Intensive Care Med (2011) 37:196–213
DOI 10.1007/s00134-010-2123-y

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Year in review in Intensive Care Medicine 2010: II. Pneumonia and infections, cardiovascular and haemodynamics, organization, education, haematology, nutrition, ethics and miscellanea

Received: 27 December 2010
Accepted: 27 December 2010
Published online: 12 January 2011

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Pneumonia

Biomarkers

Emergency physicians often face the routine challenge of predicting short- to mid-term adverse outcomes for patients with community acquired pneumonia (CAP) with low risk of complication. As biomarkers have significantly improved practices in emergency medicine, it was suggested that they could help management of CAP. Indeed, procalcitonin (PCT) measurement allows early discontinuation of antimicrobial agents in patients with CAP and may predict severity [1]. In this context, Claessens et al. [2] tested the usefulness of several biomarkers, including procalcitonin, C-reactive protein (CRP) and mid-regional pro-atrial peptide, in a large prospective multicentre study that included 419 patients with mild CAP. The initial measurement of mid-regional pro-atrial peptide accurately identified low-risk CAP patients requiring hospitalization following initial emergency department (ED) visit, with better operating characteristics than CRP and PCT.

Early onset pneumonia is frequently reported after cardiac arrest, despite the fact that therapeutic hypothermia and post-resuscitation disease manifestations make it difficult to diagnose. In order to assess the ability of serum PCT measurements to help diagnose pneumonia in this setting, Mongardon et al. [3] studied 132 consecutive patients admitted to intensive care unit (ICU) after a successfully resuscitated cardiac arrest, of whom 86 had developed pneumonia. Although PCT was significantly higher in patients with pneumonia at day 1, negative predictive values were 39% at admission, 42% at day 1 and 52% at day 2, whereas positive predictive values were 72, 68 and 70%, respectively. These results confirm that the diagnostic value of PCT is poor after cardiac arrest, probably because the post-resuscitation disease itself could lead to a major increase in PCT levels.

Simple criteria allowing pneumonia to be confirmed or ruled out at an early stage of management of ICU patients requiring mechanical ventilation would be clinically useful. To evaluate the respective and combined usefulness of the Clinical Pulmonary Infection Score (CPIS), bronchoalveolar lavage (BAL) gram staining, endotracheal aspirate surveillance culture, and BAL and serum procalcitonin, Jung et al. studied 57 ICU patients clinically suspected of having developed ventilator-associated pneumonia (VAP) [4]. No differences were found in alveolar or serum procalcitonin between VAP and non-VAP patients, confirming that procalcitonin is not an accurate marker of VAP. In contrast, microbiological resources available at the time of VAP suspicion (BAL gram staining, last available endotracheal aspirate) combined or not with CPIS were helpful in distinguishing VAP diagnosed by BAL from patients with a negative BAL. Including procalcitonin in the CPIS score did not increase its accuracy (55%) for the diagnosis of VAP.

Adjuvant therapy in patients with pneumonia

Macrolides may have beneficial effects in severe CAP because of their immunomodulatory effects rather than their antimicrobial properties. Several recent studies suggest that adding macrolides to beta-lactams results in better mortality when compared with beta-lactam single-drug therapy in hospitalized patients with CAP [5] or when compared with the combination of beta-lactam plus quinolone in patients with CAP admitted to the ICU (HR 0.48, 95% CI 0.23–0.97, $p = 0.04$). When more severe patients presenting severe sepsis and septic shock were analysed in this latter study, similar results were obtained (HR 0.44, 95% CI 0.20–0.95, $p = 0.03$) [6].

The administration of corticosteroids in CAP is a controversial issue. Snijders et al. [7] performed a randomized double-blinded clinical trial comparing the administration of corticosteroids plus antibiotics with antibiotics alone. There were no differences in outcome. However, the inclusion of patients with very severe CAP (which should be the target population) was low. Not surprisingly, coadjuvant therapy with corticosteroids has also been proposed for treating patients with severe H1N1 influenza A-associated respiratory failure, with two large studies reporting the use of corticosteroids in 51–69% of patients [8, 9]. In a small series of 13 acute respiratory distress syndrome (ARDS) patients, with and without confirmed H1N1 influenza, prolonged low-to-moderate dose corticosteroid treatment in addition to oseltamivir was well tolerated and associated with significant improvement in lung injury and multiple organ dysfunction scores and a low hospital mortality [10]. However, whether or not corticosteroids are really beneficial in this setting remains highly debated [11, 12] and additional studies exploring this issue are mandatory before firm conclusions can be drawn.

Prevention of VAP

Selective digestive microbial decontamination (SDD) is hypothesized to benefit patients in ICU by suppressing Gram-negative potential pathogens from the colon without affecting the anaerobic intestinal microbiota. To provide more insight into this important issue, Benus et al. [13, 14] used fluorescent in situ hybridization to analyse the faecal microbiota from a subset of ICU patients who were enrolled in a large multicentre trial to study the outcome of SDD and selective oral decontamination (SOD) in comparison with standard care (SC). Results clearly demonstrated that the composition of the intestinal microbiota was importantly

affected by SDD, with a significant suppression of the anaerobic *F. prausnitzii* group of bacteria during SDD. This group of microbiota, which is one of the predominant bacterial groups in healthy volunteers, representing 10–15% of the intestinal microbiota on average, plays an important role in maintaining the colonization resistance, normally protecting the human host from infections. *F. prausnitzii* has also been found to promote the growth of colonocytes through its production of butyrate, preventing mucosal atrophy. Interestingly, Dutch investigators also recently reported that SOD and SDD have marked effects on the bacterial ecology of ICU patients, with rising ceftazidime resistance prevalence rates in the respiratory tract during intervention and a considerable rebound effect of ceftazidime resistance in the intestinal tract after discontinuation of SDD [15].

Prevention of VAP requires a complex approach that should include factors affecting healthcare workers' (HCWs) behaviour. In a study designed to assess which individual factors interplayed in a multifaceted program focusing on VAP prevention, Bouadma et al. [16] determined that five cognitive factors were significantly associated with knowledge at the end of the educational program: perceived susceptibility, seriousness, knowledge, benefits and self-efficacy. Behaviour changes were especially pronounced for HCWs with the lowest baseline cognitive profiles.

Polyurethane (PU)-cuffed tracheal tubes have been shown to decrease leakage of oropharyngeal secretions and thus could lower nosocomial pneumonia rates [17]. However, because of the thickness, lower resistance, and resting volume of polyurethane cuffs, cuff pressure variations are expected to be greater in these cuffs, which could decrease their efficacy. To determine the impact of polyurethane on variations in cuff pressure in intubated critically ill patients, Nseir et al. [18] continuously recorded for 24 h cuff pressure in 76 patients, including 26 with polyvinyl chloride (PVC), 22 with cylindrical polyurethane (CPU) and 28 with tapered polyurethane (TPU)-cuffed tracheal tubes. Although polyurethane did not impact variations in cuff pressure, microaspiration of gastric contents, as determined by pepsin contents in proximal airways, was less frequent in patients intubated with polyurethane-cuffed (either cylindrical or tapered) tubes compared with patients intubated with PVC-cuffed tubes, confirming the potential usefulness of these devices.

