirium are becoming more diffuse, but a universal tool has not been defined yet, and probably delirium underrating still permeates the ICU environment. Spronk [1] investigated, during daily care, intensivists' and ICU nurses' skills in identifying the presence of delirium in ICU patients. In a 3-month period, all patients in the ICU for more than 48 h were screened daily for delirium both by attending intensivists and nurses. The Confusion Assessment Method for the ICU (CAM-ICU) was used as a screening instrument for delirium. During the study period, 46 patients (30 male, 16 female; median age 73 years) with an ICU stay of 6 days (range 4–11) were evaluated. CAM-ICU scores were obtained during 425 patient days. Considering the CAM-ICU as the reference standard, delirium occurred in 50% of the patients with a duration of 3 days (range 1–9). Days with delirium were poorly recognized by doctors (sensitivity 28.0%; specificity 100%) and ICU nurses (sensitivity 34.8%; specificity 98.3%). Recognition did not differ between hypoactive or active status of the patients involved. Delirium is severely underrecognized in the ICU in daily care. These data indicated that more attention should be paid to the implementation of a validated delirium-screening instrument during daily ICU care.

The pathophysiology of delirium remains elusive. Neurotransmitters and their precursor large neutral amino acids (LNAAs) may play a role. Pandharipande [2], exploring this relationship, evaluated if plasma tryptophan (Trp), phenylalanine (Phe) and tyrosine (Tyr) levels are independent risk factors for delirium in critically ill patients. This pilot study investigated whether alterations of these amino acids were associated with a higher risk of transitioning to delirium in critically ill patients. Plasma LNAA concentrations were determined on days 1 and 3 in mechanically ventilated (MV) patients from the MENDS trial, a randomized controlled (RCT) trial comparing an alpha2 agonist versus a gamma aminobutyric acid (GABA) agonist to determine delirium rates, efficacy of sedation, analgesia and cognitive status after ICU discharge. Three independent variables were calculated by dividing Trp, Phe and Tyr plasma concentrations by the sum of all other LNAA concentrations. Delirium was assessed daily using the CAM-ICU assessment method. The 97 patients included in the analysis had a high severity of illness. After adjusting for confounders, only high or very low tryptophan/LNAA ratios ($P = 0.0003$) and tyrosine/LNAA ratios ($P = 0.02$) were associated with increased risk of transitioning to delirium. Older age, higher APACHE II scores and increasing fontanel exposure were also associated with higher probabilities of transitioning to delirium.

The months following the ICU discharge can be stressful for patients and family. One of the real problems the ICU survivors face in daily life is the distance between his/her psychological distress and the relatives' expectations. A cross-sectional study of 255 patients and 298 relatives tried to clarify this important aspect [3]. A questionnaire for post-ICU patients, tested 4–6 weeks after ICU discharge, included hospital anxiety and depression scale (HADS), impact of event scale (IES), life orientation test, ICU memory tool and memory of ICU, technical procedures, pain, lack of control and inability to express needs. Relatives were assessed for their expectations of the patients' memories and psychological distress. Twenty-five percent of the patients reported severe posttraumatic stress symptoms, IES total $\geq$35. The levels of anxiety and depression were significantly higher than in the general population; mean anxiety was 5.6 versus 4.2 ($P < 0.001$), and mean depression was 4.8 versus 3.5 ($P < 0.001$). Relatives expected more psychological distress, and the relatives thought the patient was less able to express needs than the patients reported ($P < 0.001$). Older age, unemployment, respirator treatment, pessimism, memory of pain, lack of control and inability to express needs were independent predictors of posttraumatic stress symptoms ($P < 0.01$).

Neuro-psychological syndromes often observed in critically ill patients may be induced by the initial injury, but also by the intensive care treatment itself. Two interesting reviews dealt with this crucial field: Figueroa-Ramos et al. [4] investigated mechanisms and manifestations of sleep and delirium in ICU patients. The specific clinical features of sleep disturbances (fragmentation, increase in light sleep, etc.) are presented, as well as the most common subtypes of delirium, i.e., the hypoactive and mixed-type delirium. The physiological background is demonstrated to provide a better understanding of the mechanisms and factors that contribute to sleep deprivation and delirium, guiding the development of new methods and models for prevention and treatment of these problems. Davydow et al. [5] presented a systematic review on depression in general ICU survivors. Fourteen studies from the literature were eligible, and the median point prevalence of "clinically significant" depressive symptoms was 28%.

Neither the severity of the disease nor sex nor age was a consistent risk factor, whereas early post-ICU depressive symptoms were a strong predictor for subsequent depressive syndromes. These were associated with a substantially lower quality of life. A multidisciplinary approach involving intensivists, primary care physicians and psychiatrists could ensure prompt, comprehensive evaluation and treatment, reducing morbidity and improving ICU survivors' quality of life.

Head trauma: transfusion and ICP treatment

Bleeding and hypotension are two targets in early head trauma management, mainly when associated with polytrauma. Transfusion practices have been revisited more than once in the last decades in trauma victims. The optimal hemoglobin concentration in the early phase is still a matter of debate. The fact that many actors play a role in the early treatment of traumatic brain injury, i.e., surgeons, intensivists, anesthesiologists and neurosurgeons, increases the confusion level. Their attitudes toward transfusion practices for acute traumatic brain injury have been explored using a survey in US trauma centers [6]. The aim of the research was to determine whether physician specialty influences the transfusion threshold in patients with acute severe traumatic brain injury. A scenario-based, multiple-choice instrument administered was mailed to chiefs of trauma surgery, chairs of neurosurgery, and surgical and neurosurgical ICU directors at all 187 US level I centers. The hemoglobin value used as a transfusion threshold for patients with severe acute TBI in several scenarios as well as opinions regarding the rationale for transfusion has been evaluated. The response rate was 58% (312/534). Mean time in practice was 17 ± 8 years, and 65% were board certified in critical care. Neurosurgeons (NS) used a greater mean hemoglobin threshold for transfusion of TBI patients than trauma surgeons (TS) and non-surgeon intensivists (CC) whether the intracranial pressure was normal (8.3 ± 1.2, 7.5 ± 1.0 and 7.5 ± 0.8 g/dl; NS, TS and CC, respectively, $P < 0.001$) or elevated (8.9 ± 1.1, 8.0 ± 1.1 and 8.4 ± 1.1 g/dl; NS, TS and CC, respectively, $P < 0.001$). All three groups commonly believed that secondary ischemic injury is an important problem following TBI, but fewer neurosurgeons believed that transfusions have important immunodulatory effects (25, 91 and 83%, $P < 0.001$). NS prefer more liberal transfusion of TBI patients than TS and CC, suggesting that actual practice may depend largely on which specialist is primarily managing care. The observed clinical equipoise would justify a randomized trial of liberal versus restrictive transfusion strategies in patients with TBI.

During the ICU stay, intracranial pressure pathophysiology and its treatment become an important part of the understanding and care of the TBI patients.

Lavinio [7] explored the relationship between the intracranial pressure-volume index (PVI) and cerebral autoregulation. The PVI, described originally by Marmarou, can be used to assess the cerebrospinal fluid dynamics and intracranial elastance in critically ill brain-injured patients. The dependency of PVI on the state of cerebral autoregulation within the physiologic range of cerebral perfusion pressure (CPP) can be described by mathematical models that account for changes in cerebral blood volume during PVI testing. This relationship has never been verified clinically using direct PVI measurement and independent cerebral autoregulation assessment. PVI and cerebral autoregulation were prospectively assessed in a cohort of 19 comatose patients admitted to an academic ICU. PVI was measured injecting a fixed volume of 2 ml of 0.9% sodium chloride solution into the cerebral ventricles through an intraventricular catheter. Cerebral autoregulation was assessed using transcranial Doppler transient hyperemic response (THR) test. Fifty-nine PVI assessments and 59 THR tests were performed. Mean PVI was 20.0 (SD 10.2) ml in sessions when autoregulation was intact (THR test $\geq$1.1) and 31.6 (8.8) ml in sessions with defective autoregulation (THR test <1.1) (DeltaPVI = 11.7 ml, 95% CI = 4.7–19.3 ml; $P = 0.002$). Intracranial pressure, CPP and brain CT findings were not significantly different between the measurements with intact and disturbed autoregulation. Cerebral autoregulation status can affect PVI estimation despite a normal CPP. PVI measurement may overestimate the tolerance of the intracranial system to volume loads in patients with disturbed cerebral autoregulation.

Intracranial hypertension after TBI is still a major cause of mortality and morbidity in the ICU. Recent randomized, controlled trials have failed to demonstrate any beneficial outcome from therapeutic treatments such as corticosteroids, hypothermia and hypertonic saline. Ichai [8] investigated the effect of a new hyperosmolar solution based on sodium lactate versus mannitol in controlling raised ICP. In a prospective, open, randomized study in an adult ICU, 34 patients with isolated severe TBI and intracranial hypertension were allocated to receive equally hyperosmolar and isovolumic therapy (mannitol or sodium lactate). Rescue therapy by crossover to the alternative treatment was indicated when ICP could not be controlled. Compared to mannitol, the effect of the lactate solution on ICP was significantly more pronounced (7 vs. 4 mmHg, $P = 0.016$), more prolonged (4th-h ICP decrease: −5.9 ± 1 vs. −3.2 ± 0.9 mmHg, $P = 0.009$) and more frequently successful (90.4 vs. 70.4%, $P = 0.053$). Therefore, acute infusion of a sodium lactate-based hyperosmolar solution is effective in treating intracranial hypertension following TBI. This effect is significantly more pronounced than that of an equivalent osmotic load of mannitol. Additionally, in this specific group of patients, long-term outcome was better in terms of GOS in those receiving it as compared to those receiving mannitol. Larger trials are warranted to confirm these early findings.

As a second-tier option for controlling ICP, hypothermia is still a “hot” topic. A trial for answering the question of the real utility of hypothermia in reducing ICP and ameliorating outcomes, Eurotherm3235, is going to start soon (http://www.eurotherm3235trial.eu). The debate between using invasive and non-invasive methods for inducing hypothermia is still open. In a prospective,

international, multicenter clinical trial conducted in four university hospitals, Sahuquillo [9] evaluated the feasibility, safety and effectiveness of a new method of intravascular temperature management for inducing moderate hypothermia (MHT). In a 2-year period, 24 patients with severe head injury and refractory high ICP were treated with MHT (32.5°C) by intravascular methods. Seventeen were males and seven females, with a median age of 25 years (range 15–60). The median Glasgow Coma Scale upon admission was 7 (range 3–13), and the median Injury Severity Score was 22 (range 13–43). A total of 75% of patients presented a diffuse lesion in the pre-enrollment computed tomography. Median time from injury until reaching refractory high ICP was 71.5 h after injury (minimum 14 h, maximum 251 h). Twelve patients (50%) reached this situation within the first 72 h after injury. MHT was attained in a median time of 3 h. Pre-enrollment median ICP was 23.8 mmHg and was reduced to 16.8 mmHg upon reaching target temperature. At 6 months after injury, nine patients had died (37.5%), six were severely disabled (25%), two moderately disabled (8.3%) and seven had a good recovery (29.2%). Of the nine patients who died, four had a rebound of ICP during rewarming, one death was attributed to accidental potassium overload, two to septic shock, one to cardiac arrest of unknown origin and the ninth to a pulmonary embolism. Intravascular methods to induce MHT combined with precooling with cold saline at 4°C appear to be feasible and effective in reducing ICP in patients with high ICP refractory to first-line therapeutic measures.

ICU-acquired weakness and heat stroke sequelae

Hough et al. [10] investigated the incidence and outcomes of ICU-acquired neuromyopathy and the role of methylprednisolone in survivors of persistent acute lung injury. They performed a secondary analysis on 128 patients who survived 60 days or hospital discharge from the acute respiratory distress syndrome (ARDS) Network RCT study of methylprednisolone versus placebo for persistent ARDS. Forty-three (34%) of these patients had evidence of ICU-acquired neuromyopathy, which was associated with prolonged mechanical ventilation and delayed return to home after critical illness. Treatment with methylprednisolone was not significantly associated with an increase in risk of neuromyopathy (OR 1.5; 95% CI 0.7–3.2). ICU-acquired neuromyopathy was common among survivors of persistent ARDS and was associated with poorer clinical outcomes. Limitations of this study preclude definitive conclusions about the causal relationship between corticosteroids and ICU-acquired neuromuscular dysfunction, but the association appears less strong than before.

As stressed by Herridge in the accompanying editorial [11], ICU-acquired weakness is common and consequential, but we still know very little about its risk factors, pathophysiology, natural history and potential treatment. The very first step should be to acknowledge that we have not been looking hard enough for this problem and are currently engaged in clinical practices that obscure our ability to diagnose this problem.

The issue of ICU-acquired weakness was also addressed by Kesler and co-workers [12] in a retrospective cohort study of MV patients with status asthmaticus. The study compared asthmatic patients receiving mechanical ventilation before ($n = 96$) and after ($n = 74$) a clinical practice change in 1995 that markedly restricted the use of paralytics. Even though the duration of neuromuscular paralysis markedly declined, no significant difference in the incidence of weakness was observed, highlighting that prolonged deep sedation remains a risk factor for weakness.