Non-invasive ventilation (NIV) has been described among other measures as a potential strategy to prevent VAP and the recommendation to use NIV whenever possible has been incorporated in guidelines for VAP prevention [19]. To compare the characteristics of pneumonia cases associated with different types of ventilation and the spectrum of associated pathogens, Kohlenberg et al. [20] analysed the pooled data of 400 German ICUs participating in the German nosocomial infection surveillance system with respect to three categories of nosocomial pneumonia: pneumonia associated with invasive mechanical ventilation (MV), pneumonia associated with NIV and pneumonia not associated with ventilation. The study included 779,500 patients, totalizing 1,068,472 invasive MV days and 101,569 NIV days; a total of 6,869 cases of pneumonia were reported. The mean pneumonia incidence densities were 1.58 and 5.44 cases per 1,000 ventilator days for NIV and invasive MV, respectively. Pneumonia cases associated with invasive MV were younger, had a longer ICU stay before onset of pneumonia and were more often associated with gram-negative bacteria than cases associated with NIV; however, there were no differences in the proportion of secondary sepsis and death.

The concept of bundles, a series of coordinated interventions devoted to VAP prevention through guideline implementation, was proposed by a European task force in order to rationalize prevention practices [21]. The resulting VAP care bundles were non-ventilatory circuit changes unless specifically indicated, alcohol hand hygiene, appropriately educated and trained staff, incorporation of sedation control and weaning protocols into patient care, and oral care with chlorhexidine.

Treatment of VAP

The appropriateness of empirical antimicrobial therapy for VAP is a determinant for patient outcome and is mostly related to difficult-to-treat pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and/or oxacillin-resistant *Staphylococcus aureus*. In a large cohort study on 218 patients with microbiologically documented VAP, empirical antimicrobial therapy was inappropriate in 40% of the patients with VAP due to difficult-to-treat bacteria and 5% in cases of non-difficult-to-treat bacteria ($p = 0.001$) [22]. In almost half of the cases, inappropriate empirical antimicrobial therapy for difficult-to-treat bacteria was due to non-adherence to the local guidelines, suggesting some room for improvement by implementing educational programs.

Emergence of multidrug-resistant strains in ICUs has renewed interest in colistin, which often remains the only available antimicrobial agent active against resistant *P. aeruginosa* or *A. baumannii*. In a study performed in ventilated piglets with inoculation pneumonia caused by *P. aeruginosa*, Lu et al. [23] showed high colistin lung tissue deposition following nebulization, contrasting with the absence of any detectable deposition following intravenous administration. In the aerosol group, the high lung deposition was associated with rapid and efficient bactericidal activity. Interestingly, colistin distal lung deposition decreased with severity of pneumonia and aeration loss, as shown previously with nebulized ceftazidime [24].

Epidemiology

Infection is the most frequent cause of acute respiratory distress syndrome. However, little is known about the influence of infection sites on ARDS. To assess the associations between infection sites and ARDS development and mortality in critically ill infected patients, Sheu et al. [25] prospectively followed 1,973 consecutive patients admitted to ICUs with bacteraemia, pneumonia or sepsis. During follow-up, 549 patients developed ARDS and 212 of them died within 60 days. On multivariate analysis, lung was the only infection site associated with increased ARDS risk [adjusted odds ratio (OR) 3.49]. Urinary tract (adjusted OR 0.43), skin/soft tissue (adjusted OR 0.64) and unknown-site infections (adjusted OR 0.38) were associated with decreased risk. No association was found between individual infection site and ARDS mortality.

The excess risk of death attributable to VAP varies considerably across studies, from 0 to 50% [26]. Several factors contribute to this variability, including definitions, case-mix, causative microorganisms, treatment adequacy and statistical methodology. Using a multistate progressive disability model that appropriately handled VAP as a time-dependent event in a high-quality database of 2,873 mechanically ventilated patients, Nguile-Makao et al. [27] showed that VAP attributable mortality (VAP-AM) was 8.1% overall. VAP-AM varied widely with case-mix, severity at admission, time to VAP onset, and severity of organ dysfunction at VAP onset. Bacterial resistance did not affect VAP-AM. These results are consistent with the 10.6% value obtained in five German ICUs using a multistate PD model [28].

Infections

Diagnosing bloodstream infections has always been associated with a diagnostic delay of at least 24 h. Considering the consequences of rapid and appropriate antimicrobial therapy in patients with ICU-acquired bacteraemia, diagnostic methods that reduce this diagnostic delay might significantly enhance the quality of patient care. Conventional microbiological methods depend on the growth of bacteria, which will take hours to yield a positive signal. Yet, with detection of bacterial DNA with polymerase chain reaction (PCR) such a signal could, in theory, be obtained within minutes. Two recent studies addressed this issue. In one study of 453 blood samples in 108 patients, PCR resulted in a higher positivity rate (114 samples) than conventional blood cultures (58 samples), but discordant results occurred in 18 of these 58 samples [29]. In the other study, of 143 patients with severe sepsis and 63 surgical controls, PCR yielded more positive results (34.7 vs. 16.5%), but PCR positivity was only obtained in 70% of the samples with growth in blood cultures. Yet PCR positivity (with negative results from culture) correlated with disease severity [30]. Another innovative approach for diagnosing ICU-acquired infections is F-18-fluorodeoxyglucose positron emission tomography (FDG-PET CT). In 33 patients with a clinical suspicion of ICU-acquired infection, the diagnostic accuracy of PET-CT, when added to standard diagnostic procedures, was estimated to be 91%, with 79% specificity and 100% sensitivity [31]. Therefore, although promising, the clinical values of the PCR-based detection of bacterial DNA in blood samples and of FDG-PET CT remain to be determined.

Transmission of multi-resistant bacteria is increasingly creating difficult-to-treat infections, and effective infection control measures are needed. The role of antibiotics in the transmission is difficult to quantify. Temporary use of a certain class on antibiotics (cycling) has been proposed as a measure to reduce antibiotic selective pressure, as compared to a more chaotic approach of antibiotic prescription. Yet, predominant use of fluoroquinolones had devastating effects on the acquisition of resistance to cephalosporins and fluoroquinolones by Enterobacteriaceae in a Dutch ICU [32]. In contrast, implementing quality improvement measures over a period of 8 years (such as ICU relocation, antibiotic stewardship, dedicated infection control nurses and alcohol-based hand rub solution) was associated with a decrease in the endemic rates of MRSA in an Australian ICU [33]. Daily skin cleansing with chlorhexidine has been associated with lower infection rates and lower transmission rates of antibiotic-resistant bacteria. Yet, when analysed in a pragmatic design in a surgical ICU, this intervention failed to reduce rates of central line-associated bacteraemias, although the blood culture contamination rate did decline [34].