During August 2003, France sustained an unusual heat wave that lasted 9 days and caused epidemic classic heatstroke. The course of early organ dysfunction in a cohort of patients admitted to the ICU suffering classic heatstroke has been described by Pease [13]. Clinical and biological data of 22 patients were analyzed. Median body temperature on admission was 41.1°C. Respiratory, circulatory, hematological, hepatic and renal function all deteriorated within the first 24 h of admission. ICU mortality was 63.6%. Cooling time, serum lactate, serum cardiac troponin I and creatinine were significantly higher in non-survivors. Early ICU mortality (within 7 days of ICU stay) was due to multiple organ failure. Late ICU mortality was due to neurological disability.

Hemodynamics

Intensive Care Medicine published several articles on cardiovascular problems and failure in 2009.

The incidence of right ventricular failure (RVF) in patients with ARDS and its impact on short-term outcome was assessed by Osman et al. [14]. This is a substudy of the previously published French Pulmonary Artery Catheter (PAC) study. A total of 145 ARDS patients were included in the substudy. The RVF was defined by the concomitant presence of: (1) a mean pulmonary artery pressure (MPAP) >25 mmHg, (2) a central venous pressure (CVP) higher than pulmonary artery occlusion pressure (PAOP) and (3) a stroke volume index <30 ml/m^2. RVF was present in 9.6% of patients. Mortality was 68% at day 90 with no difference between patients with or without RVF. In multivariate analysis, PaO_2/FiO_2, mean arterial pressure, arterial pH, SvO_2, MPAP and presence of CVP > PAOP, but not RVF, were independently

associated with day-90 mortality. Although $PaCO_2$ did not seem to influence RVF in Osman's paper, it seemed to play an important role in the development in RVF in 11 ARDS patients in the paper by Mekontso Dessap et al. [15]. RV function was assessed by transesophageal echocardiography. Compared to low PEEP, PaO_2/FiO_2 ratio and alveolar recruitment were increased with high PEEP. Alveolar dead space remained unchanged. High-PEEP strategies induced both higher $PaCO_2$ levels [71 (60–94) and 75 (53–84), vs. 52 (43–68) mmHg] and lower pH values [7.17 (7.12–7.23) and 7.20 (7.16–7.25) vs. 7.30 (7.24–7.35)], as well as RV dilatation, LV deformation and a significant decrease in cardiac index. The decrease in stroke index tended to be negatively correlated to the increase in alveolar recruitment with high PEEP.

Although a decrease in vascular tone after cardiac surgery occurs frequently, its mechanism is unknown. Based on data already published in sepsis, Jochberger and co-worker [16] evaluated arginine vasopressin (AVP) and copeptin plasma concentrations in patients with vasodilatory shock after cardiac surgery. Both biomarkers were reduced in the vasodilatory shock group. Furthermore, except during continuous veno-venous hemofiltration, AVP and copeptin correlated significantly with each other.

Monge Garcia and co-workers [17] evaluated whether arterial pressure response during a Valsalva maneuver could predict fluid responsiveness in spontaneously breathing patients. A 10-s Valsalva maneuver was performed before and after volume expansion. Arterial response during the Valsalva maneuver seems to be a feasible tool for predicting fluid responsiveness in patients without mechanical ventilatory support.

The research on cardiac arrest has received a new impulse in the last few years. Carr and co-workers [18] showed that mortality after in-hospital cardiac arrest had decreased over 5 years in the US. This result is based on a national sample of US hospitals identifying patients resuscitated after cardiac arrest from 2000 to 2004. A total of 109,739 patients were identified. Mortality after cardiac arrest was lower at urban, teaching and large hospitals.

Evaluation of hemodynamic alterations

Significance of hypotension

Hypotension can be life threatening and is one of the most frequent reasons for requesting ICU admission. Hypotension is associated with a poor outcome, but the level of hypotension associated with a poor outcome needs to be determined. Two manuscripts addressed this issue from different perspectives. Marchick et al. [19] evaluated the impact of non-sustained (less than 60 min) hypotension in a large database of 700 patients admitted with sepsis to the emergency department (ED) of a single large urban hospital in the USA. Among these, 150 developed non-sustained hypotension. Mortality increased from 3.6% in the general population to 10% in patients with non-sustained hypotension. More severe hypotension was associated with higher mortality, emphasizing that hypotension, even when transient, should not be neglected in patients with sepsis.

Dunser et al. [20] evaluated the impact of prolonged hypotension in 274 patients with septic shock. They collected mean and systolic arterial pressure values from the data management system and computed the hourly time integral for different threshold values. They observed a curvilinear association between time spent with hypotension and poor outcome. However, it was quite surprising to notice that even time spent below the highest mean arterial pressure tested, 75 mmHg, was significantly associated with a poor outcome. These results suggest that not only the severity of hypotension, but also time spent even with moderate hypotension is associated with a poor outcome.

How to predict the response to fluids

Fluids are a key component of the resuscitation of critically ill patients, but excessive fluid administration should also be avoided. Accordingly, techniques to predict the response to fluids are crucial. Respiratory induced pulse pressure variations (PPV) have been shown to predict response to fluids. Unfortunately, PPV is sensitive to tidal volume (TV) [21], as a TV higher than 8 ml/kg is required. The main reason is that the respiratory changes in pleural/pericardial pressures are low when TV is low. Vallee et al. [22] hypothesized that correcting PPV for driving pressure, as evaluated by plateau minus PEEP, could be better predictive of fluid responsiveness than PPV alone, even in patients with low TV. In opposition to their expectations, correction of PPV by driving pressure failed to improve the predictive value for fluid responsiveness in patients with low TV, whereas it effectively did so in patients with high TV. As highlighted in the accompanying editorial by Lefrant and De Backer [23], transmission of alveolar pressure to pleural and pericardial space is altered in ARDS patients who require ventilation with low TV. Accordingly, respiratory driving pressure fails to reflect respiratory changes in pleural and pericardial pressures that really drive the changes in left and right ventricular preload.

Passive leg raising (PLR) can also help to predict the response to fluids [24]. This maneuver evaluates rapid changes in stroke volume in response to an acute change in posture. Jabot et al. [25] evaluated whether this maneuver should include PLR only, without movement of the torso, or whether it should also include a rapid shift in

torso position from 30 to 0°, in addition to raising the legs. The authors decomposed the movement and reported that PLR and torso inclination were responsible for similar mobilization of blood from the peripheral to the central compartment, as evidenced by a similar increase in CO with the two movements. They concluded that PLR should include inclination of the torso from 30 to 0°.

Devices and techniques

Different technologies can be used to estimate CO. One of the major issues when introducing a new technology is to evaluate its reliability. As no gold standard exists, the new device is often compared with existing devices/techniques, and often thermodilution is used as the comparator. Often these comparisons are made at predefined times, but one of the major issues is to evaluate whether the technique is able to adequately track changes. No clear methodology exists for this purpose. In a special article, Squara et al. [26] discussed the various aspects needed to evaluate new devices. In addition to accuracy and precision (static estimates), response time and accuracy of estimation of amplitude of the response (dynamic estimates) should also be provided when introducing new techniques. For this purpose, they proposed to evaluate the changes in CO occurring after a known intervention and to evaluate response time and amplitude with new and reference techniques. The definition of clinical acceptability of these estimates will need to be defined.

CO can be measured by various techniques analyzing the morphology of the arterial curve. According to the algorithm, it may be necessary to calibrate the system with an independent measurement of CO. With the LiDCO device, lithium dilution is used to calibrate the pulse power analysis of the arterial trace, allowing for accurate continuous measurements of CO. However, this process carries an inherent risk of error, and great care should be taken when performing calibrations. Cecconi et al. [27] evaluated the reproducibility of lithium dilution measurements, performing four subsequent lithium dilution measurements. They observed that the coefficient of variation of a single measurement was 8%, which implies that the technique is able to detect significant changes in CO of at least 24%. Averaging two and three lithium boluses decreased the coefficient of variation to 6 and 5% and the least significant detectable difference in CO to 17 and 14%, respectively. It did not further improve when additional lithium injections were performed. The authors concluded that at least three bolus injections should be performed to calibrate the LiDCO device.

Dancona et al. [28] tested a continuous cardiac output (CO) recording system that operates on the thermal conservation principle, and they compared it with the reference standard transit time flow measurement. There was a significant underestimation of CO with the continuously recording system, but it may be useful to detect trends over time.

Another important aspect is evaluating whether CO is adequate. Mixed-venous and central venous ($ScvO_2$) O_2 saturations are often used for this purpose. In addition, $ScvO_2$ is used to guide the early resuscitation in septic shock [29]. However, these require insertion of a central venous line, which is not always easily available in the early phases of resuscitation. In 40 consecutive patients with severe sepsis, Mesquida et al. [30] evaluated whether the non-invasive measurement of tissue O_2 saturation (StO_2) of the thenar eminence with near infrared spectroscopy (NIRS) could predict $ScvO_2$ values. Even though a StO_2 value below 75% was associated with a$ScvO_2$ lower than 70% with a high specificity (0.93), many patients with a StO_2 value above 75% could still have a low $ScvO_2$ (sensitivity 0.44). Accordingly, the positive predictive value of StO_2 was high (0.92), whereas the negative predictive value was low (0.52). Accordingly, when abnormal, this test can easily detect low $ScvO_2$, but a normal StO_2 value should not be considered reassuring.

A new look at the microcirculation

Several studies have reported the implication of the microcirculation in sepsis [31], cardiac failure [32] and hemorrhagic shock [33], but its implication in other disease states remains to be demonstrated. Jhanji et al. [34] investigated the sublingual microcirculation in 25 patients admitted to the ICU after major abdominal surgery. Microcirculatory perfusion was close to normal on ICU admission, but slightly deteriorated in the following 8 h in patients developing complications, whereas there was full normalization in patients who did not develop complications. Global hemodynamic measurements did not differ between patients developing complications and patients with an uneventful postoperative course. Even though obtained in a small group of patients, these preliminary data suggest that microcirculatory alteration may play a key role in the development of postoperative complications.

When looking at the microcirculation, one is sometimes limited by the scoring systems. In most articles, semi-quantitative assessment is performed, as automated analysis still requires multiple human interventions. A limitation for future wide application at bedside of these techniques of direct visualization of the microcirculation is that theses semi-quantitative scoring systems need to be performed off-line and are rather time consuming. Ideally, eyeball evaluation of key microcirculatory features at bedside should be obtained by analogy with eyeballing of the ejection fraction at bedside, which has been proven to be as reliable as more cumbersome

off-line determinations [35]. Arnold et al. [36] evaluated whether rapid eyeball evaluation of the microcirculation (in a point of care fashion) could reliably estimate the microculation, as compared to off-line analysis. They obtained 205 paired measurements in 18 subjects. There was no bias between measurements, and agreement between point of care and off-line analysis was excellent (0.19, representing a percentage error smaller than 10%). The authors concluded that point of care evaluation of the microcirculation can reliably assess the sublingual microcirculation.

We are still looking for interventions that could specifically (or at least predominantly) improve the microcirculation. Vasodilatory agents seem promising, but these have not been widely tested. Den Uil et al. [32] evaluated the effects of nitroglycerine on the sublingual microcirculation in 17 patients with heart failure ($n = 8$) or cardiogenic shock ($n = 9$). More importantly, they evaluated the dose response to this agent, using incremental doses up to 133 μg/min. They observed that all patients improved their microcirculation with nitroglycerin, but that the dose required to achieve this effect varied widely among patients. More importantly, even though nitroglycerin was also associated with systemic effects, the improvement in microvascular perfusion occurred at lower doses than the systemic effects, suggesting that this agent could be used to specifically improve the microcirculation at doses not resulting in significant hypotension.

How to treat hemodynamic alterations

The quest for the ideal fluid for hemodynamic resuscitation is still ongoing. In particular, there is still a huge discussion going on about the potential benefits and risks of colloid solutions, and in particular of starches. This issue was raised in the Journal in a pro-con debate between Hartog and Reinhart [37] defending the contra side and Boldt [38] defending the pro side. Hartog and Reinhart raised the issue of storage of hydroxyethylstarch (HES) molecules in the reticulo-endothelial system and skin, which may lead to pruritus. In addition, they highlighted that nephrotoxicity has been suggested to occur in several randomized trials and that the volume-expanding capacities of these solutions may be lower than the expected 4–1. They concluded that in the absence of a clearly demonstrated beneficial effect and in the presence of potential side effects, one should refrain from using these solutions. Boldt supported the opposite point of view. This author highlighted that the side effects, especially nephrotoxicity, have been observed using only hyperoncotic HES of large molecular weight. Based on data from small interventional trials, he suggested that new-generation HES may not be associated with nephrotoxicity and that there is no reason to ban these new solutions.

In a before and after trial, Schabinski et al. [39] compared the effects of a predominantly HES- and predominently non-HES-based fluid therapy on renal function in surgical patients. In this single center, the authors compared the cohort of patients admitted between January and June 2005 receiving a fluid therapy mostly based on HES and a cohort of patients admitted from January to June 2006 receiving mostly gelatins as part of their fluid resuscitation. The two cohorts were relatively well balanced both in numbers (1,383 vs. 1,528) and main diagnoses (even though there were more cardiac surgery and neurosurgery and fewer digestive tract surgery patients in the gelatin group). The incidence of renal failure did not differ between the two groups (5.8 and 5.6%). By multivariate analysis, the authors identified that a cumulative dose of either HES or gelatin of at least 33 ml/kg body weight was associated with an increased incidence of renal failure and death, but again without a difference between the two groups.