Careful preparation is needed when an influenza pandemic or other mass disaster is expected. Recommendations for ICU preparation have been formulated, in order to minimize the inevitable mortality associated with such circumstances [35]. During an influenza outbreak many patients will need ICU admission because of severe community-acquired pneumonia. Distinction between patients with viral, bacterial or mixed infection is relevant for optimizing treatment strategies. In a small subset of 25 patients, CRP, and to a lesser extent procalcitonin, assisted in distinguishing pneumonia due to bacterial causes and H1N1 influenza [36]. Currently, moxifloxacin is frequently used to treat severe community-acquired pneumonia and the main pharmacokinetics/pharmacodynamics parameter predicting its clinical efficacy is the AUC/MIC. It was demonstrated that when using 400 mg moxifloxacin once daily in critically ill patients this parameter can be considerably lower than in healthy

volunteers, suggesting that dosage adjustments are needed [37].

There are differences in the literature regarding the impact of nosocomial infections on attributable mortality and resource consumption. In a cohort of 2,392 patients from 34 Austrian ICUs, with a length of stay (LOS) greater than 2 days, 683 (28.6%) developed at least one nosocomial infection [38]. The most common infection was pneumonia ($n = 456$), followed by central venous catheter (CVC) infections ($n = 101$). Risk-adjusted mortality rates (standardized mortality ratios) were significantly increased for infected patients [0.91 (0.83–0.99) vs. 0.68 (0.61–0.74)]. Significant attributable risk-adjusted mortality was found for patients with pneumonia, combined infections (both 32%) and CVC-related infections (26%). LOS in the ICU increased significantly for all infections. All infections were associated with increased resource consumption. The authors suggested that effective infection control measures could improve both clinical outcome and use of ICU resources.

Low monocyte human leukocyte antigen-DR expression (mHLA-DR) has been proposed as a global biomarker of sepsis immunosuppression. A very recent study included 209 septic shock patients for whom HLA-DR was measured by flow cytometry at days 3–4 and 6–9 after the onset of shock [39]. This study first confirmed that non-survivors ($n = 51$) exhibited lower mHLA-DR values, expressed as means of fluorescence intensities, than survivors ($n = 102$) (33 vs. 67). It also showed that patients who developed nosocomial infections exhibited lower mHLA-DR values than those who did not. Persistent low mHLA-DR ($\leq$54) was independently associated with nosocomial infection occurrence after adjustment for clinical parameters.

Cardiovascular and haemodynamics

Haemodynamic management of severe sepsis

Restoring blood pressure is one of the main aims of the management of septic shock. As recommended, low blood pressure should be first restored, as early as possible, by fluid loading, followed, in case of failure, by the administration of vasopressors.

Whether beneficial effects of fluid loading are only related to improvement in global haemodynamics or might be related to improved local microcirculation remains unclear. It has been recently shown that fluid administration improved microvascular perfusion in the early but not late phase of sepsis [40]. The proportion (%) of perfused small vessels increased from 65 (60–72) to 80 (75–84) ($p < 0.01$) in the early phase and from 75 (66–80) to 74 (67–81) ($p =$ not significant, ns) in the late phase. This beneficial effect of fluid administration in severe sepsis was independent of global haemodynamic (cardiac index, mean blood pressure) effects and the type of solution.

The choice of vasopressor is still unclear. Maybauer and Walley [41] advocate the concept of tailored therapy. In terms of choosing a vasopressor in patients with septic shock, they wrote that a "winner-takes-all" approach is likely not the way to go. The recently published literature does not give definitive results in favour of one particular vasopressor. In addition to the need of restoring blood pressure, intensivists should also consider the clinical context: arrhythmia, lactate level, cardiac failure. Thus norepinephrine may be a better vasopressor in cases of arrhythmia or elevated lactate level. Arginine vasopressin might have an additive value when catecholamines failed to restore blood pressure. In advanced vasodilatory shock already receiving catecholamines, two arginine vasopressin (AVP) dose regimens were recently tested on the haemodynamic response, catecholamine requirements, AVP plasma concentrations and organ function [42]. Patients requiring more than 0.6 μg/kg/min of norepinephrine received a supplementary AVP infusion either at 0.033 IU/min ($n = 25$) or 0.067 IU/min ($n = 25$). The latter dose (0.067 IU/min) restored cardiovascular function more effectively than AVP at 0.033 IU/min. AVP administration was associated with a decrease in heart rate, norepinephrine requirement, lactate and an increase in blood pressure.

Pulse pressure variation and fluid responsiveness

Pulse pressure variation (PPV) is increasingly used to predict fluid responsiveness in mechanically ventilated patients. However, the impact of tidal volume (VT) and airway driving pressure (Ppla-PEEP) remains unclear. Effect of fluid challenge was assessed in 57 mechanically ventilated and sedated patients with signs of hypoperfusion (oliguria and catecholamine use) and requiring cardiac output (CO) measurement [43]. Most of the patients (71%) were responders. At baseline, central venous pressure (CVP) was lower and PPV was higher in responders. The areas under the receiver operating characteristics (ROC) curves were similar with PPV and CVP (0.76). Furthermore, in patients mechanically ventilated with low VT, PPV values less than 13% did not rule out fluid responsiveness, especially when (Pplat-PEEP) was no greater than 20 cmH_2O.

Risk stratification of acute myocardial infarction admitted in ICU

ARIAM is a Spanish database that prospectively collected data from 6,458 ICU patients admitted for acute myocardial infarction (AMI) [44]. Main demographic

parameters were the following: 77% males, age 65 years, APACHE-II score 9 points and ICU mortality 8.9%. In multivariate analysis, ICU mortality was related to APACHE-II (OR 1.16), age (OR 1.05), gender (OR 1.64), previous AMI (OR 1.57), anterior AMI (OR 2.05) and delay longer than 180 min (OR 1.37) and Killip class.

Evaluation of haemodynamic alterations

Fluid management: can we better predict fluid requirements?

Techniques predicting the response to fluids are becoming more and more popular. Passive leg raising is based on the fact that rapid postural changes induce an acute increase in ventricular preload which would lead to an increase in cardiac output in patients who will subsequently respond to fluid administration [45]. However, to be effective this test should effectively increase preload. It has been shown that the increase in cardiac output is dependent on the amount of blood mobilized, and that raising the legs together with changing torso position from 30 to 0° maximally increases preload [46]. However, even when fluid mobilization is maximal it can still be insufficient to effectively increase preload (such as in patients with increased intrathoracic pressure or severe peripheral vasoconstriction). In order to ensure that preload is effectively manipulated, Lakhal et al. [47] elegantly proposed to use the changes in CVP induced by passive leg raising. They hypothesized that an absence of change in CVP would suggest that the change in preload was insufficient, so that no conclusions can be drawn based on the test. In this multicentric trial (four centres), the authors investigated 102 patients estimated to need a fluid challenge. All patients were under mechanical ventilation and equipped with a haemodynamic monitoring device. The passive leg raising test had a satisfactory predictive value for fluid responsiveness, as assessed by a ROC curve area of 0.89. When changes in CVP were considered, the ROC curve area was higher in the 49 patients experiencing an increase in CVP by at least 2 mmHg than in the others (0.98 vs. 0.83). These data suggest that this easy to apply measurement can be used to improve the predictive value of passive leg raising test.

Another important aspect in this test is the method used to determine the changes in cardiac output. Lakhal et al. also showed that cardiac output should be measured as indirect assessment of changes in pulse pressure gave lower predictive values (0.74 vs. 0.89). However, invasive or semi-invasive monitoring devices are not always available in these patients. Benomar et al. [48] investigated whether measurements of cardiac output with bioreactance, a totally non-invasive device, could be used. The authors investigated 75 consecutive patients after cardiac surgery. In the postoperative period, all patients underwent a passive leg raising test and a subsequent fluid challenge. The authors first determined the least minimal significant change in cardiac output that was found to be at 8.9%. Using this cut-off value during passive leg raising test, the authors observed that the test had 68% sensitivity and 95% specificity for detecting a positive response to fluid challenge.

Another aspect of management that is often neglected is the risk of developing hypovolaemia when fluids are withdrawn during haemofiltration/haemodialysis. Guiotto et al. [49] used echocardiography to evaluate respiratory variations before and after fluid removal by slow continuous haemofiltration in 24 patients with decompensated heart failure. Overall fluid withdrawal of 5.8 L over 20 h was well tolerated, as mean arterial pressure and heart rate remained unaltered. Respiratory variations in inferior vena cava diameter increased significantly but reached 30% only in the two patients developing hypotension. Unfortunately, this study investigated patients only before and at the end of fluid withdrawal, and sequential measurements were lacking. Hence, it was not feasible to evaluate whether respiratory variations in inferior vena cava occurred well before occurrence of hypotension so that they could be used as a warning signal or whether they occurred only when symptomatic hypovolaemia already developed.

A systematic review of the published evidence on the ability of passive leg raising-induced changes in cardiac output (PLR-cCO) and in arterial pulse pressure (PLR-cPP) to predict fluid responsiveness was published in the September issue [50]. Nine articles including a total of 353 patients were included in the final analysis. The pooled sensitivity and specificity of PLR-cCO were 89.4% (84.1–93.4%) and 91.4% (85.9–95.2%), respectively. Diagnostic odds ratio was 89.0 (40.2–197.3). The pooled area under the receiver ROC curve was 0.95 (0.92–0.97). The pooled difference in mean PLR-cCO values between responders and non-responders was 17.7% (13.6–21.8%). No significant differences were identified between patients adapted to ventilator versus those with the persistence of spontaneous breathing and between patients in sinus rhythm versus those with arrhythmias. The pooled difference in mean PLR-cPP values between responders and non-responders was 10.3% (6.5–14.1%). The authors concluded that passive leg raising-induced changes in cardiac output can reliably predict fluid responsiveness regardless of ventilation mode and cardiac rhythm, and can be recommended for routine assessment of fluid responsiveness in the majority of ICU patients. The PLR-cCO has a significantly higher predictive value than the PLR-cPP.

Devices and techniques

Different technologies can be used to estimate CO. Galstyan et al. [51] evaluated the ability of an ultrasound dilution technique to measure cardiac output and to

estimate intrathoracic blood volumes. In this method an external loop in which blood circulates at constant flow is used to transiently make blood circulate. Injection of small saline bolus is used to measure dilution, the changes in ultrasound transmission properties induced by this bolus being detected in the external loop. This technique also allows one to compute central blood volume.

The authors measured cardiac output and intrathoracic volumes in 30 patients with transpulmonary thermodilution (PiCCO, Pulsion) and ultrasound dilution (Transonic Systems). Regarding cardiac output measurements, there was very good agreement between the two methods, with a bias of 0.03 L/min and a percentage error of 20%. However, measurements of global end diastolic volumes with PiCCO were 2.5 times larger than ultrasound-derived central blood volumes. In the absence of alternate measurement of heart volumes, the authors speculated that the ultrasound dilution technique measured left heart chambers while global end diastolic volumes include left and right heart chambers and large vessels. Additional studies are required to confirm this hypothesis and to validate this measurement as an estimate of left heart chambers.

Impact of fluid type

The impact of the type of fluids on haemodynamics and on potential side effects is still a matter of debate. In a randomized trial, Trof et al. [52] evaluated the haemodynamic response to fluid challenge with colloids ($n = 24$) or crystalloids ($n = 24$) in a cohort of 48 critically ill patients, including 24 septic and 24 non-septic patients. Cardiac output and global end diastolic volume were measured by using transpulmonary thermodilution. The authors observed that cardiac index increased more with colloids than with crystalloids (12 vs. 2%, $p < 0.05$) and this was related to a greater increase in preload as estimated by a greater increase in central venous pressure and in global end diastolic volume (both $p < 0.05$). There were no differences between septic and non-septic patients. These data confirm that for a given volume, plasma expansion induced by colloids is greater than with crystalloids. However, these observations were restricted to a 90-min period and the duration of plasma expansion with the two solutions was not evaluated.

Schortgen et al. [53] evaluated the impact of oncocity of infused fluids on the development of secondary ARDS. The authors had a retrospective look at a large database of prospectively collected data from patients receiving fluid administration during a 4-week observation period. After exclusion of patients presenting ARDS at inclusion, the authors evaluated the development of secondary ARDS. Patients were separated according to the predominant type of fluids received, hypooncotic for crystalloids and low concentrations colloids (such as 5% albumin solutions) or normo- or hyperoncotic fluids (20% albumin, starches). Nine percent of the 905 patients developed secondary ARDS, with no difference between hypo- and normo/hyperoncotic group (10.4 vs, 7.7%, $p =$ ns). It is possible that the trial was underpowered to detect a difference of this magnitude; however, other factors such as sepsis or positive fluid balance were identified to be associated with the onset of secondary ARDS. This study does not identify oncocity of fluid infused as a factor associated with development of secondary ARDS.