Finally, Boldt et al. [40] evaluated the influence of the ionic content of fluid solutions. These authors compared a HES solution dissolved in 9% saline and another solution of the same HES dissolved in a balanced solution. Saline solutions present the disadvantage of carrying an excess of chloride anions compared to sodium, which can generate hyperchloremic acidosis. Balanced solutions contain equivalent amounts of anions and cations,but both sodium and chloride are present in physiologic ranges, electrical neutrality being provided by additional lactate or acetate. The authors randomized 50 elderly patients submitted to cardiac surgery and evaluated the impact of these two solutions on inflammatory response. They reported that patients treated with HES in balanced solution, compared to HES in saline solution, had lower levels of interleukin 6 and 10 and soluble intracellular adhesion molecule-1 (ICAM-1), representing a blunted inflammation and endothelial activation after surgery. In addition, markers of kidney injury (NGAL and alpha-GST) increased less in the balanced group, whereas creatinine was not affected in either group, suggesting a better preserved kidney integrity.

Experimental studies

Sepsis

Permissive hypercapnia is a frequent practice in patients ventilated for an ARDS. However, effects of respiratory acidosis on cell functions are not well known. Morisaki et al. [41] induced hypercapnic acidosis by ventilating rabbits with an atmosphere enriched with CO_2. Hypercapnia was associated with a reduction of gastric intramucosal pH and a reduced intestinal vascular permeability after endotoxin infusion. Interestingly,

hypercapnic acidosis did not influence endotoxin-induced gut neutrophil recruitment, suggesting that the observed protective effects might be independent of neutrophils. Using a similar approach, Gnaegi et al. [42] demonstrated that moderate hypercapnia prevented the deterioration of gut tissue energetics in endotoxemic rats. Endotoxic rats had a decrease in ATP and an increase in lactate concentrations in the gut, changes that were largely prevented by hypercapnia. Interestingly, this preventive effect of hypercapnia was not observed on liver energetic parameters. Oppositely, hypocapnia worsened shock induced by endotoxin, as well as bioenergenetic parameters measured in the circulation. In a gut ischemia/reperfusion model in rats, Di Paola et al. [43] demonstrated that glycyrrhizin, a component of licorice with anti-oxidant effects, protected against gut injury. Glycyrrhizin significantly decreased gut inflammation and neutrophil recruitment induced by a clamping and release of the splanchnic arteries, most probably by decreasing oxidative stress in this model.

Until now, the relevance of sepsis and endotoxemic models in mice has suffered from the fact that the animals were not resuscitated with fluids. Zanotti-Cavazzoni et al. [44] showed that, similarly to larger animals, the cardiovascular performance was profoundly influenced by fluid resuscitation in mice submitted to cecal ligation and puncture (CLP) and treated with antibiotics. Using echocardiography, these authors demonstrated that fluid infusion increased both left ventricular stroke volume and CO and prevented mortality in a dose-dependent manner. These results stress the importance of introducing fluid resuscitation in murine models to better mimic human septic shock and confirm the beneficial effects of early fluid loading in this condition. Baumgart et al. [45] investigated the possible role of Cu/Zn superoxide dismutase (SOD-1) in the cardiovascular response of mice submitted to CLP and resuscitated with fluids. The overexpression of SOD-1 in genetically modified mice did not ameliorate sepsis-related impairment of myocardial norepinephrine responsiveness, possibly because of the lack of increase in tissue catalase and mitochondrial SOD activity observed in this model. Using a rat endotoxic shock model described in Intensive Care Medicine in 2008 [46], Hagiwara et al. [47] investigated the effect of losartan, an antagonist of the type-1 angiotensin II receptor, on lung injury. Circulating pro-inflammatory cytokines and the alarmin HMGB-1 [48, 49] were markedly reduced in endotoxemic rats receiving losartan. Losartan also inhibited the LPS-mediated decrease in angiotensin-converting enzyme 2 activity and the labeling of this enzyme in the lung. In addition, losartan reduced pro-inflammatory activity induced by endotoxin in murine macrophages, suggesting a protective and anti-inflammatory role for antagonists of the type-1 angiotensin II receptor. Interest in vasopressin has increased recently with the VASST study of the treatment of septic shock in association with norepinephrine. Rehberg et al. [50] compared vasopressin and terlipressin in a fecal peritonitis model causing fulminant septic shock in sheep resuscitated with fluids and norepinephrine. Compared to vasopressin, terlipressin reduced the positive net fluid balance, increased central venous oxygen saturation and prolonged survival, but increased liver enzymes, a finding consistent with splanchnic ischemia. Clearly terlipressin was not equivalent to vasopressin and requires further testing before being proposed as a first-line drug in human septic shock. In another study, Wolff et al. [51] tested the modulation of the brain gene expression by iNOS inhibitors versus norepinephrine in endotoxin-treated rats. Using a microarray technique followed by a validation using PCR, these authors found that endotoxin induced a marked modification in the brain gene expression of chemokines and endothelial cell-specific proteins, mainly within the hypoccampus. Whereas norepinephrine treatment somewhat increased chemokine expression in the brain, the iNOS inhibitor had no effect. These results show that LPS-induced shock has a pro-inflammatory effect on the brain, principally on the hypoccampus, an effect that is further upregulated by the co-administration of norepinephrine. A large debate exists on the possible beneficial effects of treating septic shock patients with high-volume hemofiltration. Sykora et al. [52] tested a high versus low volume hemofiltration protocol in a hyperdynamic septic shock porcine peritonitis model. Hemofiltration was associated with less requirement of norepinephrine. However, neither low- nor high-volume hyperfitration induced a significant change in microvascular, metabolic, endothelial and lung functions compared with a non-filtrated control group of sheep in this model. Given the antiinflammatory and antiapoptotic properties of levosimendan, Scheiermann and colleagues [53] reported the effects of intravenous and nebulized levosimendan administration 3 h after the induction of CLP-induced sepsis in rats. They demonstrated a higher mean arterial pressure, arterial BE and pH; an increase in survival rate; a reduction in IL 6 and IL1β levels in plasma; and a reduction in cleaved caspase-3 concentration in the spleen in both treatment groups as compared to the control group. However, the mechanisms by which the administration of levosimendan improve cell viability and thus survival are still not understood. There are reports showing significant improvement of the cardiac index in sepsis or even refractory septic shock as a result of improving cardiac contractility by levosimendan rather than the anti-apoptotic effects. This concept is open for further studies.