Resuscitating the microcirculation

The role of microcirculatory alterations in sepsis and in their association with outcome has been largely demonstrated [54, 55]. However, the effects on the microcirculatory alterations of various interventions, and in particular fluids, remains not well defined. This issue was amply covered this year in *Intensive Care Medicine*. Boldt and Ince [56] published a systematic review on the effects of fluids on the microcirculation. They observed that many experimental trials point out that colloids administration may be associated with a greater improvement in microcirculatory perfusion than crystalloid administration. They also reported that human data were lacking at the time of their review. *Intensive Care Medicine* later published two interesting trials reporting the effects of fluids on sublingual microcirculation in patients with severe sepsis. In a series of 60 patients, Ospina-Tascon et al. [40] showed that fluid administration markedly improved the microcirculation in patients in the early phase of sepsis (defined as within 24 h of the diagnosis of sepsis), but did not affect microcirculation at later stages (after 48 h). There were no differences between crystalloid or 4% albumin administration. Interestingly, the microcirculatory effects could not be predicted by looking at the global haemodynamic response to fluids. Pottecher et al. [57] also evaluated the impact of fluids on the microcirculation. In a series of 25 patients with severe sepsis admitted for less than 24 h, the authors performed a passive leg raising test followed by administration of crystalloids in two steps. All patients were predicted to be fluid responders before fluid administration (based on selection by passive leg raising test). They observed that passive leg raising test significantly improved the microcirculation and that a similar effect was observed with the first aliquot of fluids (computed to be equivalent to the amount of fluid mobilized by leg raising). These effects were associated with an increase in cardiac index. Interestingly, the second part of the fluid challenge (the subsequent 200-mL aliquot) was not associated with further changes in microcirculatory perfusion, while cardiac index further increased. As mentioned by an accompanying editorial [58] the aspects common to the two trials were emphasized (relative lack of dependency from cardiac output, importance of fluids in the early phase). It was also noticed that we still need more evidence

to determine whether the type of fluid may be associated with a different response.

Another aspect of microvasculature was investigated by Georger et al. [59]. These authors investigated the effects of correcting hypotension on microvascular vasoreactivity in 28 patients with septic shock. The latter was evaluated by using a transient occlusion test and measuring microvascular oxygen saturation by near-infrared spectroscopy. The authors observed that an increase in mean arterial pressure from 54 to 77 mmHg also increased basal microvascular O_2 saturation from 75 to 78% ($p < 0.05$) but the clinical significance of these changes remains quite limited. More interestingly, the recovery slope increased by 50% ($p < 0.05$). These effects suggest either an intrinsic effect of the vasoactive agent (norepinephrine) or, more likely, a beneficial impact of restoring a minimal perfusion pressure on microvascular responsiveness. These results should be looked at cautiously, as there was no proof that these effects on near-infrared spectroscopy derived variables were associated with improved microvascular perfusion.

Long-term effect of goal-directed therapy in high-risk surgery patients

Many trials have shown that perioperative haemodynamic optimization is accompanied by an improvement in short-term outcome. However the question remains whether this was just a transient phenomenon (benefit lost after a few weeks) or whether long-term benefit could also be observed. Rhodes et al. [60] evaluated the very long-term impact on outcome of perioperative haemodynamic optimization in a cohort of patients in whom short-term beneficial effects on 28-day survival had been reported. Fifteen-year follow-up was obtained in 106 of the 107 patients included in the original cohort. At 15 years, 21% of the intervention arm and 8% of the control group were still alive ($p = 0.09$) while median survival time was significantly longer in the intervention cohort (1,781 vs. 674 days, $p < 0.005$). Multivariate analysis identified goal-directed therapy, age and avoidance of cardiac complications as independent factors associated with better outcome.

Can we improve resuscitation procedures?

Cardiopulmonary resuscitation remains associated with variable success, and improved resuscitation procedures would be more than welcome. The use of an automated load distribution chest compression device has been suggested to potentially improve quality of resuscitation. However, human data are still lacking. Duchateau et al. [61] evaluated the effects of such a device on arterial pressure during cardiopulmonary resuscitation (CPR) in 29 patients with out-of-hospital cardiac arrest. Compared with manual CPR, automated CPR was associated with an increase in systolic (from 72 to 106 mmHg, $p < 0.05$) and diastolic (from 17 to 23 mmHg, $p < 0.05$) pressures. However, there was no change in end-tidal CO_2, suggesting that the impact of this intervention on cardiac output may be limited. Although promising, these results need to be evaluated in a larger cohort of patients.

Critical care organization and outcome

Early management of critically ill patients has been advocated by three manuscripts in *Intensive Care Medicine* this year. Konrad et al. [62] evaluated the impact of a medical emergency team (MET) implementation on the incidence of cardiac arrests and hospital mortality. In a before/after trial they compared outcomes in 203,892 patients admitted before MET implementation, with outcomes of 73,825 patients managed after MET implementation. Cardiac arrests per 1,000 admissions decreased from 1.12 to 0.83, OR 0.74 (95% CI 0.55–0.98, $p = 0.035$). MET implementation was associated with a reduction in total hospital adjusted mortality by 10%, OR 0.90 (95% CI 0.84–0.97, $p = 0.003$). Hospital mortality was also reduced for medical patients by 12%, OR 0.88 (95% CI 0.81–0.96, $p = 0.002$) and for surgical patients not operated upon by 28%, OR 0.72 (95% CI 0.56–0.92, $p = 0.008$). Thirty-day and 180-day mortality rates were 25 and 37.5%, respectively, during the pre-MET period and 7.9 and 15.8%, following MET.

The relationship between ICU admission time and in-hospital mortality has been studied in the 149,894 patients included in the Dutch national ICU registry from 2002 to 2008 [63]. The relative risk (RR) for mortality outside office hours was 1.059 (1.031–1.088). During the weekend the RR was 1.103 (1.071–1.136) in comparison with the rest of the week.

Several studies have been published on various aspects of quality of care and ICU-acquired events in the critically ill. Seguin et al. [64] prospectively evaluated the effectiveness of simple daily sensitization of physicians to the duration of central venous and urinary tract catheterization (UTC) and related infection rates. During the intervention period, a red square, added to the patient's daily care sheet, questioned the physician about the utility of the CVC and/or UTC. If the response was "No", the CVC and/or the UTC were removed by a nurse. The duration of catheterization was significantly reduced [period 1, $n = 676$; 5 (3–9) days, period 2, $n = 595$; 4 (3–7) days, $p < 0.001$, for CVC, 5 (3–11) days to 4 (3–8) days, for UTC]. The incidence and density incidence of CVC infection decreased in period 2 compared with period 1 (from 1.8 to 0.3%, $p = 0.010$, and from 2.8 to 0.7/1,000 CVC-days, $p = 0.051$), whereas UTC infections were not

significantly different (4.3 to 3.0%, $p = 0.230$, and 5.0 to 4.9/1,000 UTC-days, $p = 0.938$, respectively).

Knowing the reasons for ICU admission during pregnancy, delivery and puerperium has important organization implications. Zwart et al. [65] collected prospective data on ICU admissions in all 98 Dutch maternity units. There were 847 obstetric ICU admissions in 358,874 deliveries, the incidence being 2.4 per 1,000 deliveries. Twenty-nine maternal deaths occurred, resulting in a case fatality rate of 1 in 29 (3.5%). Most frequent reasons for ICU admission were major obstetric haemorrhage (48.6%), hypertensive disorders of pregnancy (29.3%) and sepsis (8.1%). Assisted ventilation was needed in 34.8%, inotropic support in 8.8%. Initial antenatal care by an obstetrician was associated with a higher risk and home delivery with a lower risk of ICU admission.

Iatrogenic errors received growing attention in the last few years with the intent of establishing organization plans for their identification and correction. Mercier et al. [66] determined the incidence, risk factors, severity and preventability of iatrogenic events (IEs) as a cause of ICU admission. Admission to the ICU for IE concerned 103 (19.5%) out of 528 patients. IE was considered as probably preventable in 73.8% of cases. Length of stay was higher in IE patients. Catecholamine drugs, blood transfusion and parenteral nutrition were more frequently required in the IE group. Severity, surgical admissions and admission for shock were more frequent in the IE group.

Ford et al. [67] assessed whether simulation-based learning reduced medication error rates in critically ill patients. Twenty-four nurses were observed administering medications. Documentation included drug name, dose, route, time and technique during observation and active medication orders in the patient's chart. Interventions were two types of educational sessions with content developed from baseline medication administration error data: simulation-based training for critical care unit (CCU) nurses and a didactic lecture for medical intensive care unit (MICU) nurses. Quizzes completed before and after the interventions were used to assess knowledge. After the simulation-based educational intervention in the CCU, medication administration error rates decreased from 30.8 to 4.0% ($p < 0.001$) in the initial post-intervention observation and were sustained in the final post-intervention observation (30.8 to 6.2%; $p < 0.001$).

Intensive care medicine has developed rapidly and to a considerable extent throughout the past 10–15 years. Hence, it is mostly important to implement and adapt programs for training the physicians. In this context, the generation of guidelines is increasingly challenging. A critical appraisal of the quality of these guidelines was presented within a special review [68]. The investigators concentrated on the evaluation of the strength of recommendation from a total of 24 clinical practice guidelines (CPG) over a time from 1966 until 2008. Specific aims were clarity, scope/purpose, rigour of development, editorial independence, stakeholder involvement, and applicability of the recommendations. The investigators found that 36% of recommendations are supported by high-quality evidence, thus recommending appraisal of CPG quality and the caliber of supporting evidence prior to applying recommendations.

A special supplement of *Intensive Care Medicine* concentrated on a similar issue, but with a specific aim: a group of authors gave recommendations for standard operating procedures (SOP) for ICU and hospital preparations for an influenza epidemic or mass disaster, which was broadly discussed in 2010 due to the H1N1 pandemia. This supplement is highly recommended to those who are involved in this issue, and it is far beyond the scope of this review to cover all single topics. Roughly, the key issues were coordination and communication [69], surge capacities and infrastructure [70], collaboration between the ICU and other key stakeholders [71], manpower [72], essential equipment, pharmaceuticals and supplies [73], protection of patients and staff [74], critical care triage [75], protocols and procedures [76] and emergency executive control groups [77].

Outcomes

In a retrospective analysis, Polverino et al. [78] retrospectively analysed the time course of patients' characteristics, clinical outcomes and medical staff utilization in five Italian respiratory ICUs (RICUs) by comparing three periods of five consecutive years (from 1991 to 2005). Over the different time periods, the number of co-morbidities per patient and the previous ICU stay increased over time. The doctor-to-patient ratio significantly decreased over time, whereas the physiotherapist-to-patient ratio mildly increased. The overall weaning success rate decreased. Fewer patients were discharged to home and more patients to nursing home, acute hospitals and rehabilitative units. The mortality rate increased over time (from 9 to 15%).

Two studies have assessed qualitative outcomes in critically ill patients. In a two-step trial comprising a phase of item generation conducted in one ICU and a phase of psychometric evaluation during a multicentre prospective cohort study in 14 ICUs, Kalfon et al. [79] developed and validated the IPREA questionnaire for the assessment of discomfort perceived by patients related to their ICU stay. On the day of ICU discharge, a nurse asked 868 patients to rate the severity of 16 discomfort sources, from 0 to 100. Ten per cent of patients were randomly chosen to be questioned again to assess the reproducibility. The highest scores were for sleep deprivation, being restrained by tubing, wires, and cables, pain and thirst.

Vainiola et al. [80] compared the EQ-5D and 15D in critically ill patients. A total of 929 patients filled in both the EQ-5D and 15D HRQoL instruments 6 and 12 months

after treatment at an intensive care or high-dependency unit. The utility scores produced by the instruments and their distributions were different. Agreement between the instruments was only moderate. The 15D appeared more sensitive than the EQ-5D both in terms of discriminatory power and responsiveness.

Education

The European Society of Intensive Care Medicine through the Competency Based Training in Intensive Care medicine collaboration (CoBaTrice) has recently developed the international standards for programmes of training in intensive care medicine for Europe [81]. Growing importance and emphasis has been given to professionalism. However, insight into the elements of professionalism as perceived relevant for intensivists from the fellows' (residents) view, and how these are taught and learned, is limited. In order to address these issues, van Mook et al. [82] carried out a nationwide study (2007–2008) among intensive care medicine fellows in The Netherlands. Ninety intensive care medicine fellows were sent a questionnaire pertaining to quantity and quality of formal and informal learning methods. Analyzing the answers of the 75.5% ($n = 68$) respondents, van Mook et al. concluded that almost all elements of professionalism were considered relevant to intensivists' daily practice and that learning by personal experiences and informal ways quantitatively and qualitatively plays a more important, and more valued role than learning by formal teaching methods.

Sandroni et al. [83] identified factors associated with candidate outcome in the European Resuscitation Council (ERC) advanced life support (ALS) provider courses. Candidates [$n = 269$ (95.1%)] who passed were younger and attained a higher pre-course score than those who failed the final evaluation. A higher pre-course score [OR 1.18 (95%CI 1.09–1.28)] and a basic life support (BLS) certification [OR 5.00 (95%CI 1.12–22.42)] were independent predictors of candidate success, while older age was associated with a significantly higher risk of failing [OR 0.90 (95%CI 0.83–0.97)].

Methodology plays an important role in education and research evaluation. The January issue of *Intensive Care Medicine* contained a review on meta-analysis [84]. Despite the validity of this approach, which combines evidence from multiple trials, meta-analyses of studies with substantial heterogeneity among patients within trials (a common condition in intensive care) can lead to incorrect conclusions if performed by using aggregate data. Use of individual patient data (IPD) can avoid this concern, increase the power of a meta-analysis and is useful for exploring subgroup effects. Barriers exist to IPD meta-analysis, most of which are overcome if clinical trials are designed to prospectively facilitate the incorporation of their results with other trials. Authors review the features of prospective IPD meta-analysis and identify those of relevance to intensive care research. As a concluding remark, the authors suggested that the potential effect of variations in baseline risk and intercurrent care is sufficiently large in intensive care to threaten the validity of any meta-analysis based in aggregate data. This article has an accompanying editorial comment [85].