Leukocyte reprogramming with a dominant immunosuppressive phenotype is a hallmark of sepsis and is

believed to play a significant role in the propensity of septic patients to acquire nosocomial infections. In a series of elegant experiments, Leendertse et al. [54] tested the hypothesis that a sublethal peritonitis (CLP) would influence the capacity of mice to clear a second bacterial infection caused by vancomycin-resistant enterococci (VREs). VREs did not induce the local inflammatory reaction required for their clearance when injected intraperitoneally in mice previously rendered septic by CLP. VRE bacterial loads were found increased in the peritoneum and in distant organs when compared with mice with a sham operation. This study highlights the critical importance of bacteria-induced inflammation as a key mechanism required for the clearance of bacteria. When the inflammatory reaction is small or absent due to a previous sepsis injury, the immune system is paralyzed and inefficient in fighting against a secondary bacterial infection, a situation that is reminiscent of that of human septic shock patients at high risk of developing (severe) nosocomial infections from commensal bacteria. Mediators responsible for the immune anergy observed during septic shock are not very well known. Although circulating anti-inflammatory cytokines such as IL-10 have been implicated in this phenomenon, it has also recently become apparent that immune deactivating cells such as CD4(+)CD25(+)Foxp3(+) regulatory T cells (Tregs) are increased during sepsis and may play a role in the so-called sepsis-associated "immune paralysis." Venet et al. [55] investigated whether Tregs participated in lymphocyte anergy during septic shock. They showed that the proliferation capacity of T cells was markedly impaired by the presence of Tregs. An inverse correlation was observed between the number of circulating Tregs and the proliferation of target T cells. They elegantly showed in septic mice that the ex vivo silencing of Foxp3, a Treg protein essential for their "immunosuppressive" effects, restored the proliferative capacity of T cells.

Nebulization of antibiotics is becoming a valuable therapeutic option in the treatment of pneumonia in critically ill patients. Many of the technical aspects of drug delivery to the lung by nebulization have been tested and optimized in animals, showing much higher airway concentrations compared to an IV route [56]. Ferrari et al. [57] compared treatment of ceftazidime delivered either by nebulization or IVs in pigs inoculated into the lungs by a strain of *P.aeruginosa* with a decreased sensitivity to this antibiotic. They demonstrated that the IV route was much less efficient than the nebulization route in controlling bacterial proliferation in all lung segments cultured. These results suggest that nebulization is capable of depositing higher bactericidal concentrations of antibiotics into the lung than the IV route, an effect that is particularly valuable in patients infected with bacteria with reduced sensitivity to antibiotics.

Mechanical ventilation and acute lung injury

Several studies compared different approaches to the lung recruitment maneuver in animal models of acute lung injury and provided our readers with interesting findings. It is important to identify the most reliable readouts to set adequate individual levels of open lung PEEP during recruitment. In a sheep model of acute lung injury induced by bilateral lung lavage, Caramez et al. [58] compared parameters measured during a decremental PEEP trial with those obtained from P-V curves following recruitment maneuvers. The authors observed a similar PEEP identified by the dynamic tidal respiratory compliance, maximum PaO_2, maximum PaO_2 and $PaCO_2$, minimum shunt, the inflation limb of lower Pflex or deflation limb upper Pflex from quasi-static P-V curves in their study set following a recruitment maneuver. However, it is unknown whether the parameters of readouts reported in Garamez's study are sensitive enough to detect the differences of lung recruitment. Interestingly, Dellaca et al. [59] assessed lung recruitment by monitoring the amount of derecruited lung using the forced oscillation technique in piglets. The investigators simultaneously measured the oscillatory compliance by using the forced oscillation technique and the percentage of non-aerated lung tissue by CT scan. Measurements were conducted before and after several interventions including mono- and bilateral atelectasis, and lung recruitment maneuvers. They reported a linear correlation between the two methods in measuring lung volume and suggested that the forced oscillation technique may be a useful tool for the non-invasive measurement of lung recruitment or derecruitment in addition to the existing methods.

To achieve optimal open lung results, Steimback et al. [60] evaluated the effects of frequency and inspiratory plateau pressure during recruitment maneuvers in paraquat-induced lung injury in rats. Two sigh frequencies at 10 or 180 sighs/h were applied in combination with a plateau pressure of either 20 or 40 cmH_2O, respectively. The authors demonstrated that a higher sigh frequency led to lung and kidney epithelial cell apoptosis associated with increased gene expression of the extracellular matrix protein type III procollagen. They further showed that a combined strategy of high sigh frequency with a lower plateau pressure may even worsen lung injury. A different picture was seen by Pellicano et al. using high-frequency oscillatory ventilation in combination with different stepwise escalating pressures [61]. The researchers compared four methods of lung volume recruitment during high frequency oscillatory ventilation in an acute lung injury model of neonatal piglets after repeated saline lavage. The four methods included a stepwise increase in pressure over 6 min to a peak mean airway pressure 12 cmH_2O above basal pressure; a sustained dynamic inflation for 20 s to the same peak pressure; a sustained

dynamic inflation repeated six times for 1 s each; and mean airway pressure set directly at basal pressure. The investigators reported that all methods resulted in a reduction in non-aerated lung, with the greatest redistribution to normally aerated lung being with stepwise recruitment. The studies are of interest with respect to searching for optimal approaches to lung recruitment. It would be good for our readers to know about the gas volume distribution within an injured lung after lung recruitment maneuvers, as overinflation in previously well-aerated lung is designated to be minimal.

Acute lung injury is characterized by excessive inflammatory responses. To further explore the mechanisms by which inadequate mechanical ventilation induces lung injury, Martínez-Caro et al. [62] demonstrated that increased formation of reactive oxygen and nitrogen species is involved in ventilator-induced vascular dysfunction in rats. The authors reported that the use of TV at 35 ml/kg and zero PEEP resulted in hypotension, systemic acidosis, hypoxemia and hyperlactatemia in vivo, and impaired vasoconstriction in response to acetylcholine and norepinephrine challenge in aortic rings. Immunostaining for both superoxide and nitrotyrosine was increased in aortic rings; thus, pre-treatment of the vascular rings with tempol (an intracellular superoxide scavenger) or MnTMPyP (a superoxide and peroxynitrite scavenger) improved acetylcholine- or norepinephrine-induced vasoconstriction. These data suggest a role of intracellular reactive oxygen and nitrogen species in ventilation-induced vascular dysfunction. In another study, Bueltmann et al. [63] examined the effects of inhaled milrinone, a phosphodiesterase 3 inhibitor, in models of acute lung injury following infusion of oleic acid in rats or intratracheal instillation of hydrochloric acid in mice. They demonstrated that a single inhalation of milrinone decreased myeloperoxidase activity and neutrophil counts, reduced protein concentration and TNF-α production in bronchoalveolar lavage, and attenuated lung injury. The lung protective effects of aerosolized milrinone administration were further enhanced when milrinone was repeatedly inhaled. They two further support that there may be a place for pharmacological intervention by targeting inflammatory responses in reducing ventilator-induced lung injury.

Ischemia/reperfusion and sepsis associated distal organ failure

Several studies investigated regional blood flow and oxygenation during ischemia and reperfusion injury, which may help enhance our understanding of the pathophysiology of distal organ injury.