Another interesting review was published on a statistical approach recently applied in the field of intensive care medicine, often used to correct the lack of randomization in clinical studies: the propensity score (PS) methods [86]. PS methods have been increasingly used in the last 10 years. In this review article, the authors briefly explain the theory of propensity scores, assess the use and the quality of reporting of PS studies in intensive care and anaesthesiology, and finally they evaluate how past reviews have influenced the quality of the reporting. Forty-seven articles published between 2006 and 2009 in the intensive care and anaesthesiology literature were evaluated. Of the 47 articles reviewed, 26 used matching on PS, 12 used stratification on PS and 9 used adjustment on PS. The method used was reported in 81% of the articles, and the choice to conduct a paired analysis or not was reported in only 15%. The comparison with the previously published reviews showed little improvement in reporting in the last few years. The authors also provided some recommendations to investigators in order to improve the reporting of PS analyses. It was concluded that the quality of reporting PS in intensive care and anaesthesiology literature should be improved.

Haematology

In a prospective, observational, multicentre cohort study, investigators of the ANZICS Clinical Trials Group assessed the relationship between clinical practice and national guidelines for the transfusion of red blood cells (RBCs), fresh frozen plasma (FFP), platelets and cryoprecipitate in Australian and New Zealand ICUs [87]. A total of 874 patients receiving any type of blood transfusion were studied. The proportions of transfusions not adherent to guidelines were 2% for RBC, but 53% for platelets, 29% for FFP and 88% for cryoprecipitate (RBC vs. other transfusion $p < 0.001$ for all).

To compare evolution in organ dysfunction (OD) between haematologic malignancy patients with and without bacterial infection (BI), Vandijck et al. [88] performed a retrospective analysis in haematologic malignancy patients admitted to their ICU between 2000 and 2006. Patients admitted because of BI had more severe OD on day 1, but a more rapidly reversible OD within the first 3 days and a lower in-hospital (43.2 vs. 62.9%, $p < 0.001$) and 6-month mortality (52.1 vs.

71.7%, $p < 0.001$) than patients with other complications. BI remained independently associated with a lower risk of death (OR 0.20, 95% CI 0.1–0.4, $p < 0.001$).

The October issue of *Intensive Care Medicine* published an interesting article on critical care management of patients with haemophagocytic lymphohistiocytosis (HLH) [89]. A retrospective search (from 1998 to 2009) on this life-threatening condition associated with multiple organ dysfunction was performed in a medical ICU. A total of 72 patients were identified as having an HLH, and data on 56 patients with complete follow-up were reported. Precipitating factors consisted of 43 tumoral causes, 13 non-viral infections and 10 viral infections. Underlying immune deficiency was present in 38 (67.8%) patients. Etoposide was used in 45 patients, corticosteroids in 31 and intravenous immunoglobulins in 3. Hospital mortality was 51%. By multivariate analysis, factors associated with increased hospital death were shock at ICU admission (OR 4.33) and platelet count below 30×10^9/l (OR 4.75). B cell lymphoma and Castleman's disease were associated with increased hospital survival. It was concluded that aggressive supportive care combined with specific treatment of the precipitating factor can produce meaningful survival in these patients.

Ventilatory approach of haematological patients outside the ICU might be important. Squadrone et al. [90] randomized haematological patients in the wards with acute respiratory failure to received either oxygen ($n = 20$) or oxygen plus continuous positive airway pressure (CPAP, $n = 20$). CPAP reduced the relative risk for intubation.

Nutrition and metabolism

Enteral nutrition

Enteral feeding is a cornerstone of ICU nutrition, and documentation around safety is important. In the REGANE study Montejo et al. [91] demonstrated that a gastric residual volume of 500 mL is not associated with a higher complication rate as compared with 200 mL. Furthermore the nutrition target was achieved somewhat faster using the higher limit for gastric residual volume. This Spanish multicentre study gives good evidence that naso-gastric feeding can be used safely and efficiently in an unselected group of mechanically ventilated patients. In another Spanish single-centre study Acosta-Escribano et al. [92] reported that transpyloric feeding is associated with a lower incidence of pneumonia and a higher volume of received nutrition as compared with gastric feeding. The use of probiotics in enteral feeding is highly controversial, related to the strain(s) of *Lactobacilli* used and the patient selection. Barraud et al. [93] reported on a single-centre study where 167 patients in a medical ICU on short-term mechanical ventilation were randomised to probiotics or placebo. The results were contradictory in different predefined subgroups of septic patients, and the authors conclude that prophylactic treatment with probiotics cannot be encouraged presently.

Parenteral nutrition

Parenteral nutrition (PN), either alone or in combination with enteral nutrition, can improve nutrient delivery to critically ill patients. Lipids provide a key source of calories within PN formulations, preventing or correcting energy deficits and improving outcomes. Calder et al. [94] reviewed the role of parenteral lipid emulsions (LEs) in the management of critically ill patients. Soybean-oil-based LEs with high contents of polyunsaturated fatty acids (PUFA) may be associated with increased rates of infection and lipid peroxidation, which can exacerbate oxidative stress. More recently developed parenteral LEs employ partial substitution of soybean oil with oils providing medium-chain triglycerides, omega-9 monounsaturated fatty acids or omega-3 PUFA. Many of these LEs have demonstrated reduced effects on oxidative stress, immune responses and inflammation. However, the effects of these LEs on clinical outcomes have not been extensively evaluated. The authors concluded that current data are limited and sometimes inconsistent because of the heterogeneity of the study designs and patient populations. Consequently, the prescription of PN containing LEs should be based on available clinical data, while considering the individual patient's physiologic profile and therapeutic requirements.

Metabolism

The use of predictive markers give information that may add to the conventional scoring systems. Piton et al. [95] reported that the plasma citrullin concentration may add predictive value to SOFA scoring in ICU patients without renal or intestinal failure. It is not clear if this finding is independent from the well-known fact that a low plasma glutamine concentration is an independent predictor of ICU outcome. Lindner et al. [96] reported from a retrospective analysis of 2,700 patients undergoing cardiothoracic surgery that ICU-acquired hypernatraemia is an independent risk factor for ICU mortality. If this finding is confined to this specific patient group or can be generalised to other groups of ICU patients remains to be elucidated. Iron deficiency in ICU patients may be difficult to diagnose as the general inflammation seen in most ICU patients induces anaemia by itself. By the analysis of serum hepcidin Lasocki et al. [97] showed that anaemia related to iron deficiency in ICU patients can be separated and hepcidin therefore may be a useful marker.

The inflammatory response seen in conjunction with sepsis may be regarded as an asset or a threat for the individual patient. Andreasen et al. [98] studied patients with type II diabetes and reported that the cytokine response to an endotoxin challenge is attenuated when compared with that seen in healthy controls. This may explain the higher susceptibility to sepsis in this patient group. Pittet et al. [99] reported that an attenuated inflammatory response occurred in healthy volunteers pretreated with fish oil rich in $n-3$ polyunsaturated fatty acids. This particular study was a dose-finding exercise showing a more pronounced blunting when a moderate dose of fish oil was given immediately before the endotoxin challenge.