Dubin et al. [33] measured systemic hemodynamics as well as microcirculatory changes at different vascular beds during progressive hemorrhage in anesthetized and MV sheep. The investigator reported that over a broad range of CO and superior mesenteric artery blood flow, the changes in intestinal serosal and mucosal capillary microvascular blood flow, and red blood cell velocities are more susceptible than the changes of mean arterial blood pressure, arterial pH and base excess, and intramucosal-arterial PCO_2 in response to progressive bleeding. They suggested that the microcirculatory changes measured by the semi-quantitative flow index may help detect microcirculatory alternations at an early stage prior to global hemodynamic deterioration. The concept of measuring microcirculation at the organ system is of importance. The regional blood flow device is yet to be tested in other experimental conditions, and the feasibility of using the invasive technique is yet to be investigated at bedside monitoring. This study by Dubin et al. is in agreement with previous studies showing that global hemodynamics may fail to reflect changes in regional blood flow at distal organs. In another interesting study, Dyson et al. [64] compared the changes of global oxygenation with that measured in liver, kidney, muscle and bladder in response to a variety of inspired oxygen concentrations during progressive hemorrhage in spontaneously breathing, anesthetized rats. The authors observed that survival times following progressive hemorrhage were similar in animals breathing room air, 60 or 100% O_2, but significantly worse in rats breathing 15% O_2. However, a decreased blood pressure and aortic blood flow and an increased lactatemia were observed in the hypoxemic and hyperoxemic groups compared to normoxemic animals. It appears that high FiO_2 or hyperoxemia cannot compensate for the low CO and thus tissue perfusion. This study indicates that hypoxemia and hyperoxemia both altered organ perfusion during severe and progressive hemorrhage. In an editorial, Dr. Douzinas [65] stated that we should keep in mind that CO and mixed venous oxygen tension are higher in isovolemic anemia than hypovolemia or hypoxemia. Therefore, it would be interesting to resuscitate the animals at different levels of blood volume loss and, by varying FiO_2 and measuring oxidative parameters, to determine if the management should mainly lie with O_2 therapy or with resuscitation efforts.

To further explore the relationship between systemic perfusion and tissue oxygenation, Hare et al. [66] investigated the effects of oxygen affinity for optimal tissue oxygen delivery in extreme hemodilution status by administration of a hemoglobin-hydroxyethyl starch conjugate (HRC 101) in rats. They reported that hippocampal tissue oxygen tension was best maintained after hemodilution with low but not high affinity HRC 101 at Hb 100 and 70 g/l after near complete blood volume exchange in rats. This is an interesting study that tests oxygen delivery with a hemoglobin-based oxygen carrier that can be constructed to have high and low oxygen affinity. The rationale for this model was that it would be

easier to compare otherwise identical Hb in the absence of red blood cells in which the Hb would be the primary contributor to oxygen delivery.

In a rat intestinal ischemia-reperfusion model, Liu and colleagues [67] demonstrated that immediate but not delayed postconditioning carries protective effects. The underlying mechanisms may involve inhibiting oxidant generation and reducing the release of proinflammatory mediators, etc. There are two major findings, namely that post-conditioning and pre-conditioning exert an apparently synergystic effect in this model, and if post-conditioning is deferred until several minutes of reperfusion have elapsed, the apparent protective effect is lost. Both of these observations may have important clinical implications. The observations regarding timing may explain the apparent failure of post-conditioning in some series and has important implications for future trial design.

It has been known for many years that cooling alters or reduces the coagulation system, and clinical data show that "NovoSeven" will not work in hypothermic patients. Hypothermia also results in changes in the cell surface lipid membrane, reduced platelet function and altered platelet morphology observed during hypothermic bypass surgery. Krouzecky et al. [68] elegantly demonstrated that cooling of blood in the extracorporeal circuit of continuous veno-venous hemofiltration enables preventing in-circuit clotting without the need to use any other anticoagulant. Dr. Davenport made comments that, as any young transplant surgeon knows, clotting and bleeding during any major transplant operation in heart, lung and liver differ when operating on pigs, dogs and humans. So it must be stressed that these results are from pig experiments. Secondly, in humans extracorporeal clotting during dialysis for example can occur independently of activation of factor XII, which was measured in the study by Krouzecky and colleagues. Also, as pointed out by Bagshaw and Davenport [69], the study only applied regional blood cooling of the extracorporeal circuit in their experimental model for a short duration. Additional investigations using a longer duration of CRRT with regional blood cooling in their model are needed to evaluate both efficacy and effectiveness, but also importantly safety, specifically in terms of temperature-induced hemolysis with repeated blood cooling and re-warming.

Pharmacology and sedation

Drug-drug interactions are a difficult field of intensive care medicine because of the application of multiple different classes of drugs and the large heterogeneity of the patients. One aspect in this context is the involvement of CYP450-mediated interactions, which is reason enough to give priority to this issue for a Mini Series on Basic Research-Related Topics in Intensive Care Medicine: Mouly et al. [70] concentrated on the basic science in Part 1 of the Mini Series. The authors present the clinical rationale for this important field of research to introduce the reader to the basics of the CYP450 system. Subfamilies of this enzyme group are mentioned, as well as inducers and inhibitors of the major CYP enzymes. In vitro systems to assess drug metabolism and interactions are shown to act as potentially useful tools during the preclinical step of drug development. Finally, "computer-assisted" prediction systems are presented as an interesting view into the future. Spriet et al. [71] focus on the clinical aspects including relevant CYP450-mediated drug interactions in the ICU. Multiple drug therapies are common for ICU patients, and the practicing intensivist must remain aware of the major mechanisms for drug-drug interactions. This manuscript covers a practical overview of clinically relevant interactions. Frequently used medications, such as benzodiazepines, immunosuppressive agents, opioids, certain anticonvulsants, the azoles and macrolides, have the potential to interact with the CYP450-mediated metabolism and may lead to toxicity or therapeutic failure. Especially this second part is an extremely important tool for every intensivist!

Adverse drug reactions (ADR) are a noxious, unintended and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis or therapy. The incidence of serious and fatal ADR is high. Schwake et al. [72] aimed (1) to determine the prevalence of ICU admissions resulting from an ADR and (2) to compare affected patients with patients admitted to the ICU for the treatment of deliberate self-poisoning using medical drugs. A total of 1,554 patients admitted on 1 January 2003 to 31 December 2003 in a 14-bed medical ICU were prospectively studied. Ninety-nine patients were admitted to the ICU with a diagnosis of ADR (6.4% of all admissions); 269 admissions (17.3%) were caused by deliberate self-poisoning. Patients admitted for treatment of ADR had a significantly higher age, a longer treatment duration in the ICU, a higher SAPS II score and a higher 6-month mortality than those with deliberate self-poisoning. Most patients (71.7%) suffering from ADR required advanced supportive care in the ICU, whereas the majority of patients (90.7%) with deliberate self-poisoning could be sufficiently treated in the integrated intermediate care area. All diagnostic and therapeutic procedures in the ICU except mechanical ventilation were performed significantly more often in patients with ADR. It was concluded that ADR is a frequent cause of admission to medical ICUs resulting in a considerable use of ICU capacities and that patients with ADR required longer and more intense medical treatment in the ICU than those with deliberate self-poisoning.

In an observational case series from Western Australia, Brown et al. [73] reported that early clotting factor

replacement to treat snake venom-induced comsumption coagulopathy resulted in earlier recovery.

It is especially appreciated when investigators have the courage to present research on very rare, but sometimes important topics in intensive care medicine. One example is the paper by Struck et al. [74], who reviewed the current literature on severe cutaneous adverse reactions that are not associated with burn injuries. They presented life-threatening examples, such as cases of Steven-Johnson syndrome and toxic epidermal necrolysis, and concluded that these patients will substantially benefit from early interdisciplinary care and thorough consideration of complications during transport and intensive care treatment. The attending medical team should be aware of possible underlying diseases and instigating substances, and these patients should be treated in a manner similar to severe burn patients.

Short-term analgosedation with intravenously administered short-acting drugs is associated with significant cost. Analgosedation by inhalative agents appears to be an intriguing alternative, which was investigated in 17 ICU patients requiring mechanical ventilation [75]. The feasibility of sedation with sevoflurane using the anesthetic conservative device (AnaConDa) for short-term sedation was tested. The application was found to be safe, and hemodynamic tolerance was good, but the induction and termination waking times were longer than when using remifentanil and propofol.

The hepatic metabolism of another commonly used drug, midazolam, is altered during critical illness. Kirwan et al. [76] used this property to explore the reliability of a single measurement of midazolam concentration as an indicator of hepatic drug metabolism. The findings of this study indeed confirmed a satisfactory correlation between the single midazolam concentration and the area under the curve of the plasma concentrations. The presence of acute kidney injury was associated with increased midazolam concentration.

In a pilot, phase III, double-blind multicenter study of 85 randomized medical and surgical patients, Ruokonen et al. [77] compared dexmedetomidine (1.4 μg/kg/h) with propofol/midazolam for long-term sedation. Target RASS was reached in 64% of patients receiving dexmedetomidine and in 63% of control patients. Similarly, the length of ICU stay was similar. Dexmedetomidine was comparable to propofol/midazolam in maintaining sedation targets of RASS of 0 to −3. However, patients with a RASS target of −4 or less reached the target in 42% of the cases with dexmedetomidine and in 62% with propofol/midazolam ($P = 0.006$).

In a prospective study, Chanques et al. [78] validated an adaptation of the Behavioral Pain Scale for use in non-intubated delirious patients (BPS-NI). One physician and the bedside nurse rated the level of pain during catheter dressing change and turning in 30 consecutive adult patients. Delirium was assessed by the CAM-ICU. Pain scores were higher during painful procedures than at rest, whereas no changes in pain scores were found during non-nociceptive procedures. The BPS-NI showed good internal consistency, good inter-rater reliability and good responsiveness.

Tardy-Poncet et al. [79] reported danaparoid cross-reactivity with heparin-induced thrombocytopenia antibodies in 12 patients treated with lepirudin. They concluded that the absence of any increase in platelet count after 3–5 days of danaparoid therapy and/or the occurrence of a new thrombotic event should lead to suspicion of danaparoid cross-reactivity.

A case of acute respiratory failure after charcoal aspiration with recurrent release of charcoal from an intrapulmonary cavern has been reported by Francis et al. [80].

Communication and teaching

Rego Lins Fumis and Deheinzelin reported on satisfaction and prevalence of symptoms of anxiety and depression in family members of 300 critically ill cancer patients [81]. Prevalence of anxiety and depression in family members was 71 and 50.3%, respectively. Anxiety was independently associated with prolonged mechanical ventilation, relative's gender and religion. Factors associated with symptoms of depression were presence of metastasis and relative's gender.

Stricker et al. [82] assessed family satisfaction in the relatives of 996 Swiss ICU patients. Overall, proxies were satisfied with care and with information/decision-making. Higher severity of illness was associated with higher satisfaction, whereas a higher patient:nurse ratio and written admission/discharge criteria were associated with lower overall satisfaction. The need for improving emotional support, coordination of care and communication was highlighted.

In a multicenter before/after observational study, Tremey et al. [83] assessed the compliance and impact of a teaching program on guidelines for the management of severe bleeding under oral anticoagulation therapy in EDs. Forty-five patients with severe bleeding under oral anticoagulation therapy were included in 2003 and 54 patients in 2005. The intervention consisted of a training program on management of severe bleeding under oral anticoagulation therapy performed by an expert physician. The primary end-point was the use of a prothrombin complex concentrate-vitamin K combination between the two study periods. Nine patients (20%) in 2003 and only 29 patients (54%) in 2005 received this combination ($P < 0.01$). Almost one-third of patients had only withholding of oral anticoagulation therapy. Adverse events and mortality rate did not differ between the two phases.

Chalumeau-Lemoine et al. [84] evaluated the impact of limited training of ICU physicians without knowledge of ultrasound in performing basic general ultrasonography. After 8.5 h of training comprising a 2.5-h didactic course that included essential views of normal and pathologic conditions and three hands-on sessions of 2 h each, an ICU resident and a senior radiologist performed the same examination in a blind manner. The questions addressed concerned the presence of pleural effusion, intra-abdominal effusion, acute cholecystitis, intrahepatic biliary duct dilation, obstructive uropathy, chronic renal disease and deep venous thrombosis. The answers to 129 questions were analyzed. Residents answered 84.4% of the questions correctly. Most of the discrepancies concerned small non-drainable pleural or abdominal effusions. For questions with a potential therapeutic impact, residents answered 95% of the questions correctly. Residents completed the examination in 37 ± 39 min compared with 296 ± 487 min for the radiologists.

Intensive care medicine has developed rapidly and to a considerable extent throughout the past 10–15 years. Hence, it is most important to implement and adapt programs for training the physicians. Years ago, the European Society of Intensive Care Medicine (ESICM) was one of the first contributors to the CoBaTrICE program (Competency-Based Training in Intensive Care MedicinE). Meanwhile, this program has been established, and the CoBaTrICE Collaboration presented the results from a recent survey in 28 European countries in a report [85]. It was demonstrated that, although more than half of the countries have modified their training programs since CoBaTrICE was initiated, national standards for approving hospitals as training centers vary widely, and there is considerable diversity in pedagogic structures and processes. Nonetheless, the Collaboration will continue to harmonize and develop international standards for quality assurance of training programs.

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