Ethics

Intensive Care Medicine published several articles on ethics during 2010.

Predictions of the need for critical care within the H1N1 influenza pandemic suggested overwhelming need beyond potential resources, necessitating rationing of care via triaging. In the June issue, Eastman et al. [100] described a triage model derived from informed discourse within a conjoined UK National Health System (NHS) and University Clinical Ethics Committee, supplemented by specialists in intensive care and infectious diseases. The model, which partially suspends usual clinical judgment applied to individuals in favour of also utilizing organ failure scores, includes minimization of aggregate influenza morbidity and mortality, and minimization of psychological stress upon staff making triaging decisions. A mismatch appears between a clinically and ethically acceptable model of triaging, based upon a public health approach, and the law, based upon the paradigm of the individual patient. Fortunately, the H1N1 pandemic was less severe than predicted, allowing time for calm consideration, debate and decision making about what model of triaging should be adopted whenever it might be necessary in the future.

Another paper addressed a similar issue [101], with the attempt of providing a revised definition, process and purpose of triage to maximise the number of patients receiving intensive care during a crisis. The authors redefined the decision-making processes regarding treatment decisions during a pandemic, recommending new methods of intensive care provision and the use of a 'ranking' system for patients excluded from intensive care, defining the role of non-intensive care specialists, and applying two types of triage as 'organisational triage' and 'treatment triage' based on the demand for intensive care. This different approach could maximise the number of patients receiving intensive care based on individual patients' best interests.

Le Conte et al. [102] in a 4-month prospective survey described the characteristics of patients who died in 174 French and Belgian emergency departments and the decisions to withhold or withdraw life support. Of 2,512 patients enrolled, life-support therapy was initiated in 1,781 patients (73.6%). Palliative care was undertaken for 1,373 patients (56.7%). A decision to withhold or withdraw life-sustaining treatments was taken for 1,907 patients (78.8%) and mostly concerned patients over 80 years old, with underlying metastatic cancer or previous functional limitation. Decisions were discussed with family or relatives in 58.4% of cases. The decision was made by a single ED physician in 379 cases (19.9%), and by at least two ED physicians in 1,528 cases (80.1%). The authors concluded that training of future ED physicians must be aimed at improving the level of care of dying patients, with particular emphasis on collegial decision-taking and institution of palliative care.

Research in the emergency and intensive care medicine poses difficult problems about consent.

Deferred consent has been proposed as a strategy to allow the enrolment of patients in these specific contexts, but the inability to obtain deferred consent due to early death in emergency research may affect validity of clinical trial results. Jansen et al. [103] analysed the unadjusted and adjusted primary outcome measures in the field of intensive care medicine including ($n = 348$) or excluding ($n = 289$) patients with missing deferred consent from a randomized controlled trial. Thirty-nine patients (11%) died early, before the patient or his/her proxy could be approached and consent be obtained. In another 20 patients (6%), it was not possible to inform proxies and ask consent within the period of study procedures. A significant treatment effect ($p = 0.006$) in the adjusted analysis became non-significant ($p = 0.35$) when the patients with missing deferred consent were excluded. It was concluded that the exclusion of patients without obtained deferred consent can reduce statistical power, introduce selection bias, make randomization asymmetrical, decrease external validity and thereby jeopardize study results.

At present no consensus exists on uniform criteria for defining a potential organ donor. Although the term is increasingly being used in recent literature, it is seldom defined in detail. De Groot et al. [104] explored the difficult issue of potential organ donors on imminent brain death. The authors organized meetings with representatives from the fields of clinical neurology, neurotraumatology, intensive care medicine, transplantation medicine, clinical intensive care ethics and organ procurement management. During these meetings, all possible criteria were discussed to identify a patient with a reasonable probability of becoming brain dead focusing the practical usefulness of two validated coma scales (Glasgow Coma Scale and the FOUR Score), brain stem reflexes and respiration to define imminent brain death. Furthermore the criteria to determine irreversibility and futility in acute neurological conditions were discussed. Through this multidisciplinary dicussion a patient fulfilling the criteria of imminent brain

death was defined as a mechanically ventilated deeply comatose patient, admitted to an ICU, with irreversible catastrophic brain damage of known origin. The condition of imminent brain death should require either a Glasgow Coma Score of 3 and the progressive absence of at least three out of six brain stem reflexes or a FOUR Score of E(0)M(0)B(0)R(0).

A 12-month, prospective, multicentre observational study was conducted in 84 Italian ICUs to appraise the end-of-life decision-making and to evaluate the association between the average inclination to limit treatment and overall survival [105]. Data collection included description, treatment limitation and decision-makers, involvement of patients and relatives, and organ donation of 3,793 consecutive patients who died in ICU or were discharged in terminal condition during 2005. Treatment limitation preceded 62% of deaths. In 25% of cases, nurses were involved in the decision. Half the limitations were do-not-resuscitate orders, with the remaining half almost equally split between withholding and withdrawing treatment. Units less inclined to limit treatments (OR <0.77) showed higher overall standardized mortality ratio (1.08; 95% CI 1.04–1.12). The authors concluded that treatment limitation is common in Italian ICUs and still principally under physicians' responsibility. Units with below-average inclination to limit treatments have worse performance in terms of overall mortality. This result was important as it showed that limitation is not against the patient's interests, but vice versa the inclination to limit treatments at the end of life can be taken as an indication of quality in the unit.

Miscellanea

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 a review by Struck et al. [106] on the current literature on severe cutaneous adverse reactions that are not associated with burn injuries. They present life-threatening examples such as Stevens–Johnson syndrome and toxic epidermal necrolysis, and conclude 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. Although touching a quite different field of intensive care medicine, the review on the use of hypothermia in acute liver failure is also very interesting and possibly a bit nearer to the daily practice of the intensivist [107]. The investigators evaluated the present data on the safety and efficacy of induced moderate hypothermia combined with intracranial pressure (ICP) monitoring in critically ill patients with acute liver failure. They selected five case series in the literature with significant heterogeneity, as expected. Nonetheless, they demonstrated that this approach consistently improved ICP, cerebral perfusion pressure (CPP) and cerebral blood flow (CBF), concluding that well-designed prospective clinical trials are warranted. Finally, the use of direct thrombin inhibitors in intensive care medicine was the topic of another literature review [108]. The specific question was whether this group of alternative anticoagulants provides safety and efficacy when used in the field of intensive care medicine. For this purpose, the investigators present a synopsis of scientific evidence, expert opinion, open forum commentary and clinical feasibility data. They conclude that these drugs could offer potential advantages over heparins due to their direct antithrombotic potential without direct activation of platelets. Nonetheless, cautious dosing and close drug monitoring are required, with special regard to existing multiple organ dysfunctions and numerous comedications.

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